ORIGINAL ARTICLE

Adjuvant Treatment of Gastric Cancer in the D2 Dissection Era: A Real-life Experience from a Multicenter Retrospective Cohort Study

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Abstract

Background: The role of radiotherapy in the adjuvant treatment of gastric cancer (GC) remains to be elucidated. This study aimed to assess the additional benefit of radiotherapy in the adjuvant treatment of GC.

Materials and methods: In this retrospective cohort study, we included 230 gastric adenocarcinoma patients who underwent D2 dissection between January 2004 and December 2019. Patients without R0 resection, who underwent metastasectomy at surgery, and treated with the neoadjuvant treatment were excluded. The co-primary endpoints were overall survival (OS) and disease-free survival (DFS). The secondary endpoints were the locoregional and distant metastasis risk and adverse events (AEs) leading to treatment discontinuation.

Results: One hundred and sixty-six and 64 patients were included in the chemoradiotherapy (CRT) and chemotherapy (ChT) arms, respectively. The median OS was 135.8 months [interquartile range (IQR): 99.4–172.2] and 97 months (IQR: 59.7–134.3) in the CRT and the ChT arms, respectively. No statistical significance was observed between the arms in OS ($p = 0.3$). Locoregional or distant recurrence rates were similar in each group. AEs leading to treatment discontinuation were higher in the CRT arm than in the ChT arm (13.2 vs 9.3%), and the difference between the arms was not statistically significant ($p = 0.4$).

Conclusion: In this real-life study, we established that there was no additional benefit of RT in GC patients who underwent D2 dissection.

Keywords: Chemoradiation, Chemotherapy, Gastric cancer.

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Introduction

Surgery is the mainstay of treatment in gastric and gastroesophageal junctional (GEJ) adenocarcinoma patients. The intergroup 0116 trial (INT 0116) showed that operable gastric or GEJ cancer patients treated with chemoradiotherapy (CRT) had better relapse-free survival and overall survival (OS) than those without adjuvant therapy.[1] After this landmark trial, CRT became the standard in the adjuvant treatment of gastric cancer (GC) patients. However, the ARTIST trial, including patients with D2 lymph node dissection, revealed no additional benefit of radiotherapy (RT) in patients who underwent extended lymph node dissection.[2,3] Despite different patients' characteristics and treatment approaches, the ARTIST 2 and the CRITICS trials did not show the additional benefit of RT in the adjuvant setting.[4,5] Due to the conflicting results from the trials comparing CRT and chemotherapy (ChT) in the adjuvant treatment of GC, there are still controversies regarding the use of adjuvant RT in GC patients. A meta-analysis including six randomized clinical trials showed that 5-year disease-free survival (DFS) was better in the CRT arm than in the ChT arm. However, no statistical significance was observed between the arms in the 5-year OS rate.[6]

Besides, the CLASSIC trial revealed that GC patients who underwent surgery with D2 lymph node dissection and received capecitabine plus oxaliplatin in the adjuvant setting had better survival outcomes than those who underwent surgery alone.[7] In compliance with the results of the CLASSIC trial, guidelines recommend the use of capecitabine plus oxaliplatin without RT as category I for GC patients undergoing D2 dissection.[8,9]

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Despite the latest data from the phase III clinical trials, the role of RT in the adjuvant treatment of GC remains to be elucidated. In this multicenter study, we aimed to compare CRT and ChT in the adjuvant treatment of GC patients who underwent D2 dissection.

Materials and Methods

This retrospective cohort study was conducted in two tertiary cancer centers in Turkey. The local ethical committee approved this study in compliance with the *"Declaration of Helsinki"* and local guidelines.

Patients Selection

We retrospectively searched the electronic medical records software for GC patients who underwent gastrectomy between January 2004 and December 2019. Gastric adenocarcinoma patients who underwent D2 lymph node dissection and received adjuvant ChT or CRT were included in this study. However, patients undergoing R1 resection and who received neoadjuvant treatment and performed liver metastasectomy at the same time as gastrectomy were excluded.

Treatment Approaches

Radiotherapy Delivery

Patients were simulated after 2–3 hours fasting to ensure an empty stomach and enhance daily treatment reproducibility. Radiotherapy planning computed tomography (CT) scan of 3–5 mm thickness was obtained in the supine position with arms overhead using wing board/Vac-Lok, including the area between the top of the diaphragm (for stomach) or carina (for tumor of GEJ or cardia) and the bottom of L4. Immobilization with a Vac-Lok, especially in treatment with intensity-modulated radiotherapy techniques (IMRT), was preferred. Intravenous contrast was given in order to guide clinical target volume (CTV) delineation in patients with normal kidney function, particularly for lymph nodes; preoperative CT scans were used to identify preoperative tumor volume and nodal groups. CTV included the gastric tumor bed, the anastomosis or stumps, and the regional lymphatic nodes depending on the location of the primary disease as well as the status of the lymph node metastasis (Fig. 1). Planning target volume (PTV) margin of 0.5–1 cm considering organ motion and setup uncertainties was given. A total dose of 45 Gy in 25 fractions was delivered with either 3D conformal radiation therapy or IMRT using high-energy (6–18 MV) photons.

Chemotherapy

Fluorouracil-based ChT regimens (i.e., 5-fluorouracil, capecitabine) were performed in combination with RT. Various ChT regimens based on 5-fluorouracil and platin were used in the adjuvant treatment of patients. On the contrary, distinctions between the centers might contribute to the variations in adjuvant ChT approaches.

Data Extraction

We extracted the clinical [e.g., age of diagnosis, sex, date of surgery, starting and ending date of adjuvant treatment, adjuvant ChT regimens, total radiotherapy dose, adverse events (AEs) leading to treatment discontinuation, recurrence sites, date of recurrence, date of the last control, or death] and pathological [e.g., histological type, tumor location, pathological T and N stage according to American Joint Committee on Cancer (AJCC) eighth edition for the TNM staging, tumor grade, and the presence of lymphovascular invasion (LVI) and peritoneal invasion] data to a database from the electronic medical records system or patients' files. The median value of 0.18 was determined as the cutoff for the ratio of metastatic-to-total dissected lymph nodes (LNR).

Endpoints

The co-primary endpoints were OS and DFS. OS was calculated from the date of surgery to death. DFS was calculated from the date of surgery to disease recurrence or death. The secondary endpoints were the locoregional or distant recurrence risk and AEs leading to treatment discontinuation. LR recurrence was defined as the recurrence in the locoregional lymph nodes, gastrectomy region, and peritonea. The recurrences in all remaining areas were accepted as distant metastasis.

Statistical Analysis

To summarize the data, *mean ± standard deviation* or *median with interquartile range (IQR)* and *percentages* were used for continuous and categorical variables, respectively. *Independent samples t-test* or *Mann–Whitney U* test and *Chi-square* or *Fisher's exact test* were also performed to compare the means or medians and frequencies, respectively. Kaplan–Meier method was used to estimate survival. Univariate and multivariate survival analyses were done with the

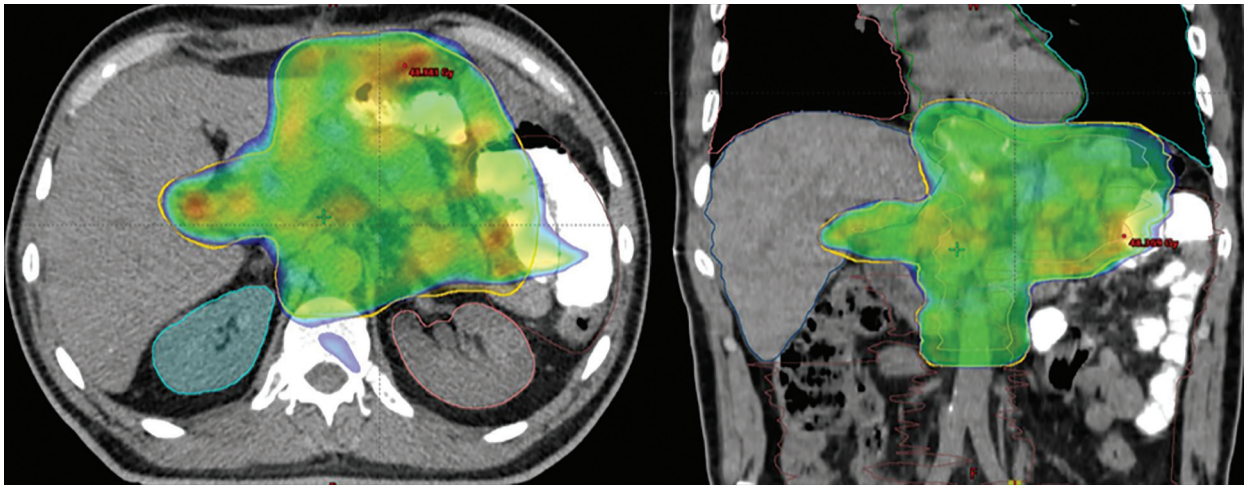


Fig. 1: An IMRT treatment plan of one of our T4N1M0 gastric adenocarcinoma diagnosed patients after subtotal gastrectomy. (Left) Dose distribution on PTV covered by 95% of the prescribed dose in axial view of planning computed tomography; (Right) Dose distribution on PTV covered by 95% of the prescribed dose in coronal view of planning computed tomography

log-rank test and *Cox proportional hazards regression model*. A *p*-value of less than 0.05 was accepted as statistically significant. We used SPSS 27.0 for Mac (IBM Corp., Armonk, New York) and R Studio (version 1.4.1106) for all statistical analyses.

Results

A total of 230 patients were included in this study. One hundred and sixty-six patients received CRT, while 64 patients were treated with ChT in the adjuvant setting. The median age was 55 years (IQR: 47–64) and 58 years (IQR: 53.25–65) in the CRT and ChT arms, respectively. About two out of the three patients were male in each group. The median RT dose was 45 Gy (IQR: 45–45). Approximately 40% of all patients in the ChT arm received XELOX (capecitabine plus oxaliplatin) or FOLFOX [5-fluorouracil (5-FU) plus leucovorin plus oxaliplatin] regimens. All adjuvant ChT regimens are shown in Table 1. In comparison with RT, 121 patients (73.5%) received 5-FU plus leucovorin, and 33 patients (19.9%) received capecitabine. Most patients had grade two or three gastric adenocarcinomas (91% in the CRT arm and 92% in the ChT arm). In addition, the majority of patients in each arm had T3 or T4 (88% in the CRT arm and 94% in the ChT arm) tumor. The rate of patients with metastatic lymph nodes was 88 and 79% in the CRT and ChT arm, respectively. On the contrary, LVI was observed in 91 and 93% of patients in the CRT and ChT arms, respectively. About one out of the three patients had signet-ring cell adenocarcinoma in each arm. All baseline characteristics except for peritoneal invasion were similar in CRT and ChT arms. In this regard, the rate of patients with peritoneal invasion was higher in the ChT arm than in the CRT arm (30 vs 18%, $p = 0.04$). All baseline characteristics of patients in each group are shown in Table 1.

Survival Outcomes

With the median of 38.6 months (IQR: 20.3–68.5) of follow-up, the median OS was 135.8 months (IQR: 99.4–172.2) and 97 months (IQR: 59.7–134.3) in the CRT and the ChT arms, respectively. However, the difference between the arms was not statistically significant (*log-rank* $p = 0.3$). The 5-year survival rates were similar in each arm (69% in the CRT arm and 70% in the ChT arm). Kaplan–Meier estimates of OS are shown in Figure 2A.

The median DFS was 59.1 months (IQR: 17.0–101.2) and 30.8 months (IQR: 14.5–47.1) in the CRT and the ChT arms, respectively. The difference between the arms was not statistically significant (*log-rank* $p = 0.1$). The 5-year DFS rates were similar in each arm (49% in the CRT arm and 42% in the ChT arm). Kaplan–Meier estimates of DFS are shown in Figure 2B.

Locoregional and Distant Recurrence Risk

Sixty-four patients (38%) and 26 patients (40%) had disease recurrence in the CRT and the ChT arms, respectively. Locoregional and distant recurrence rates were similar in each arm ($p = 0.7$). Recurrence rates for locoregional and distant metastasis in each arm are shown in Table 2.

Table 1: Baseline characteristics

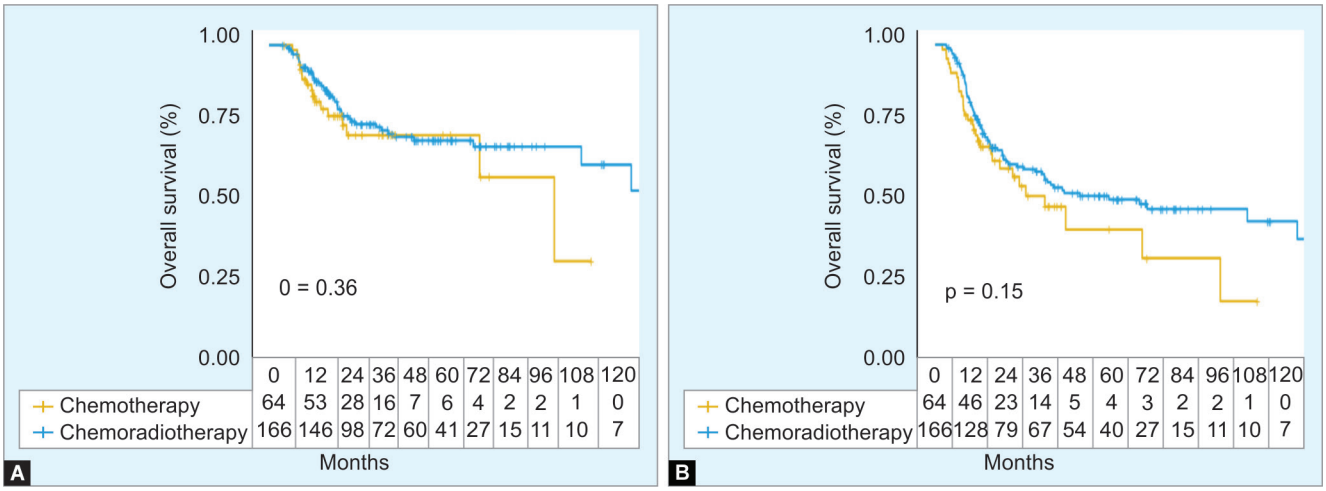
	CRT		*ChT*		
	n = 166	*(%)*	*n = 64*	*(%)*	*p value*
Age-years, median (IQR)	55 (47–64)		58 (53.25–65)		0.07
Sex					0.4
Male	113	*(68)*	40	*(63)*	
Female	53	*(32)*	24	*(37)*	
Tumor location					0.1
Proximal	40	*(29)*	23	*(43)*	
Mid	28	*(20)*	9	*(16)*	
Distal	70	*(51)*	22	*(41)*	
Grade					0.1
1	12	*(9)*	4	*(8)*	
2	49	*(36)*	11	*(22)*	
3	74	*(55)*	35	*(70)*	
LVI					0.4
No	11	*(9)*	4	*(7)*	
Yes	114	*(91)*	51	*(93)*	
Pathological T stage					0.5
1	7	*(4)*	2	*(3)*	
2	13	*(8)*	2	*(3)*	
3	73	*(45)*	30	*(47)*	
4	71	*(43)*	30	*(47)*	
Pathological N stage					0.1
0	20	*(12)*	13	*(21)*	
1	36	*(22)*	8	*(12)*	
2	41	*(25)*	13	*(21)*	
3	68	*(41)*	29	*(46)*	

(Contd...)

Table 1: *(Contd...)*

	CRT		*ChT*		
	n = 166	*(%)*	*n = 64*	*(%)*	*p value*
Stage (TNM AJCC 8th)					0.2
I	5	*(3)*	0	*(0)*	
II	43	*(27)*	21	*(33)*	
III	115	*(70)*	42	*(67)*	
Histological type					0.2
Signet-ring cell	57	*(34)*	24	*(38)*	
Mucinous	4	*(2)*	4	*(6)*	
Not specified	105	*(64)*	36	*(56)*	
Peritoneal invasion					0.04
No	137	*(82)*	45	*(70)*	
Yes	29	*(18)*	19	*(30)*	
Gastrectomy type					0.1
Subtotal	96	*(58)*	44	*(69)*	
Total	70	*(42)*	20	*(31)*	
LNR					0.7
>0.18	84	*(51)*	33	*(53)*	
≤0.18	82	*(49)*	29	*(47)*	
Adjuvant ChT					N/A
CapeOX/FOLFOX	0	*(0)*	27	*(42.2)*	
5-FU/LV or capecitabine	164	*(98.7)*	13	*(20.3)*	
DCF	0	*(0)*	11	*(17.2)*	
FLOT	0	*(0)*	5	*(7.8)*	
Cisplatin + Capecitabine	0	*(0)*	2	*(3.1)*	
Other	2	*(1.3)*	6	*(9.4)*	

AJCC, American Joint Committee on Cancer; CapeOX, capecitabine + oxaliplatin; ChT, chemotherapy; CRT, chemoradiotherapy; DCF, docetaxel + cisplatin + 5-fluorouracil; FLOT, 5-fluorouracil + leucovorin + oxaliplatin + docetaxel; FOLFOX, 5-fluorouracil + leucovorin + oxaliplatin; IQR, interquartile range; LNR, lymph node ratio (metastatic lymph node/total lymph node); LV, leucovorin; LVI, lymphovascular invasion; 5-FU, 5-fluorouracil



Figs 2A and B: Survival analysis (CRT and ChT). (A) Kaplan–Meier estimates of OS; (B) Kaplan–Meier estimates of DFS

Subgroup Analyses

In subgroup analyses of OS for age, sex, tumor location, histological type, tumor grade, T and N stage, LVI and peritoneal invasion, and surgery type, no difference was observed between the CRT and the ChT arms. However, there was a trend toward increased OS in lymph node-positive patients, but it did not reach the statistical significance (HR: 0.60; 95% CI: 0.33–1.09; $p = 0.09$). All subgroup analyses of OS are shown in Figure 3.

DFS was longer in antral gastric adenocarcinoma patients treated with CRT than those treated with ChT (HR: 0.48; 95%

CI: 0.25–0.94; $p = 0.03$). On the contrary, there was a trend toward increased DFS in patients who received CRT if they had metastatic lymph node (HR: 0.67; 95% CI: 0.43–1.06; $p = 0.09$) or grade two or three tumors (HR: 0.62; 95% CI: 0.38–1.00; $p = 0.054$). All subgroup analyses of DFS are shown in Figure 4.

Table 2: Locoregional and distant recurrence rates

Recurrence	*CRT n (%)*	*ChT n (%)*	*p value*
Locoregional	31 *(48.5)*	12 *(46.2)*	0.7
Distant	31 *(48.5)*	14 *(53.8)*	
Missing	2 *(3.0)*	0 *(0.0)*	
Total*	64 *(38.5)*	26 *(40.0)*	

*Total percentages are for all patients in each arm

Safety

Treatment was completed in 78.3 and 73.4% of patients in the CRT and the ChT arms, respectively. In the CRT arm, treatment was discontinued due to toxicity in 12.7% of patients. However, the rate of treatment discontinuation due to toxicity in the ChT arm was 9.4%. Neutropenia was the most observed AEs leading to treatment discontinuation in each arm (3.6% in the CRT arm and 3.3% in the ChT arm). The rate of gastrointestinal AEs leading to treatment discontinuation was higher in the CRT arm than

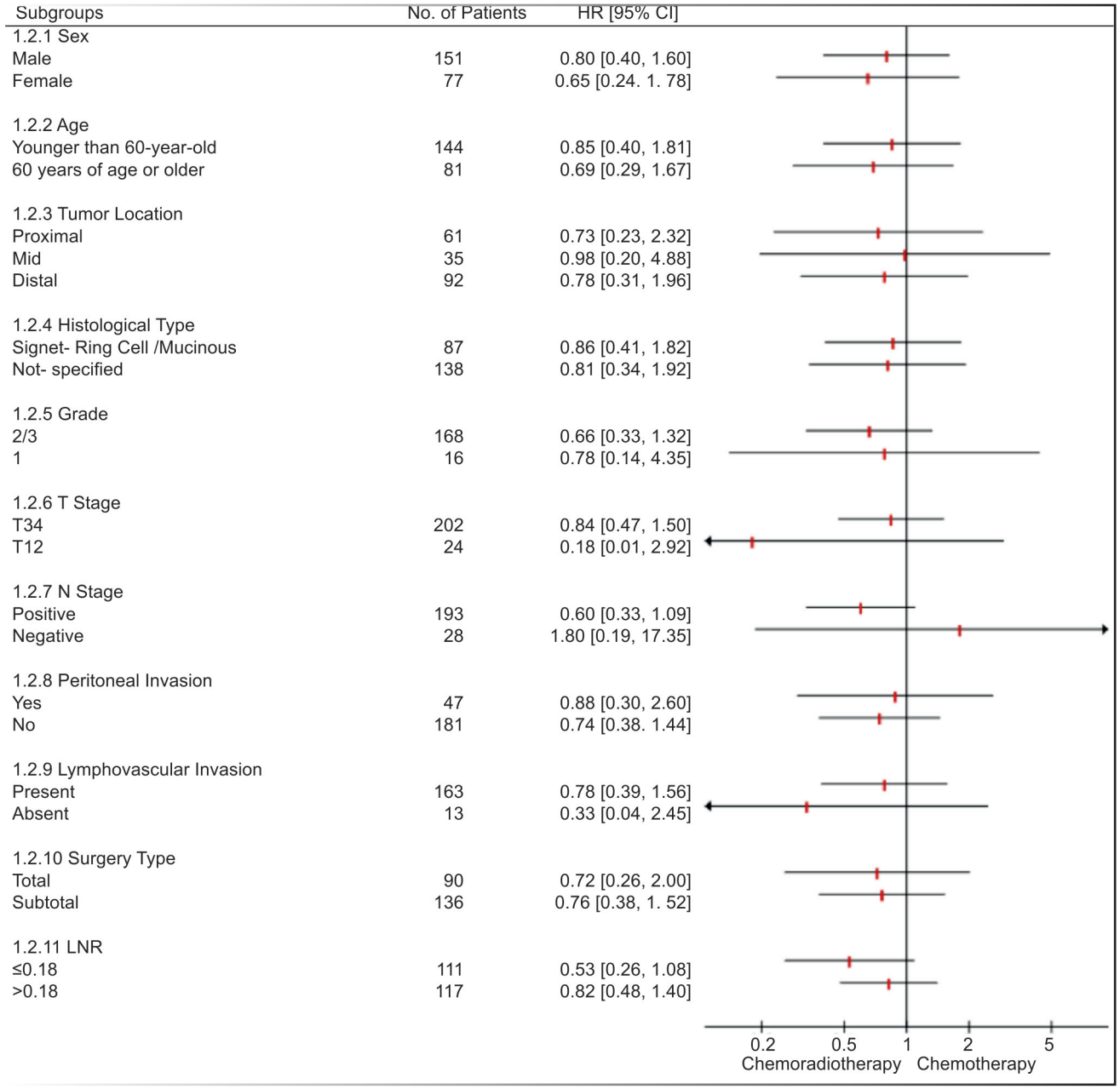


Fig. 3: Forest plot of OS according to subgroups. CI, confidence interval; HR, hazard ratio; LNR, lymph node ratio (metastatic lymph node/total lymph node); N, TNM stage lymph node; T, TNM stage tumor

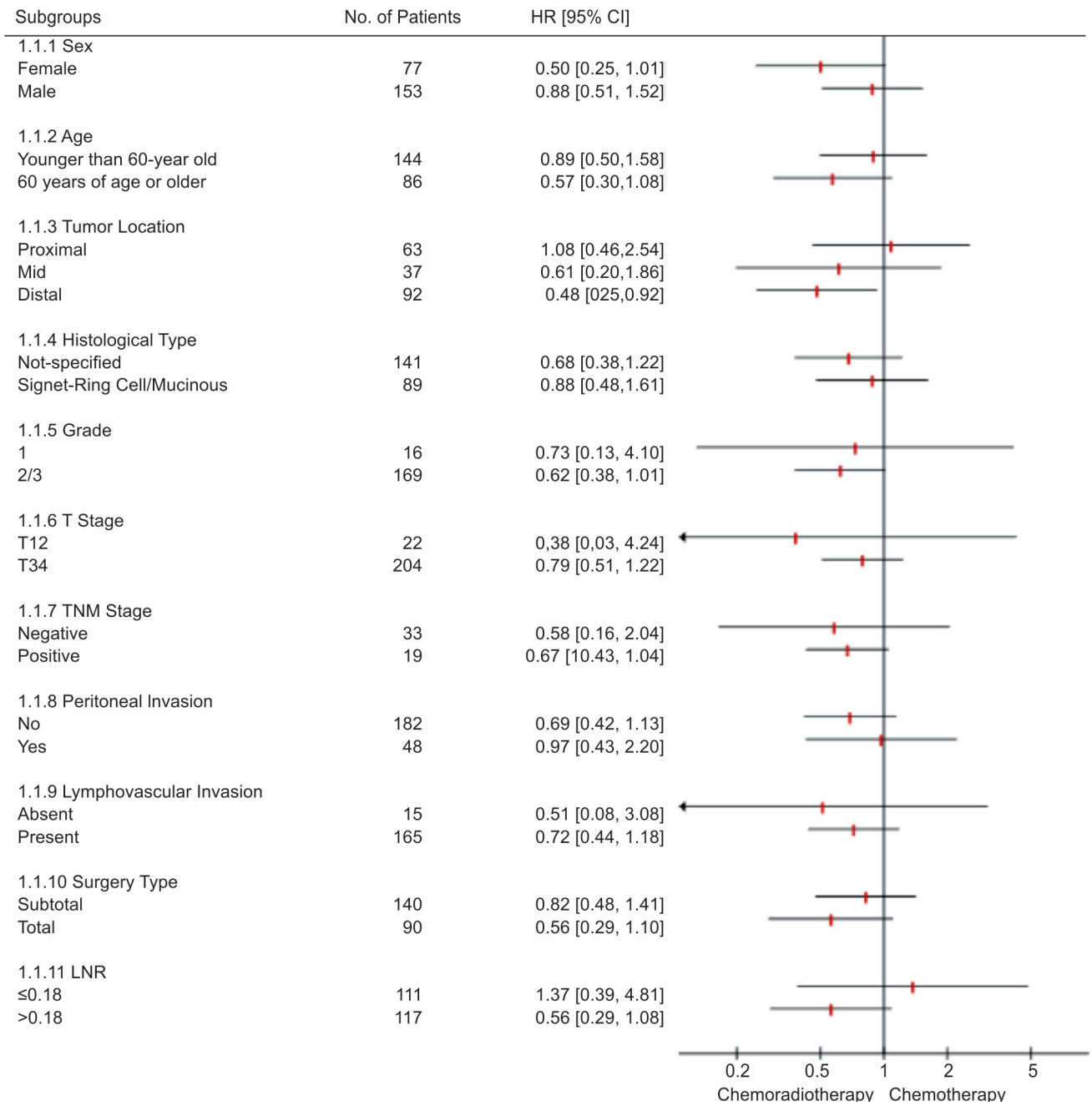


Fig. 4: Forest plot of disease-free survival according to subgroups. CI, confidence interval; HR, hazard ratio, LNR; lymph node ratio (metastatic lymph node/total lymph node); N, TNM

in the ChT arm. However, no statistically significant difference was observed between the groups (4.9 vs 3.1%, $p = 0.7$). All AEs leading to treatment discontinuation are shown in Table 3.

Discussion

This retrospective multicenter study showed no additional benefit of RT in gastric adenocarcinoma patients who underwent D2 dissection. Both OS and DFS were similar in the CRT and ChT arms. Additionally, there was no difference in locoregional and distant metastasis rates between the arms. Furthermore, AEs leading to treatment discontinuation were similar in each arm.

The INT 0116 was a game-changer trial in the adjuvant treatment of GC, especially for western countries. After this study, CRT was accepted as the mainstay of treatment in the adjuvant setting.[1] In contrast to western countries, extended lymph node dissection had become a standard approach in Asian countries earlier.[10] Because of this reason, the rate of patients with D1 dissection was >50% of all included patients in the INT 0116 trial. This issue was one of the main things criticized in this trial. In compliance with the higher D1 dissection rates, locoregional recurrence rates were higher up to 70% in the INT 0116 trial.[1] On the contrary, in the updated results of this trial, no additional benefit of RT was observed among patients who underwent D2 dissection.[1]

Table 3: Treatment-related AEs leading to treatment discontinuation

	CRT n (%)	*ChT n (%)*	*p value*
Neutropenia	6 *(3.6)*	2 *(3.3)*	1.0
Nausea/vomiting	5 *(3.0)*	1 *(1.5)*	1.0
Cardiovascular	2 *(1.2)*	1 *(1.5)*	1.0
Thrombocytopenia	2 *(1.2)*	0 *(0.0)*	1.0
Ileus	2 *(1.2)*	1 *(1.5)*	1.0
Liver toxicity	2 *(1.2)*	0 *(0.0)*	1.0
Infection	1 *(<1.0)*	1 *(1.5)*	0.4
Diarrhea	1 *(<1.0)*	0 *(0.0)*	1.0
Fatigue	1 *(<1.0)*	0 *(0.0)*	1.0
Total	22 *(13.2)*	6 *(9.3)*	0.4

The ARTIST trial that compared the adjuvant CRT and ChT in patients who underwent D2 dissection showed no additional benefit of RT in those patients.[2,3] However, in the subgroup analysis of this trial, DFS was longer in patients treated with CRT than those treated with ChT among node-positive patients.[2,3] Of note, this trial did not reach its planned event numbers during the follow-up period. It has been criticized as a weak side of this trial. With this regard, ARTIST 2 trial was conducted to evaluate the effect of adjuvant RT in lymph node-positive patients who underwent D2 dissection.[5] DFS was better in the oxaliplatin plus S-1 and CRT arms than in the S-1 single-agent arm. The primary aim was not to show the superiority of either oxaliplatin plus S-1 or CRT in this trial. However, there was no difference in DFS between the S-1 plus oxaliplatin and CRT arms.[5] In contrast to the ARTIST 2 trial, there was a trend toward increased OS and DFS in lymph node-positive patients. However, it did not reach statistical significance.

In the INT 0116 trial, the majority of patients had a locoregional recurrence.[1] In contrast, similar to our study, there was no difference between the arms in locoregional or distant metastasis rates in the ARTIST trial.[2] It was most likely associated with the extended lymph node dissection in the ARTIST trial and our study. With this regard, our study also confirmed that extended lymph node dissection and adjuvant ChT effectively reduced both locoregional and distant recurrences.

The CRITICS trial was conducted to evaluate whether CRT improves survival outcomes in GC patients treated with neoadjuvant ChT.[4] Unfortunately, this trial did not establish the additional benefit of adjuvant RT in those patients. Additionally, patients who underwent D1 dissection were included in this study. Interestingly, OS was not better in the adjuvant CRT arm than in the adjuvant ChT arm despite the inclusion of those patients.[4]

One may argue that despite D2 dissection, approximately two out of three patients in our study received CRT. It was more likely to be associated with the results of the INT 0116 trial. Of note, the number of patients treated with CRT has decreased over the last 2 years of the patients' inclusion period in our study.

In subgroup analyses, CRT showed a better DFS in antral GC patients in our study. One explanation of this result is that antral tumors usually consist of the intestinal subtype of gastric adenocarcinoma. In the subgroup analysis of the ARTIST trial, patients with intestinal subtypes of gastric adenocarcinoma were more likely to have a longer DFS with CRT.[2,3] Additionally, antral tumors may be more pretended to metastasis to the regional lymph nodes.[11]

In our study, the rate of AEs leading to treatment discontinuation was higher in the CRT arm than in the ChT arm. However, no statistically significant was observed between the groups. It is hard to compare the AEs profile in our study and previous clinical trials due to the retrospective nature of our study. On the contrary, most patients in the CRT arm of our study received 5-FU concurrent with RT. In contrast to our study, patients received platin combinations with S-1 or capecitabine in the ARTIST and ARTIST 2 trials.

When it comes to adjuvant ChT trials that consisted of surgery-only patients in the control group, the CLASSIC and ACTS-GC trials revealed that ChT improved survival outcomes in patients with D2 dissection.[7,12] Based on these two studies, adjuvant ChT is recommended for gastric adenocarcinoma patients who underwent D2 dissection.[8,9] However, since these trials did not directly compare CRT and ChT in the adjuvant setting, they did not answer the questions regarding the use of RT in the adjuvant GC treatment.

Our study's 5-year survival rates were similar to eastern countries' trials and were about 70%.[5,7] Conversely, this rate was approximately 40% in the trials enrolling patients from western countries.[4] This made us consider that our patient population was more similar to the eastern countries than Europe and North America.

Our study has several limitations. First, this was a retrospective study. Because of this reason, we did not reach all patients' data. One of the most important examples of this issue was that we did not evaluate all AEs. Second, the number of patients in each group was not similar, and approximately two out of three patients received CRT. Third, we had a wide range of adjuvant ChT options. For instance, some patients received 5-FU plus leucovorin or capecitabine alone. However, ARTIST 2 trial showed that combination regimens and CRT were better than S-1 as a single agent.[5] Fourth, despite the similar baseline characteristics, the rate of peritoneal invasion was higher in the ChT arm than in the CRT arm. However, there was no difference in DFS and OS between the CRT and ChT arms in the subgroup of patients with peritoneal invasion.

In conclusion, our study established no additional benefit of RT in gastric adenocarcinoma patients who underwent D2 dissection. However, there was a trend toward increased OS and DFS in some subgroups of patients, especially among lymph node-positive patients. It is hard to say that RT is definitively unnecessary in the adjuvant treatment of GC patients who underwent D2 dissection. However, we need well-designed clinical trials seeking the answer to this question to determine the patients who will benefit from RT.

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