ORIGINAL RESEARCH

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Prognostic Factors Associated with Locally Advanced Gastric Cancer in Patients Treated with Adjuvant Chemotherapy

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ABSTRACT Objective: Surgery followed by chemotherapy with or without radiotherapy and perioperative chemotherapy represents the standard treatment modality in locally advanced gastric cancer patients. Adjuvant radiotherapy has been shown to have no benefits in these patients, especially those undergoing D2 dissection without neoadjuvant treatment. The goal of our study was to identify the prognostic factors associated with adjuvant treatments, particularly radiotherapy. **Material and Methods:** We evaluated the clinical, laboratory, and histological features and survival in locally advanced gastric cancer patients who underwent upfront gastric resection without neoadjuvant therapy and were subsequently treated with adjuvant chemotherapy comprising capecitabine-oxaliplatin. Parameters with significant p-values in univariate analysis were included in multivariate Cox regression analysis. **Results:** A total of 56 patients were included, and the median follow-up period was 33.2 months. The mean age was 61.23±8.89 years. The median disease-free survival (DFS) was 37.80 months (95% confidence interval: 22.30-53.30). The 5-year DFS and overall survival (OS) rates were 43.4% and 60.8%, respectively. In univariate analysis, lymph node involvement, diffuse histology, presence of lymphovascular invasion, positive surgical margin, presence of perineural invasion, absence of radiotherapy, and high lactate dehydrogenase (LDH) levels were found to be associated with shorter DFS and OS. In multivariate Cox regression analysis, diffuse histology, absence of radiotherapy, and high LDH levels were found to be associated with shorter DFS and OS. **Conclusion:** The long-term survival rates in our study were encouraging. Inflammatory markers, tumor histology, and radiotherapy might have prognostic value in identifying high-risk patients who could benefit from intensive therapy.

Keywords: Gastric cancer; adjuvant chemotherapy; prognostic factor

Although the incidence of gastric cancer has decreased in the United States of America and Northern Europe in recent years, it is still a severe public health problem, especially in eastern Asia.[1,2] Although it is the 5th most common type of cancer, it ranks 3rd in cancer-related deaths.[3] Treatment approaches for gastric cancer patients vary geographically. In East Asian countries, where D2 dissection is routinely performed, adjuvant chemotherapy is used. In contrast, perioperative treatment is preferred in Europe and North America. The assessment of the efficacy of combined treatment with adjuvant chemotherapy, comprising cisplatin plus capecitabine, and radiotherapy on disease-free survival (DFS) in the ARTIST study revealed that radiotherapy did not impart any additional benefits to the outcome of patients undergoing D2 dissection.[4] Previous studies showed that several prognostic factors, such as lymphovascular invasion, tumor grade, and resection type, are associated with the overall survival (OS) of patients that underwent adjuvant chemotherapy.[5,6] In this study, we aimed to evaluate the efficacy of radiotherapy and determine other significant prognostic factors in patients with resected locally advanced gastric cancer who received adjuvant chemotherapy comprising oxaliplatin and capecitabine.

MATERIAL AND METHODS

This study included individuals over 18 years of age, diagnosed with gastric cancer, who had not received

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any neoadjuvant treatment. Patients' data who received adjuvant capecitabine-oxaliplatin therapy between January 2016-September 2021 were reviewed retrospectively. The patients whose pathology results could not be obtained and those who continued their treatment at another hospital were excluded from the study. The patients' age, gender, operation date, tumor, node, metastasis stage, tumor pathology, laboratory parameters, and survival times were recorded. D1 dissections include perigastric lymph node dissections (lymph node stations 1-6). D2 dissections include perigastric lymph node dissections plus left gastric artery (station 7), common hepatic artery (station 8), celiac axis (station 9), splenic artery (station 11), and proper hepatic artery (station 12). The upper limit for the normal lactate dehydrogenase (LDH) range is 248 units/L.

The relationship between clinical and pathological features and survival outcomes was examined using Kaplan-Meier analysis. The p-value of 0.05 was considered statistically significant. Those with a univariate p-value of 0.200 were included in the COX multivariate analysis. Statistical Package for the Social Sciences v26 (IBM Inc, Armonk, NY, USA) program was used for all statistical analyses.

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Hacettepe University (date: July 5, 2022, no: 2022/12-70).

RESULTS

Fifty-six individuals with locally advanced gastric cancer who were operated on and treated with adjuvant chemotherapy, with or without radiotherapy, were included in the study. The median follow-up period was 33.2 months. The mean age of the patients was 61.23±8.89 years. Seventeen patients had stage 2 disease and 39 had stage 3 disease. The demographic and histological characteristics of the patients are shown in Table 1.

TABLE 1: Demographic and histological characteristics of the patients.

	Number (%)
Age (mean)	61.23±8.89
Gender	
Female	13 (23.21)
Male	43 (76.78)
Tumor histology	
Intestinal	29 (51.78)
Diffuse	27 (48.21)
Surgery type	
Subtotal gastrectomy	26 (46.42)
Total gastrectomy	30 (53.57)
Lymphovascular invasion	
Yes	40 (76.90)
No	12 (23.10)
Perineural invasion	
Yes	35 (68.62)
No	16 (31.37)
Resection margin	
Positive	12 (21.42)
Negative	44 (78.57)
Dissection type	
D1	37 (66.07)
D2	19 (33.92)
Radiotherapy	
Yes	40 (71.42)
No	16 (28.57)
T stage	
2	5 (8.92)
3	19 (33.92)
4	32 (57.14)
N stage	
0-1-2	43 (76.78)
3	13 (23.21)
TNM stage	
2	17 (30.35)
3	39 (69.64)
ECOG score	
0	50 (89.28)
1	6 (10.71)
LDH level	
Normal	46 (82.14)
High	10 (17.85)

TNM: Tumor, node, metastasis; ECOG: Eastern Cooperative Oncology Group; LDH: Lactate dehydrogenase.

The median OS time was not reached, and the median DFS was 37.80 (95% CI: 22.30-53.30) months (Figure 1, Figure 2, respectively). The 5-year DFS and OS rates were 43.4% and 60.8%, respectively.

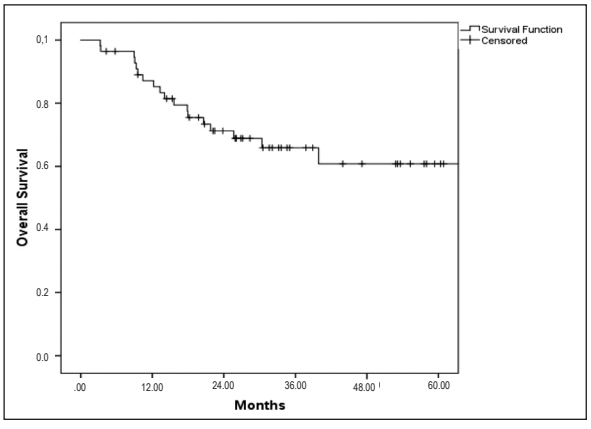


FIGURE 1: Overall survival graph.

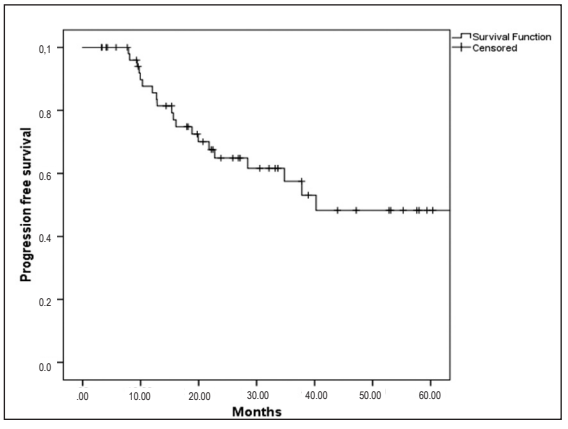


FIGURE 2: Disease-free survival graph.

In the univariate analysis for DFS, diffuse histology [17.97 months (95% confidence interval "CI": 12.96-22.98) vs. non-available (NA) for intestinal types, p=0.003], high lymph node burden [40.26 months for N0-2 vs. 15,63 months (95% CI: 6.80-24.46) for N3, p=0.004], presence of lymphovascular invasion [34.76 months (95% CI: 15.35-54.18) for presence vs. NA for absence, p=0.042], positive surgical margin (16.10 months 95% CI: 10.90-21.96 for positive surgical margin vs. NA for negative surgical margin p<0.001), presence of perineural invasion [21.80 months (95% CI: 15.93-21.67) for presence vs. NA for absence p=0.062], presence of radiotherapy [NR, 18.86 months (95% CI: 9.21-28.51), p=0.041], high LDH level (9.40 months (95% CI: 7.97-10.82) vs. NA p<0.001) were found to be associated with shorter DFS. In multivariate Cox regression analysis, diffuse histology, absence of radiotherapy, and high LDH level were associated with shorter DFS (p=0.003, p=0.009, and p<0.001, respectively; Table 2).

In the univariate analysis for OS, lymph node involvement [NA for N0-2 vs, 15.63 months (95% CI: 11.74-19.51) for N3, respectively; p=0.001], diffuse

TABLE 2: Multivariate regression analysis of factors associated with disease-free survival.

	Hazard ratio	95% confidence interval	p value
Lymph node involvement (N0-1-2 vs. N3)	1.605	0.554-4.646	0.383
Resection margin (negative vs. positive)	1.865	0.740-4.699	0.186
Tumor histology (intestinal vs. diffuse)	2.738	1.044-7.181	0.041
Radiotherapy (presence vs. absence)	3.341	1.352-8.259	0.009
LDH level (normal or high)	7.714	2.888-20.603	<0.001

LDH: Lactate dehydrogenase.

TABLE 3: Multivariate regression analysis of factors associated with overall survival.

	Hazard ratio	95% confidence interval	p value
Resection margin (negative vs. positive)	1.516	0.527-4.361	0.444
Lymph node involvement (N0-1-2 vs. N3)	2.543	0.0.775-8.348	0.124
Radiotherapy (presence vs. absence)	3.506	1.204-10.206	0.021
Tumor histology (intestinal vs. diffuse)	4.505	1.537-13.205	0.006
LDH level (normal or high)	10.907	1.083-8.655	0.035

LDH: Lactate dehydrogenase.

histology [39.90 months (95% CI: 12.81-66.98) vs. NA, p=0.006], presence of lymphovascular invasion (NA for presence of LVI vs. NA for absence of LVI, p=0.011), positive surgical margin [17.86 months (95% CI: 8.40-27.33) for positive surgical margin vs. NA for negative surgical margine, p=0.002], presence of perineural invasion (39.90 months for presence of PNI vs. NA for absence of PNI, p=0.025), presence of radiotherapy (NA for presence of RT, 39.90 months for absence of RT; p=0.155), high LDH level [12.20 months (95% CI: 6.84-17.55) for high LDH level vs. NA for normal LDH level, p<0.001] were found to be associated with shorter OS. In multivariate Cox regression analysis, diffuse histology, absence of radiotherapy, and high LDH level were associated with shorter OS (p=0.006, p=0.021, and p<0.001, respectively; Table 3).

DISCUSSION

In this study, diffuse histology and high LDH level were associated with poorer DFS and OS. However, adjuvant radiotherapy was associated with better DFS and OS of individuals with resected gastric cancer who received adjuvant oxaliplatin plus capecitabine regimen.

Adjuvant chemotherapy is used to treat locally advanced gastric cancer in areas where upfront surgery with D2 dissection is the standard practice, such as in East Asia and Japan. The recently published ARTIST and CRITICS trials reported no additional benefits of adjuvant radiotherapy in these patients.[4,7] Adjuvant radiotherapy may still be used in patients with R1 resection, less than D2 dissection, or insufficient lymph node retrieval.[8,9] Adjuvant radiotherapy is now less commonly used in patients with D2 dissection after the results of the ARTIST and CRITICS trials were published. Still, it was the standard of care during our study period. In our study, we observed that adding radiotherapy positively affected the DFS and OS of the patients. The fact that 66% of the patients in this study underwent D1 dissection seems significant to the contributory role of radiotherapy.

Previous studies revealed that lymphovascular invasion was the most important prognostic factor in patients treated with surgery, adjuvant chemotherapy, and radiotherapy.[10-12] In our study, the presence of lymphovascular invasion was found to be associated with poor DFS and OS. However, due to the limited number of patients in the study and the incomplete data in some pathology reports, lymphovascular invasion and perineural invasion were excluded from the multivariate analysis.

Margin positivity is a significant issue, particularly in proximal gastric cancer patients. Woo et al. found that a positive surgical margin was associated with shorter DFS and OS.[13] Bickenbach et al. reported that R1 resection was associated with shorter OS than R0 resection, independent of dissection type, lymph node involvement, and tumor size. They also reported positive surgical margins in 4.5% of the patients in this study.[14] Another study reported a positive surgical margin in 8.2% of the patients.[14,15] In our study, we found a positive surgical margin in 21.42% of the patients. Furthermore, we found that surgical margin affected DFS and OS in univariate analysis but not multivariate analysis. The significant benefit of adjuvant radiotherapy observed in our study can be attributed to high rates of R1 resection. This finding warrants careful consideration of preoperative chemotherapy or radiotherapy in these patients.

Previous studies showed that diffuse histology has a worse prognosis than intestinal histology.[16,17] In the study of Becker et al., intestinal histology was found to respond better to neoadjuvant therapy.[18] In our study, diffuse histology was found to be an unfavorable prognostic factor on DFS and OS.

Many studies have found lymph node involvement to be an important prognostic factor associated with OS.[19,20] Fifty percent of the patients with gastric cancer have lymph node metastases at the time of diagnosis, and the 5-year survival rate in these patients is around 30%.[21] In our study, the presence of N3 disease was found to be a negative prognostic factor for both DFS and OS.

A previous study demonstrated that cancer cells consume more glucose and produce more lactate than normal cells.[22] Another study showed that elevated LDH is a prognostic marker of advanced gastric cancer.[23] In our study, high LDH level was found to be a negative prognostic factor of DFS and OS.

Our study's limitations are that it was retrospective and included patients who underwent surgery at various centers. Other significant limitations included no standardization of patient doses (especially based on medical condition and age), lack of radiotherapy dose data, and lack of adverse event data.

CONCLUSION

We observed that the same factors influenced the DFS and OS of advanced gastric cancer patients. Moreover, adding radiotherapy to adjuvant chemotherapy was found to benefit patients who undergo D1 dissection.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hasan Çağrı Yıldırım, Deniz Can Güven, Hakan Taban, Feride Yılmaz;* ***Design:*** *Hasan Çağrı Yıldırım, Serkan Yaşar, Elvin Chalabiyev, Fatih Kuş;* ***Control/Supervision:*** *Hasan Çağrı Yıldırım, , Deniz Can Güven, Arif Akyıldız, Süleyman Çağın Gürbüz, Hüseyin Sayın, Gözde Kavgacı, Şuayip Yalçın;* ***Data Collection and/or Processing:*** *Hasan Çağrı Yıldırım, Ömer Dizdar;* ***Analysis and/or Interpretation:*** *Hasan Çağrı Yıldırım, Deniz Can Güven, Ömer Dizdar;* ***Literature Review:*** *Hasan Çağrı Yıldırım, Deniz Can Güven, Şuayip Yalçın;* ***Writing the Article:*** *Hasan Çağrı Yıldırım, Ömer Dizdar;* ***Critical Review:*** *Hasan Çağrı Yıldırım, Ömer Dizdar;* ***References and Fundings:*** *Hasan Çağrı Yıldırım, Ömer Dizdar;* ***Materials:*** *Hasan Çağrı Yıldırım, Deniz Can Güven, Ömer Dizdar.*

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