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Prognostic factors for survival in patients with gastric cancer: Single-centre experience

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ABSTRACT

OBJECTIVE: We aimed to investigate survival outcomes and survival-related prognostic factors in gastric cancer patients who were followed-up or received adjuvant therapy in our center.

METHODS: Patients with gastric cancer treated between 2005 and 2016 were evaluated retrospectively. We included 345 non-metastatic (stage I-III) gastric cancer patients in the study. The clinical, demographic, histologic data of the patients and treatment characteristics were obtained from the patient's files.

RESULTS: While 50 patients were stage I, 94 patients were stage II, 201 patients were stage III. While 221 patients (64%) presenting with serosal or adjacent visceral organ invasion or with involved lymph nodes were treated with adjuvant chemoradiotherapy, 124 patients presenting with early-stage disease were followed after surgery. Median follow up time was 34 months (4–156 months). While the median overall survival (OS) was 51 months, median disease-free survival (DFS) was 35 months. Overall survival and disease-free survival rates for 1st, 3rd and 5th years were 85%, 55%, 45% and 72%, 49%, 38%, respectively. According to univariate analysis, tumor size, T stage ($p<0.001$), N stage ($p<0.001$), TNM stage ($p<0.001$), grade ($p<0.001$) and presence of lymphovascular invasion ($p=0.005$) were determined as prognostic factors that affect overall survival significantly. According to the multivariate analysis, only T and N stage ($p<0.001$) were determined as independent prognostic factors for overall survival.

CONCLUSION: Many different prognostic factors have been defined for gastric cancer. In concordance with the literature, we found T and N stages as prognostic factors in univariate and multivariate analysis.

Keywords: Chemoradiotherapy; gastric cancer; prognostic factors.

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Gastric cancer is the sixth most common cancer and an important cause of cancer-related deaths worldwide [1]. According to cancer statistics in Turkey, gastric cancer is the 5th most common cancer both in men and women [2]. Genetic and environmental risk factors are responsible for the etiology of gastric cancer. Among those smoking, alcohol usage, smoked and salted foods, helicobacter pylori infection, pernicious anemia, chronic atrophic gastritis, intestinal metaplasia, previous gastric operations, peutz-jeghers syndrome, li-fraumeni syndrome and hereditary diffuse gastric cancer syndrome are the most important ones [3–6]. International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM stage is the most important determinant of prognosis after surgery [7]. Studies reported that there are also many other prognostic factors that affect survival, such as lymphovascular invasion, grade, resection type and performance status [8, 9].

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Although nowadays remarkable progress has been made in gastric cancer treatment, gastrectomy with regional lymphadenectomy still remains the primary treatment for the resectable disease. Surgical resection alone with no pre- or postoperative treatment provides a five-year overall survival (OS) rate of approximately 20–30% [10, 11]. For potentially resectable patients, several randomized trials indicated a significant survival benefit of different adjuvant treatment approaches in comparison to surgery alone [11–15]. Adjuvant chemoradiotherapy is one of these approaches where survival benefit was demonstrated in the landmark SWOG 9008/INT-0116 trial [12]. Perioperative (preoperative plus postoperative) chemotherapy is another option for these patients whose survival benefit has been demonstrated in the MAGIC trial [11]. Nowadays, adjuvant treatment decision is mainly made according to the TNM stage, performance status, comorbidities of the patient, and toxicities of adjuvant chemotherapy and radiotherapy.

We aimed to investigate the factors that affect the survival of gastric cancer patients treated in our center and compare our results with the literature.

MATERIALS AND METHODS

Patients with pathological diagnosis of gastric cancer who were operated and either followed-up or received adjuvant therapy after operation or who were inoperable and treated with definitive chemoradiotherapy in our center between 2005 and 2016 were evaluated retrospectively in this study. Patients were staged according to the AJCC staging system (7th edition). All of the patients were older than 18 years, and their performance status scores were ≤2 according to the ECOG (Eastern Cooperative Oncology Group) scoring system.

Patient Characteristics

In this study, 232 out of 345 patients were male, while 113 out of 345 patients were female. The median age was 57.1. While 11 (3%) patients were locally advanced and underwent endoscopic biopsy only, total gastrectomy was performed in 166 patients (48%) and subtotal gastrectomy was performed in 168 patients (49%). Regarding the lymph node status of the patients, 258 patients (75%) had nodal metastases, while 76 patients (22%) were confirmed to be node-negative based on pathologic examination. According to staging, 50 out of 345 patients were stage I, 94 out of 345 patients were stage II, and 201 out of 345 patients were stage III. Perineural invasion was identified in 203 (59%) patients, and lymphovascular invasion was identified in 238 (69%) patients. Histologic grades of the patients were as follows, 41 patients had grade 1 (12%), 107 patients had grade 2 (31%), and 186 patients had grade 3 (54%) disease. The patient characteristics are summarized in Table 1.

Treatment and Follow-up

Two hundred twenty-one patients (64%) presenting with serosal or adjacent visceral organ invasion or with involved lymph nodes were considered suitable for adjuvant chemoradiotherapy. The adjuvant treatment plan was similar to the intergroup-0116 trial presented in 2001 by MacDonald et al. [12]. The radiation was administered by 1.8 Gy fractions per day, five days per week, either 45 Gy in 25 fractions in 180 patients or 50.4 Gy in 28 fractions in 28 patients. Thirteen patients could not complete 45 Gy due to toxicity. Radiation therapy was planned by either three-dimensional (3D) conformal technique in 165 patients or two-dimensional (2D) technique in 56 patients. All of the patients received bolus or infusional 5-fluorouracil, one cycle before and one cycle after radiation treatment. Different concomitant chemotherapy schemes were used, including either bolus fluorouracil and leucovorin, or infusional fluorouracil or oral capecitabine. Treatment characteristics of the patients are summarized in Table 2. While bolus fluorouracil (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) were administered at the first four and the last three days of radiotherapy, infusional fluorouracil (225 mg/m^2/day) was given continuously throughout the radiotherapy, and oral capecitabine (825 mg/m^2/twice a day) as well.

In the first two years after surgery, patients were followed up regularly with three monthly intervals and then every six months in the third year and annually thereafter. During the follow-up visits, patients underwent physical examination, complete blood tests, chest radiography and computerized tomography or magnetic resonance imaging as clinically indicated. Upper gastrointestinal endoscopy was used to verify locoregional recurrence.

Statistical Analysis

Recurrence-free survival (RFS) is defined as the time span from the date of diagnosis to the date of histologically or radiologically confirmed the first relapse, and overall survival (OS) is defined as the time span from

Table 1. Demographic and clinicopathologic characteristics of the patients

Characteristics	n	%
Gender		
Male	232	67
Female	113	33
Age (yr), mean±SD	57.1±11.5	
Tumor location		
Gastroesophageal junction	11	3
Fundus, cardia	85	25
Corpus	100	29
Antrum, pylorus	149	43
Surgical resection type		
Total gastrectomy	166	48
Subtotal gastrectomy	168	49
Unresectable	11	3
Tumor size		
<5 cm	139	41
5–10 cm	170	49
>10 cm	36	10
Lymphovascular invasion		
Yes	238	69
No	96	28
Unknown	11	3
Perineural invasion		
Yes	203	59
No	131	38
Unknown	11	3
Grade		
I	41	12
II	107	31
III	186	54
Unknown	11	3
Surgical margin		
Negative	294	85
Positive	40	12
Inoperable	11	3
T-Stage		
T1/T2	98	39
T3/T4	247	71
N-Stage		
N0	76	22
N1	68	20
N2	90	26
N3a	74	21
N3b	26	8
NX	11	3
TNM Stage		
IA	10	3
IB	40	12
IIA	44	13
IIB	50	14
IIIA	70	20
IIIB	62	18
IIIC	69	20

SD: Standard deviation.

Table 2. Treatment characteristics of the patients

	n	%
Adjuvant radiotherapy		
Yes	221	64
No	124	36
Radiation technique		
Two-dimensional radiotherapy	56	25
Three-dimensional radiotherapy	165	75
Radiation dose		
<45 Gy	13	6
45 Gy	180	81
50.4 Gy	28	13
Concomitant chemotherapy		
Bolus 5-FU*	107	48
Infusional 5-FU	78	35
Oral Capecitabine	36	17

*5-FU: 5-fluorouracil.

Table 3. Overall survival according to pathological stage

Stage	Patients (n)	1 year survival (%)	3 years survival (%)	5 years survival (%)	Median survival (month)
IA	10	100	90	90	Not reached
IB	40	95	89	85	Not reached
IIA	44	95	83	74	71
IIB	50	94	73	62	66
IIIA	70	89	54	48	40
IIIB	62	82	44	28	30
IIIC	69	50	24	13	12

the date of diagnosis to the date of death or last control date of the patients. The survival analysis was calculated using the Kaplan–Meier method, and the log-rank test was used for the univariate analysis. A Cox proportional hazard model was utilized for multivariate analysis in order to determine independent prognostic factors. All the tests were two-sided, and a p-value of <0.05 was considered to be statistically significant. Statistical analyses were performed using The Statistical Package for Social Sciences (SPSS 17, Chicago, IL, USA). Informed consent has been obtained from all the patients. The

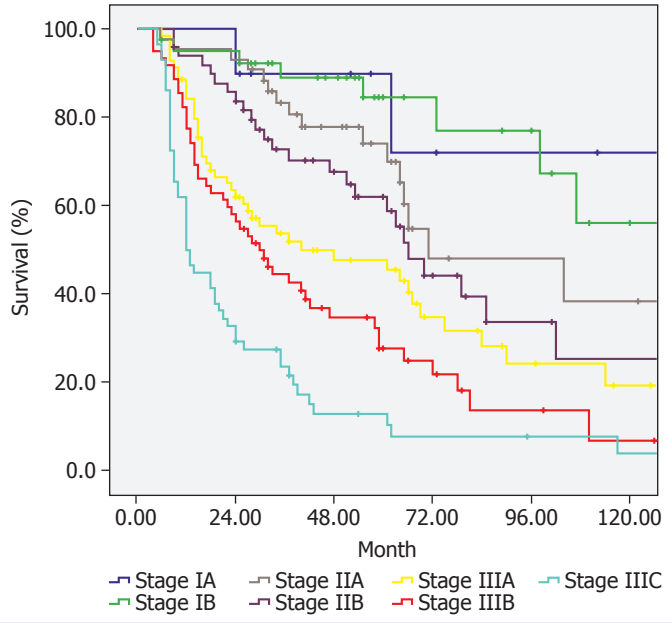

FIGURE 1. Overall survival according to the stage.

local Ethical Committee of our hospital approved the study in concordance with the declaration of Helsinki (2018/514/136/1).

RESULTS

Median follow up time was 34 months (4–156 months). Median overall survival (OS) was 51 months and OS rates for 1st, 3rd and 5th years were 85%, 55% and 45%, respectively. Median overall survival has not been reached for stage IA and IB disease. Overall survival according to pathological stages is summarized in Table 3 and Figure 1. Median recurrence-free survival was 35 months and RFS rates for 1st, 3rd and 5th years were 72%, 49% and 38%, respectively. While locoregional recurrence was detected in 56 patients (16.2%), distant metastasis was observed in 147 patients (42.6%). At the time of analysis, 10 patients were still alive despite recurrence, and 205 patients died related to gastric cancer.

According to the univariate analysis, tumor size (p<0.001), T stage (p<0.001), N stage (p<0.001), TNM stage (p<0.001), grade (p<0.001), and the presence of lymphovascular invasion (p=0.005) were found as factors that have an effect on survival. Prognostic factors affecting survival according to univariate analysis are summarized in Table 4. According to the multivariate analysis, the T stage was determined to be an independent prognostic factor for overall survival and there was a threefold increase in mortality in patients with T4 stage as compared with the patients with T1 stage (p=0.001). The nodal stage was found as another independent prognostic factor for overall survival and mortality was increased by 4.2 fold in patients with N3 category and 2.7 fold in patients with N2 category when compared to the patients with N0 category (p<0.001). Hazard ratios for overall survival depending on the T stage and N stage are summarized in Table 5.

TABLE 4. Prognostic factors affecting survival according to univariate analysis

Univariate analysis	p
Tumor size	<0.001
T- Stage	<0.001
N- Stage	<0.001
Lymphovascular invasion	0.005
Grade	<0.001
TNM stage	<0.001

TABLE 5. Prognostic factors affecting survival according to multivariate analysis

	p	HR	95% CI
T Stage	<0.001		
T1			
T2	0.33	1.44	0.69–2.99
T3	0.07	1.88	0.95–3.74
T4	0.001	3.01	1.55–5.87
N Stage	<0.001		
N0			
N1	0.2	1.43	0.83–2.47
N2	<0.001	2.7	1.67–4.36
N3	<0.001	4.12	2.58–6.55

HR: Hazard ratio; CI: Confidence interval.

DISCUSSION

The incidence and mortality rates of gastric cancer differ throughout the world [16]. Epidemiological studies demonstrate a decrease in gastric cancer incidence [17]. While gastric cancer incidence has decreased in the last decades in Turkey [18], its incidence is still highest among the Middle East countries [19]. Gastric cancer

is observed more frequently in males than in females [17]. Our study also demonstrated the female to male ratio as 1/2. While the incidence of proximal tumors is increasing in the western world, distal tumors continue to be predominant in Japan [20]. In Turkey, most of the cases are diagnosed at an advanced stage, and majority is located distally [21]. In our study, 72% of the patients presented with distally located tumors. Lymphovascular invasion was found to be an independent prognostic factor as in most of the studies [22–24]. Lymphovascular invasion was observed in 69% of our patients with very high frequency in contrast to the rates ranging between 31.9–44.3% reported in the literature [22–24].

Surgery is a major curative treatment. Despite the improvements in surgical techniques, surgery alone with no pre or postoperative treatment provides a fair overall survival. Recent randomized studies in resectable gastric cancer patients comparing surgery with or without preoperative chemotherapy or comparing D1 versus D2 resection demonstrated overall survival between 20–30% with surgery alone [10, 11]. Survival rates vary according to the T and N stage, being around 85–90% in T1 tumors and around 15–20% in T4 tumors and node-positive patients [25]. Loco-regional recurrence rates are important concern in resected patients [25]. Therefore, a multi-modal approach is necessary to improve surgical results. Adjuvant chemotherapy alone or concomitant with radiotherapy, or perioperative chemotherapy are the most studied and effective treatment approaches.

Adjuvant chemoradiotherapy is the preferred treatment option for resected gastric cancer patients with less than D2 lymph node dissection [26]. The landmark trial which demonstrated the role of adjuvant chemoradiotherapy is the INT0116 trial. In this study, including 281 non-metastatic gastric cancer patients, adjuvant radiotherapy concomitant with 5-fluorouracil/leucovorin were compared with observation after surgery. Three-years OS and RFS were found to be significantly better in adjuvant chemoradiotherapy arm, 50% versus 41% and 48% versus 31%, respectively, after five years of follow-up [12]. When we compared our results with the INT0116 study, with a median follow-up of 34 months, we found similar 3-years OS and RFS rates, 55% and 49%, respectively. Another study from Turkey comprising 637 patients treated with adjuvant chemoradiotherapy after curative resection demonstrated a median overall survival of 43.7 months and a median recurrence-free survival of 36.6 months [27]. The OS rates were 80%, 52%, and 38%, while the RFS rates were 75%, 48%, and 34% at 1, 3 and 5-years, respectively. Although recurrence-free survivals were found to be similar in both studies, the overall survival time in our study was better and this was probably due to the inclusion of the early-stage patients. In our study, overall survivals range between 85 to 90% for stage I disease, range between 62–74% for stage II disease, and between 13–48% for stage III disease as summarized in Table 3. Tumor penetration through the gastric wall, and the presence of lymph node involvement have been shown as two important prognostic factors in the literature [26, 28, 29]. Hochwald and Gunji et al. [29, 30] demonstrated that the number of involved nodes had a negative impact on RFS and OS. In a study from Japan [28], the anatomic distribution of involved lymph nodes was found to have prognostic importance. Marchet et al. [31] demonstrated the importance of extent of the lymph node dissection and the number of metastatic lymph nodes. In our study, N stage, which represents the number of metastatic lymph nodes, was found as a prognostic factor for OS both in univariate and multivariate analysis.

Dockerty [32] reported that when the tumor was confined to the mucosa, the 5-year survival rate was 100%, and when the tumor invades below mucosa, the 5-year survival rate was 61%, and it was 44% when the tumor invaded the entire stomach wall. We found the T stage as a prognostic factor for survival both in univariate and multivariate analysis. The five-year survival rate was 84.3% in T1 tumors, 64.8% in T2 tumors, 48.9% in T3 tumors, and 29.2% in T4 tumors.

In the Turkish study mentioned above [27], while tumor grade, T stage, N stage, surgical resection type and surgical margin were reported as prognostic factors for RFS and OS in the univariate analysis, T stage, N stage and surgical margin were reported as significant factors for OS in the multivariate analysis. In our study, while we found the T and N stage, tumor size, stage groups, tumor grade and presence of lymphovascular invasion as prognostic factors for OS in univariate analysis, only T and N stage were detected as independent prognostic factors for OS in the multivariate analysis.

While adjuvant chemoradiotherapy provided a survival benefit in resected gastric cancer, certain authors have questioned the role of this adjuvant treatment modality, especially in patients who underwent D2 lymph node dissection, and in patients who received perioperative or postoperative chemotherapy. Adjuvant Chemoradiation Therapy in Stomach Cancer (ARTIST) trial compared

adjuvant chemotherapy with or without radiotherapy in D2 lymph node dissected patients [33]. In subgroup analysis, postoperative chemoradiotherapy provided a better disease-free survival with in comparison to postoperative chemotherapy alone in node-positive and intestinal-type gastric cancer patients. However, the role radiotherapy was not evident in the whole group [30]. The ongoing ARTIST II trial will elucidate if there is any benefit of adding postoperative radiotherapy to chemotherapy in D2 lymph node dissected patients when there are lymph node metastases [34].

Our study has several drawbacks. This study was retrospective; and this study included early-stage disease with no postoperative treatment, and included 2-dimensional radiotherapy techniques. Technical advances in radiotherapy, together with effective adjuvant chemotherapy combinations, will improve the treatment results obtained with surgery.

Conclusion

Our results have demonstrated that postoperative chemoradiotherapy in resected gastric cancer in the Turkish population is feasible and provides similar survival results comparable to the studies reported in the literature. Nodal involvement and tumor invasion through the gastric wall are two independent prognostic factors found to have an effect on overall survival.

Ethics Committee Approval: Kartal Dr. Lutfi Kırdar Training and Research Hospital Clinical Research Ethics Committee of approved the study in concordance with the declaration of Helsinki (date: 28.08.2018, number: 2018/514/136/1).

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Authorship Contributions: Concept – GY; Design – DT; Supervision – GY; Materials – BD; Data collection and/or processing – MP; Analysis and/or interpretation – GY; Literature review – BD; Writing – GY; Critical review – DT.

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