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Research Article

Effect of Adjuvant Chemotherapy/Chemoradiotherapy on Disease-Free Survival in Gastric Cancer

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Abstract

Objectives: The main treatment for gastric cancer is surgery. The high recurrence and metastasis rates indicate the necessity of neoadjuvant/adjuvant treatments. Our aim was to evaluate the effects of adjuvant therapy on disease-free survival (DFS) and prognostic factors with gastric cancer patients.

Methods: Gastric cancer patients who were operated between 2015-2021 were evaluated retrospectively. Clinical, pathological, surgical and therapeutic features of patients were examined. Prognostic factors, Hemoglobin Albumin Lymphocyte, Platelet Score (HALP) and metastatic lymph node ratio (MLNR) of patients were examined. 1-5 year survival rate were calculated.

Results: Adjuvant chemotherapy was applied to fifty-nine patients and adjuvant chemoradiotherapy was applied to sixty-eight patients. There was no difference in demographic and clinical characteristics between patient groups who received chemotherapy and chemoradiotherapy. DFS was 34 and 52 months with chemotherapy and chemoradiotherapy patients respectively (p=0.161). High MLNR levels of patients was poor prognostic factor. HALP score did not affect prognosis. 5-years overall survival rate was better in chemoradiotherapy group, but the difference was not statistically significant (41.2% vs 50.9%, p=0.216).

Conclusion: There was no difference in survival between patients who received adjuvant chemotherapy and chemoradiotherapy. MLNR of patients may be considered as a prognostic marker for gastric cancer patients with high nodal involvement.

Keywords: Chemoterapy, chemoradiotherapy, disease free survival, HALP score, metastatic lymh node ratio, non-metastatic gastric cancer, prognosis

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Gastric cancer, which is the second most common gastrointestinal system tumor, is the third most common cause of cancer-related deaths in the World.[1] Because the disease is asymptomatic until advanced stages and there are no active widespread screening programs, most of the patients can be diagnosed in advanced stages. Stage, performance status and comorbidities, tumor histology, pathology, localization and surgical methods affect the prognosis.[2,3] In addition, Hemoglobin, Albumin, Lymphocyte, and Platelet Score (HALP) and metastatic lymph node ratio

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(MLNR), have also been reported to be prognostic factors in gastric cancer patients.[4,5]

Geographical, genetic and dietary differences cause differences in tumor histology, localization and response to treatment between countries.[3,4] Gastric cancer, which is more common in countries such as the Far East, Korea, China, Taiwan, and Japan, is in intestinal histology and noncardia localization. In the western population, however, it is localized in diffuse histology and proximal to the stomach. [6,7] While the 5-year overall survival rates are 10-40% in the USA, it is reported to be 50% and above in Japan and South Korea.[8,9] Although surgery is the main treatment, these patients often need adjuvant treatment because of the high risk of recurrence and metastasis.

While neoadjuvant±adjuvant chemotherapy (CT) studies are prominent in the node-positive locally advanced patients in the guidelines, chemoradiotherapy (CRT), which is known to be effective especially in local control, is recommended in those who underwent inadequate lymph node dissection after surgery.[10] However, heterogeneity in the stage, surgical method and treatment regimens of the patients in the studies causes the uncertainty of whether CT or CRT is superior in adjuvant treatment. Our first aim was to evaluate the effect of adjuvant CT/CRT methods on disease-free survival (DFS) in patients who were operated on with the diagnosis of non-metastatic gastric adenocarcinoma. Our second aim was to evaluate the factors affecting the prognosis in these patients and to calculate the 5-year survival rates.

Methods

Gastric cancer patients who applied to the Medical Oncology outpatient clinic and were operated between 2015-2018 were evaluated retrospectively until November 2021.

We used the following inclusion criteria: 1) age >18 years, 2) surgery was performed on the first line for the primary tumor, 3) diagnosed with gastric adenocancer, mixt or stony ring cell carcinoma, 4) stage-IB and above according to Tumor, Node, Metastasis (TNM) 8th version.

The exclusion criteria were as follows: 1) having a synchronous or metachronous tumor, 2) having metastatic disease, 3) having other gastric tumors

The clinical and demographic characteristics of the patients, hemoglobin, lymphocyte, thrombocyte albumin and carcinoembryonic antigen (CEA) levels at the time of diagnosis, and CEA levels after treatment were recorded. HALP score calculated by multiplying hemoglobin(g/L), albumin(g/L) and lymphocyte(/L) numbers and dividing by platelet(/L) number at diagnosis. Metastatic Lymph Node Ratio (MLNR), obtained by dividing the number of metastatic lymph nodes by the total number of lymph nodes. MLNR were calculated in N2 and N3 patients who had at least 15 lymph nodes removed.[4,5,11] X-tile program was applied to find the cut-off value of the HALP score and MLNR. The type of surgery, pathological features of the tumor, treatment protocols and treatment completion status were examined.

Survival Acessement

DFS was calculated as the time of diagnosis to recurrence, and overall survival (OS) was calculated as the time of diagnosis to death or last follow-up.

Follow-up and Trace

All patients diagnosed with gastric cancer were evaluated according to their clinical laboratory and nutritional status. An adjuvant CRT scheme was planned for patients with postoperative serosal or visceral organ invasion, inadequate lymph node dissection, and R1 resection. MacDonald [Fluouracil(FU)/Folinic acid(FA) simultaneous CRT] or Capecitabine (3 cycles before and after radiotherapy, 1000-1250mg/m^2 orally twice daily on days 1-14, daily Capecitabine and simultaneously with radiotherapy for 5 weeks, weekly on days 1-5, Capecitabine 625-825mg/m^2 orally twice daily) regimens were used.[12,13] Radiotherapy treatment was given by the Radiation Oncology specialist for 5 weeks, with the same device at a dose of 1.8Gy/day, with a total dose of 45-50.4Gy. Additional dose boost was applied to patients with positive margin.

Patients who have undergone D2 lymph node dissection, or whose performance will not tolerate CRT; 8 cycles of XELOX (Oxaliplatin 130mg/m^2 and capecitabine 1000-1250mg/m2 orally twice daily on days 1-14) CT was planned once in 21 days. Capecitabine monotherapy was given to patients who could not tolerate oxaliplatin treatment.[14]

The patients were followed up with clinical examination and blood tests for 3 months in the first two years and then every 6 months. Control endoscopies were performed in the first year. In case of clinical indication, thorax and abdomen imaging were requested once every 6 months-years.

Statistical Analysis

After the obtained data were coded with numerical values, they were analyzed using SPSS program version 20. Complementary statistics of the evaluation results were given as numbers and percentages for categorical variables, median, standard deviation, minimum and maximum for numerical variables. The conformity of the data to the normal distribution was tested with the Kolmogorov-Smirnob test.

Comparisons of numerical variables between two independent groups; Since the normal distribution condition was not met, it was evaluated with the Mann Whitney U test. The differences between the ratios of categorical variables in independent groups were tested by Chi-square analysis and Fisher's Exact Test. The Kaplan Meier test was used in the survival analysis of the patients. Univariate and multivariate Cox regression analysis was used to determine Hazard ratios (HRs) and 95% Confidence intervals (CIs). Factors that were determined to be significant only according to univariate analyzes were then included in multivariate analyses. Confidence interval was determined as 95%, p value <0.05 for statistical significance.

Results

A total of 127 patients were included in the study. 90 (70.9%) of patients were male, 37 (29.1%) were female. Mean age was 59±10.29 (32-85). 59 (46.5%) patients underwent adjuvant CT and 68 (53.5%) patients underwent CRT. Demographic, clinical and pathological characteristics of patients are shown in Table 1.

Among the CT patients, 18 (30.5%) were T4, 35 were (59.3%) T3, 27 were (45.7%) N3, and 18 were (30.5%) N2, while among the CRT patients 22 were (32.3%) T4, 38 were (55.8%) T3, 22 (32.3%) were N3 and 20 (29.4%) were N2. There was no significant difference between the groups in T and N stages (p=0.998, p=0.118). 26 (44%) of patients who underwent CT and 18 (26.4%) of patients who underwent CRT were patients aged >65 years (p=0.038).

When evaluated in terms of tumor localization; While it was most common in the lesser curvature in patients who underwent both CT and CRT, tumors located in the cardia were more common in patients who underwent CT (p=0.036). D2 lymph node dissection was more common in patients who underwent CT compared to patients who underwent CRT (p<0.001). When evaluated in terms of the number of lymph nodes removed; The total number of lymph nodes removed was higher in patients who underwent CT [CT 36 (22-50) and CRT 19 (14.3-31.8), p<0.001]. However, there was no difference in the number of metastatic lymph nodes between patients who underwent CT and CRT [CT 6 (3-14) and CRT 4.5 (1-9.8), p=0.069].

The presence of lymphovascular invasion (LVI) was found to be the only factor affecting the metastatic lymph node (p=0.001). MLNR was calculated in 80 patients with N2-3 and 47 patients with N3. In the X-tile program MLNR cut-off value was determined 0.063. There were 33 N2 patients. X-tile program was applied for N2 metastatic lymph node ratio, p value (0.28) and chi-square (2.23) were not found to be statistically significant. Therefore, cut-off value was not given for N2 lymph node ratio.

While 43 patients (72.9%) received 8 cycles XELOX and 16 patients (27.1%) who could not tolerate oxaliplatin were treated as capecitabine monotherapy as CT regimen, 55 patients (80.9%) FUFA and 13 (19.1%) capecitabine regimens were applied as CRT regimens. Treatment completion rates were 58.6% (34 patients) in patients who underwent CT and 67.6% (46 patients) in patients who underwent CRT.

For the whole population, we applied the X-tile program to find the cut-off value of the HALP score in early-stage gastric cancer in terms of progression-free survival. The cut-off point of HALP score with the smallest p value (p=0.17) and the largest chi-square (chi-square=1.76) was found 27. Both p value and chi-square were not statistically significant. As a result, we found that HALP score has no prognostic significance in early-stage gastric cancer patients for recurrence.

While the mean CEA level was 14.95±100.78 ng/mL (0.38-1058) before treatment, it was 43.79±168.25 ng/mL (0.63-1059) after treatment. There was no difference in CEA levels before and after treatment between CT and CRT patients (p=0.922, p=0.564).

Local recurrence developed in five (8.4%) patients and distant metastases developed in 25 patients (42.3%) who underwent CT. Local recurrence developed in seven (10.2%) patients who underwent CRT and metastasis developed in 25 patients (36.7%). 29 patients (49.2%) who underwent CT and 39 patients (57.4%) who underwent CRT died. There was no difference between those who underwent CT and CRT in terms of local recurrence, metastasis or death (p=0.728, p=0.520 and p=0.355, respectively).

DFS was calculated 39 months (24.1-53.9) and OS was 46 months (29.8-62.2). While DFS was 34 months (16.9-51.2) and OS was 46 months (28.9-63.1) in CT patients, DFS was 52 months (24.9-79.3) and OS was 63 months (19.5-106.5) in CRT patients (p=0.161 for DFS, p=0.216 for OS, Figure 1).

DFS and OS times and 1-5 year survival rates in patients receiving CT and CRT are shown in Table 2. Addition of oxaliplatin to treatment in adjuvant CT did not increase DFS (41 vs 26 months) and OS (59 vs 41 months) (p=0.145, p=0,251, respectively). No correlation was found between CRT regimens and DFS or OS (p=0.648, p=0.512).

While in the Univariate Cox-regression analysis, the factors reducing DFS were found to be the presence of LVI, presence of perineural invasion (PNI), poor performance status, increased tumor diameter, neasrest surgical boundary, high MLNR values and high CEA levels before and after

Table 1. Patient demographic, clinical and pathological characteristics

	Total (%) n=127 (100.0)	Adjuvant Chemotherapy (%) n=59 (46.5)	Adjuvant Chemoradiotherapy (%) n=68 (53.5)	p
Age (median)	61 (54-68)	63 (54-70)	61 (53-65)	0.151[a]
Gender				
Male	90 (70.9)	39 (66.1)	51 (75.0)	0.366[b]
Female	37 (29.1)	20 (33.9)	17 (25.0)	
ECOG PS*, n:129				
ECOG 0-1	95 (74.8)	45 (76.3)	50 (73.5)	0.881[b]
ECOG ≥2	32 (25.2)	14 (23.7)	18 (26.5)	
Tumor localisation, n:124				
Lesser Curvature	53 (42.7)	20 (33.9)[c]	33 (50.8)[c]	0.036[b]
Greater Curvature	17 (13.7)	8 (13.6) [c]	9 (13.8) [c]	
Corpus	12 (9.7)	7 (11.9) [c]	5 (7.7) [c]	
Cardia	14 (11.3)	11 (18.6) [c]	3 (4.6)[d]	
Antrum and pylor	28 (22.6)	10 (22.0) [c]	15 (23.1) [c]	
Histopathological Subgroup				
PD Adenocarcinoma+	15 (11.8)	5 (8.5)	10 (14.7)	0.074[c]
GD Adenocarcinoma**	32 (25.2)	17 (28.8)	15 (22.1)	
Diffuse	31 (24.4)	11 (18.6)	20 (29.4)	
Mixt	9 (7.1)	8 (13.6)	1 (1.5)	
Signet Ring Cell	14 (11.0)	8 (13.6)	6 (8.8)	
Intestinal	20 (15.7)	7 (11.9)	13 (19.1)	
Musinous	6 (4.7)	3 (5.1)	3 (4.4)	
Tumor size (mm, median)	55 (35-75)	60 (45-80)	50 (35-70)	0.147[a]
Lymphovascular invasion				
Present	66 (52.0)	29 (49.2)	37 (54.4)	0.554[b]
Absent	61 (48.0)	30 (50.8)	31 (45.6)	
Perineural invasion				
Present	55 (43.3)	26 (44.1)	29 (42.6)	0.872[b]
Absent	72 (56.7)	33 (55.9)	39 (57.4)	
Lymph node dissection type				
D1	49 (38.6)	16 (27.1)[c]	33 (48.5)[d]	<0.001[b]
D2	65 (51.2)	41 (69.5)[c]	24 (35.3)[d]	
İnadequate	13 (10.2)	2 (3.4)[c]	11 (16.2)[d]	
Metastatic Lymph Node, (median)	5 (2-11)	6 (3-14)	4.5 (1-9.8)	0.069 [a]
MLNR++, n:48				
≥63	32 (66.7)	18 (72.0)	14 (60.9)	0.610[b]
<63	16 (33.3)	7 (28.0)	9 (39.1)	
HER-2***				
Present	12 (9.4)	5 (8.5)	7 (10.3)	0.964[b]
Absent	115 (90.6)	54 (91.5)	61 (89.7)	
Resection Type				
Resection margin 0	113 (89.0)	53 (89.8)	60 (88.2)	0.998[b]
Resection margin 1	14 (11.0)	6 (10.2)	8 (11.8)	
Type of Surgery				
Total gastrectomy	56 (44.1)	27 (45.8)	29 (42.6)	0.724[b]
Subtotal gastrectomy	71 (55.9)	32 (54.2)	39 (57.4)	
Stage				
Stage IB	4 (3.1)	2 (3.4)	2 (2.9)	0.530[b]
Stage IIA	12 (9.4)	3 (5.1)	9 (13.2)	
Stage IIB	23 (18.1)	9 (15.3)	14 (20.6)	
Stage IIIA	36 (28.3)	17 (28.8)	19 (27.9)	
Stage IIIB	35 (27.6)	18 (30.5)	17 (25.0)	
Stage IIIC	17 (13.4)	10 (16.9)	7 (10.3)	
Treatment Complated				
(+)	80 (63.5)	34 (58.6)	46 (67.6)	0.388[b]
(-)	46 (36.5)	24 (41.4)	22 (32.4)	

IQR: Interquartile range (25-75 percentile values), [a]Mann Whitney U test, [b]Chi-Square test, [c]Fisher's Exact Test; *Eastern Cooperative Oncology Group Performance Status +Poor differantiated **Good differantiated ++Metastatic Lymph Node Ratio ***Human epidermal growth factor receptor 2.

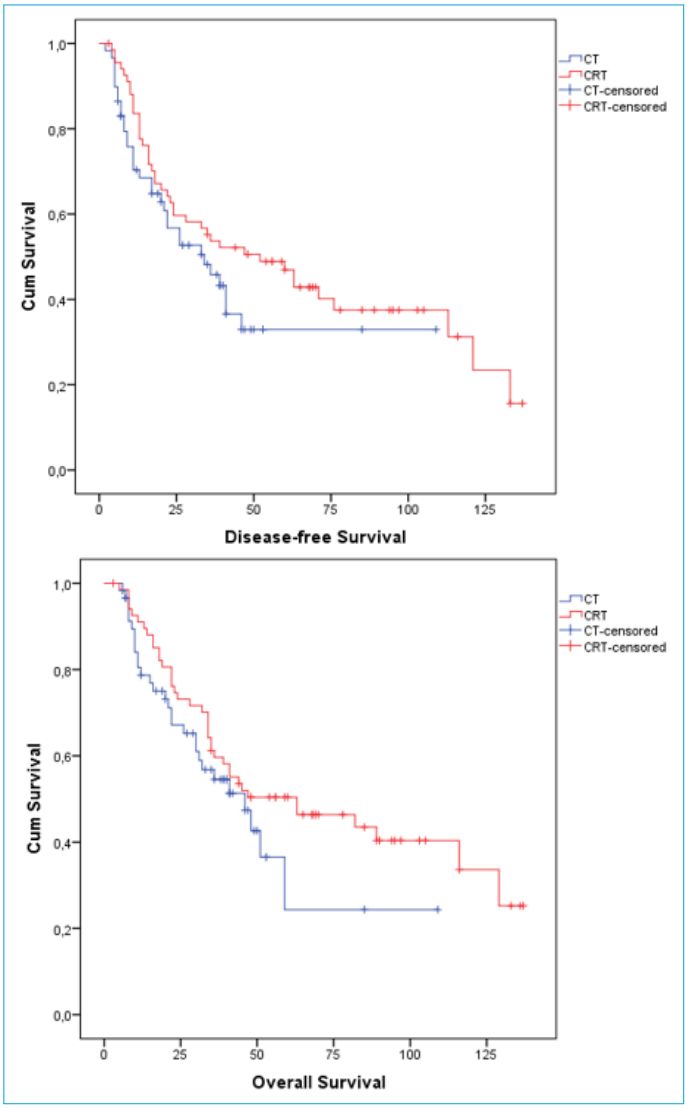

Figure 1. Comparison of disease-free survival and overall survival in patients receiving chemotherapy and chemoradiotherapy.

treatment; (p=0.003, p=0.041, p<0.001, p=0.008, p=0.031, p=0.004, p=0.008 and p=0.001, respectively); In the multivariate Cox-regression analysis; poor performance status and high MLNR values were found (p<0.010 and p=0.047, respectively). Factors affecting the OS are shown in Table 3. Factors affecting DFS and OS in patients with CT and CRT are shown in Table 4.

Discussion

In our study, no difference was found in terms of survival in patients who underwent CT and CRT. HALP score did not have a prognostic significancy. High MLNR, the presence of LVI, presence of PNI, poor performance status, elevated tumor size, number of metastatic lymph nodes, presence of recurrence/metastasis and high CEA levels before and after treatment have been shown to decrease OS. Gastric cancer is the fourth cause of cancer-related deaths in Turkey. The number of patients who can be diagnosed in the early period is limited. Surgical resection is the main form of treatment that can be cured. Despite surgery, more than 80% of patients may develop.[15] Identification of prognostic factors may pave the way for more effective treatments at an early stage.

Immune system and nutritional status are effective factors in the development of carcinogenesis. The HALP score used by Chen et al. was found to be closely related to the clinical features of gastric cancer and was shown to be an independent prognostic factor.[4] Yalav et al. also showed that the HALP score has a limited role in predicting the risk of developing perioperative complications in early stage gastric cancers and is not a prognostic factor for survival.[16] In our study, the prognostic role of HALP score could not be demonstrated in patients who received CT and CRT. Our study is the first to evaluate the prognostic significance of the HALP score in patients receiving adjuvant therapy in the western population and only Stage I-III patients were evaluated.

TNM stage is the most important prognostic factor in gastric cancer. However, stage migration can be seen in 5-15% of patients due to lymph node dissection. It was first shown by Komatsu et al. that high MLNR adversely affects prognosis in patients with operated gastric cancer N3.[17] Similar to the literature, it has been shown that high MPLR reduces survival and is a poor prognostic factor.

Because of the high risk of recurrence and distant metastasis, adjuvant therapy is recommended for patients with gastric cancer starting from Stage-IB. The articles evaluating the effect of adjuvant CT are mostly of Asian origin. With the Phase-3 CLASSIC study, a significant DFS and OS advantage was achieved with adjuvant Capecitabine+Oxaliplatin CT, especially in those undergoing D2 lymph node dissection (3 years DFS 74% and 5 years OS 78%).[14] In this study, the greatest benefit was observed in node-positive patients, and survival rates were found to be higher than in the literature. Many agents have been found to be effective in adjuvant therapy. However, in our country, fluorouracil-based regimens are used, which contribute to survival and are known to reduce the risk of death by 20-40%, due to limited access to agents such as S1, tegafur.[18] In our study, CT was performed in most of the patients (69.5%) who underwent D2 lymph node dissection. In the CT patients, where patients over 65 years of age were common, 3-year DFS was

Table 2. Comparison of disease-free and overall survival times and 1-5 year survival rates in patients receiving chemotherapy and chemoradiotherapy

	Total (%)	Adjuvant Chemotherapy	Adjuvant Chemoradiotherapy	p
Recurrence or metastasis, n (%)				
Yes	48 (37.8)	22 (37.3)	26 (38.2)	>0.99*
No	79 (62.2)	37 (62.7)	42 (61.8)	
Exitus, n (%)				
Yes	68 (53.5)	29 (49.2)	39 (57.4)	0.355*
No	59 (46.5)	30 (50.8)	29 (42.6)	
Disease-free Survival (DFS) (month)	39 (24.1-53.9)	34 (16.9-51.2)	52 (24.7-79.3)	0.161+
Overall Survival (OS) (month)	46 (29.8-62.2)	46 (28.9-63.1)	63 (19.5-106.5)	0.216+
Disease-free Survival Ratio, %				
1 year	77.5	70.4	83.6	0.161+
2 year	58.2	56.8	62.7	
3 year	50.2	45.8	53.7	
4 year	44.1	32.9	50.6	
5 year	41.2	32.9	46.9	
Overall Survival Ratio, %				
1 year	85.4	84.1	91.0	0.216+
2 year	70.4	67.2	73.1	
3 year	57.2	54.5	59.7	
4 year	53.7	42.6	50.4	
5 year	50.9	24.4	50.4	

* Chi-Square test; +Kaplan-Meier test.

calculated as 45.8% and 5-year OS 24.4% in CT patients. Although survival rates appeared lower than in the Asian population, it was similar to those in studies in the western population.[19]

The high rate of locoregional recurrence (40-65%) suggested that radiotherapy may be effective in these patients, and this situation has been investigated with studies. Although it has been observed that radiotherapy alone provides local control, the lack of a survival advantage, has revealed the necessity of simultaneous systemic control.[20] Comparing the different degrees of lymph node dissection and adjuvant CT and CRT treatments in studies, some studies found no benefit of CRT after D2 lymph node dissection, while others showed it.[21] In addition, when the degree of resection and treatment efficacy were evaluated, it was shown that CRT decreased the recurrence rates after R1 and increased survival.[22] In the Intergroup-0116 study, it was shown that fluorouracil-based CRT provides local control and survival advantage in patients with mostly D1 and inadequate lymph node dissection (36 vs 27 months, p=0.005).[12] While the 3-year OS was only 41% in the surgery group, it was increased to 50% in the CRT group. In our study, mostly patients with D1 and inadequate lymph node dissection (64.7%) were treated with intensive CRT treatment with the Intergroup-0116 study regimen. The three-year DFS and OS was found 53.7%, 59.7% in the CRT patients.

In the ARTIST study, most of which consisted of stage 1-2 patients comparing adjuvant CT and CRT; no OS benefit was achieved, although CRT contributed DFS in node-positives (3-year DFS 72% vs 76%).[10] Then, in the planned ARTIST-2 study in stage 2-3 node-positive patients, no difference was found in terms of DFS.[23] In our study, although DFS was found to be numerically better in patients receiving CRT, it did not reach statistical significance. Survival rates in both groups were similar to the literature.

The limitations of our study are that it was a retrospective study on a limited number of patients. In addition, patients who received neoadjuvant therapy were not included in the study due to the small number of patients. Application of standard treatments in a single center and long follow-up period are its advantages.

Conclusion

Gastric cancer is a heterogeneous disease with frequent

Table 3. Factors affecting Overall survival in Univariate and Multivariate Cox-regression analysis

Variables	Univariate Analysis HR (95% CI)	p	Multivariate Analysis HR (95% CI)	p
Age (years), ≥65/<65	1.154 (0.700-1.902)	0.574		
Gender, Male/female	1.383 (0.796-2.401)	0.250		
LVI*, Yes/No	2.375 (1.427-3.954)	<0.001	1.108 (0.363-3.381)	0.857
PNI+, Yes/No	1.894 (1.171-3.062)	0.009	1.375 (0.529-3.570)	0.513
Grade, Grade-1	Ref.	1		
Grade-2	0.877 (0.466-1.650)	0.683		
Grade-3	1.031 (0.575-1.851)	0.917		
Treatment Type, CT/ CRT++	1.365 (0.829-2.248)	0.222		
ECOG** score ≥2/0–1	3.368 (2.051-5.530)	<0.001	2.727 (1.147-6.483)	0.023
Operation Type, Subtotal/Total	0.857(0.530-1.387)	0.530		
Metastatic Lymph Node	1.024 (1.013-1.035)	<0.001		
Total Lymph Node	1.007 (0.997-1.017)	0.155		
Recurrence Yes/No	1.545 (0.787-3.032)	0.206		
Metastasis Yes/No	4.588 (2.749-7.658)	<0.001		
Recurrence or/and Metastasis Yes/No	5.103 (3.062-8.504)	<0.001		
Treatment Completed	1.168 (0.705-1.935)	0.546		
Resection Status R1/R0	1.827 (0.954-3.500)	0.069		
MLNR+++	2.460 (1.215-4.981)	0.012	2.252 (0.838-6.054)	0.108
CEA*** before	1.003 (1.001-1.004)	0.005		
CEA before ≥3/<3 ng/mL	1.542 (0.852-2.788)	0.152	1.009 (0.994-1.024)	0.224
CEA after	1.002 (1.001-1.003)	0.001		
CEA after ≥3/<3 ng/mL	3.320 (1.957-5.631)	<0.001		
Nearest Surgical Boundary	0.790 (0.646-0.966)	0.021	1.048 (0.817-1.343)	0.713
D1 Lymph Node Dissection,	Ref.	1		
D2 Lymph Node Dissection	1.343 (0.800-2.254)	0.265		
Inadequate Lymph Node Dissection	0.464 (0.178-1.209)	0.116		
T Stage T 3-4/1-2	2.459 (0.894-6.767)	0.081		
Tumor size, cm	1.107 (1.039-1.181)	0.002	1.026 (0.893-1.179)	0.717
Tumor size ≥3/<3 cm	3.461 (1.386-8.641)	0.008		
Tumor localisation	Ref.	1		
-Lesser Curvature,	0.973 (0.456-2.077)	0.943		
-Greater Curvature	1.040 (0.400-2.706)	0.935		
-Lesser and greater curvature	1.067 (0.440-2.591)	0.886		
-Cardia	1.473 (0.802-2.708)	0.212		
-Antrum	2.183 (0.515-9.262)	0.290		
Pathology, Intestinal	Ref.	1		
-Adenocarcinoma	0.903 (0.448-1.819)	0.774		
-Diffuse and Signet Ring Cell	1.198 (0.609-2.358)	0.601		
-Mixt	0.866 (0.243-3.079)	0.824		
-Mucinous	2.134 (0.750-6.072)	0.156		

*Lymphovascular invasion; +Perineural invasion; ++CT: Chemotherapy; CRT: Chemoradiotherapy; **Eastern Cooperative Oncology Group Performance Status; +++Metastatic Lymph Node Ratio ***Carcinoembryonic antigen.

locoregional and systemic metastases. The efficacy of targeted agents and immunotherapies in metastatic disease is known, but CT/CRT is still the gold standard treatment in adjuvant therapy and they do not have any superiority over each other. In the future, it is hoped that a better understanding of tumor biology and genetics, personalized treatments and targeting agents will improve survival.

Table 4. Factors affecting DFS and OS in patients receiving Chemotherapy and Chemoradiotherapy in Univariate and Multivariate Cox-regression analysis

Variables	Univariate Analysis HR (95% CI)	p	Multivariate Analysis HR (95% CI)	p
Factors Affecting Disease-free Survival in Adjuvant Chemotherapy				
LVI*, Yes/No	3.092 (1.488-6.424)	0.002	1.156 (0.341-3.925)	0.816
ECOG+ score ≥2/0–1	3.823 (1.872-7.808)	<0.001	2.388 (0.805-7.081)	0.116
Metastatic Lymph Node	1.035 (1.017-1.053)	<0.001		
Recurrence or/and Metastasis				
Yes/No	12.384 (5.091-30.127)	<0.001		
CEA++ before	1.012 (1.002-1.023)	0.025	1.008 (0.994-1.023)	0.251
CEA after ≥3/<3 ng/mL	3.974 (1.797-8.789)	<0.001		
Tumor size, cm	1.085 (1.001-1.175)	0.046	1.181 (0.975-1.430)	0.088
MLNR** ≥63/<63	3.699 (1.286-10.644)	0.015	2.384 (0.681-8.341)	0.174
Factors Affecting Disease-free Survival in Adjuvant Chemoradiotherapy				
ECOG score ≥2/0–1	3.512 (1.820-6.776)	<0.001	2.774 (1.411-5.455)	0.003
Metastatic Lymph Node	1.073 (1.042-1.105)	<0.001	1.064 (1.031-1.098)	<0.001
Recurrence or/and Metastasis				
Yes/No	5.180 (2.705-9.922)	<0.001		
CEA after ≥3/<3 ng/mL	2.778 (1.462-5.278)	0.002		
Factors Affecting Overall Survival in Adjuvant Chemotherapy				
LVI, Yes/No	3.506 (1.580-7.778)	0.002	1.800 (0.656-4.937)	0.254
ECOG score ≥2/0–1	5.768 (2.607-12.759)	<0.001	6.310 (2.370-16.797)	<0.001
Metastatic Lymph Node	1.016 (1.002-1.030)	0.029	1.012 (0.993-1.032)	0.220
Recurrence or/and Metastasis				
Yes/No	7.536 (3.297-17.349)	<0.001		
CEA before	1.002 (1.000-1.004)	0.015	1.001 (0.998-1.003)	0.598
CEA after ≥3/<3 ng/mL	4.606 (1.887-11.241)	<0.001		
Tumor size, cm	1.103 (1.018-1.195)	0.016	1.154 (1.045-1.274)	0.005
Factors Affecting Overall Survival in Adjuvant Chemoradiotherapy				
PNI+++, Yes/No	2.025 (1.073-3.818)	0.029	1.213 (0.421-3.491)	0.721
ECOG score ≥2/0–1	2.648 (1.359-5.158)	0.004	1.917 (0.678-5.416)	0.220
Metastatic Lymph Node	1.072 (1.041-1.105)	<0.001		
Recurrence or/and Metastasis				
Yes/No	3.769 (1.956-7.263)	<0.001		
CEA after ≥3/<3 ng/mL	2.622 (1.350-5.090)	0.004		
MLNR ≥63/<63	2.802 (1.040-7.552)	0.042	2.885 (1.045-7.964)	0.041

*Lymphovascular invasion; +ECOG Performance Status; ++Carcinoembryonic antigen; **Metastatic Lymph Node Ratio +++Perineural invasion.

Disclosures

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