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Research Article

Adjuvant Chemoradiotherapy for Gastric Tumors with D2 Dissection: A Controversial Problem

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Abstract

Objectives: What would be the optimal adjuvant therapy in operated gastric and gastro-esophageal junction (GEJ) adenocarcinoma patients who underwent D2 lymph node dissection remains to be a controversial issue in oncology. The objective of this study is to determine disease-free survival (DFS) and overall survival (OS) data in patients with gastric and GEJ adenocarcinoma with D2 dissected who receive adjuvant chemotherapy (CT) and adjuvant chemoradiotherapy (CRT), to examine the adverse effect profiles developed during treatment, to determine whether adding CRT to the treatment impacts the completion of adjuvant chemotherapy.

Methods: Fifty-seven patients older than 18 years of age with D2 dissection, pathologically stage I-IIIC who received adjuvant CT and CRT treatment were included. Patients who were metastatic at the time of diagnosis, received neoadjuvant chemotherapy or CRT, did not have adequate follow-up and whose data could not be reached were excluded from the study.

Results: In the study, while 3-year DFS was 60%, 3-year OS was 62.5%. 3-year OS was 53.3% for those with a performance score of 0-1 after CRT, while 3-year OS was 16% for those with a score of 2-3 (p=0.003). The 3-year DFS was 45% for those with 0-1 eastern cooperative oncology group (ECOG) performance score after CRT, while 3-year DFS was 16% for those with 2-3 (p=0.006). The estimated median OS and DFS were significantly shorter in 15 patients who could not complete adjuvant chemotherapy after CRT (75 months vs. 22 months for OS; p=0.00), (87 vs. 17 months for DFS; p<0.001). The most common adverse effect was fatigue (91%), and the most common hematological adverse effect was anemia (89.5%).

Conclusion: Adding CRT to adjuvant chemotherapy in operated gastric and GEJ cancer patients who underwent D2 lymph node dissection might decrease the overall adjuvant treatment completion rate and the overall performance score of the patients and cause the risk of decreasing the success of adjuvant therapy by impacting the profile of adverse effects.

Keywords: Adjuvant chemoradiotherapy, D2 dissection, gastric cancer

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Gastric cancer is one of the most common cancers and continues to be one of the major causes of cancer-related deaths.[1] In Turkey, while it is the 5th most common cancer among males, it is the 6th most common cancer among females. Prognosis is poor in patients who have undergone only surgery. Although extended lymph node dissection improve overall survival, relapse ocur within 2 years in most of the patients.[2] Efforts to improve treatment outcomes beyond those achieved by surgery alone have led to adjuvant and neoadjuvant treatment strate-

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gies. Although there is no consensus on the most effective therapeutic approach, thanks to perioperative CT an advantage of 50-month OS has been demonstrated in the FLOT4 study, which is a considerable research including patients diagnosed with locally advanced, resectable gastric or GEJ adenocarcinoma, and this regimen has been used frequently.[3] Adjuvant treatment options include CRT and CT combination or chemotherapy alone. The impact of postoperative CT and/or CRT on survival has been better demonstrated over time in patients who did not receive neoadjuvant therapy and have not undergone resection. [4] The combination of CT and CRT has almost become the standard adjuvant therapy instead of CT alone for patients who underwent D1 lymph node dissection (perigastric lymph nodes), specifically in pT3, pT4, and node-positive disease.[4,5]

The benefit of adjuvant CRT applied in addition to adjuvant CT in patients who underwent D2 lymph node dissection is one of the most controversial fields in gastrointestinal oncology. Despite multiple randomized studies and meta-analyses, the survival benefit of adding CRT to CT following gastric cancer surgery remains unclear.[6] Adding CRT to adjuvant CT is also recommended in the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines, as an alternative option for patients with D2 lymph node dissection.[7,8]

Objective of Study

The objective of this study is to determine DFS and OS data in patients with gastric and GEJ adenocarcinoma who underwent D2 dissection and who receive adjuvant CT and adjuvant CRT, to examine the side effect profiles developed during treatment, to determine whether adding CRT to the treatment affects the completion of adjuvant chemotherapy, and to determine the prognostic factors that might affect OS and DFS.

Methods

Patients diagnosed with gastric and GEJ adenocarcinoma in the medical oncology clinic of our hospital between 2013-2020 were retrospectively reviewed. Fifty-seven patients older than 18 years of age with D2 dissection, pathologically stage I-IIIC who received adjuvant CT and CRT treatment, followed up for toxicity with blood counts in each cycle were included. Patients who were metastatic at the time of diagnosis, received neoadjuvant chemotherapy or CRT, did not receive adjuvant chemotherapy or CRT, did not have adequate follow-up, and whose data could not be reached were excluded from the study. CRT doses were administered as 45 Gy of radiation at 1.8 Gy per day, 5 days per week, for 5 weeks with continuous capecitabine 825 mg/m^2 twice daily during radiotherapy or 5 FU 200 mg/m^2/day. D1 dissection was defined as excision of perigastric lymph nodes, while D2 dissection was defined as the removal of 16 or more lymph nodes, including those around the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery, as well as D1 lymph nodes. Moreover, HER-2 positivity was accepted in those who were confirmed with +3 in terms of IHC, and with FISH.

The data were collected retrospectively from the database of this research hospital. OS was calculated according to the date of death reported in the central registry (death notification form). The study was approved by the local ethics committee (January 2021 approval number: 113).

The statistical analysis was performed via the software of SPSS, version 25.0 (SPSS, Chicago, IL, USA). Categorical variables were presented as number (n) and percentage (%) values. Continuous variables were presented as median (IQR) (Interquartile Range) or mean (standard deviation). The Chi-square test was used to compare categorical data. Mann-Whitney U-test was used to compare nonparametric variables. The Kaplan-Meier method was used for survival analysis, and the log-rank test was performed for comparisons between groups. Correlation analyzes were performed to determine correlations between the variables. The results were considered statistically significant at $p<0.05$.

Results

56% of the 57 patients who were included in the study were females. The median age of the patients was 62 years (40-77). The demographic and histopathological characteristics of the patients were summarized in Table 1. Regarding the tumor localizations, 38% were located distally, while 35% were located proximal+GEJ. The ratio of patients with stage IIIb and IIIc were 38% and 12%, respectively. Total gastrectomy was performed in 45% of patients in total. Besides, 12.3% of the patients were assessed as HER-2 positive. Data on adjuvant therapy and relapse are summarized in Table 2.

As adjuvant chemotherapy, CAPEOX was administered in 35% of patients and mFOLFOX in 15% of patients. Capecitabine was administered in 72% of the patients, and 5-FU was administered in 28% of the patients, as a radiosensitizer. 26.3% (n=15) of the patients could not complete the adjuvant CT (only 3.5% (n=2) of them did not receive adjuvant chemotherapy). Adjuvant CRT was started in 55 patients (96.4%) with 2nd cycle following 1st cycle of adjuvant chemotherapy. Two patients (3.6%) did not receive adjuvant chemotherapy and only adjuvant CRT was started. 5 (8.7%) of the patients could not complete the started CRT. During follow-up, recurrence developed in 23 patients (40.4%)

Table 1. Summary of patient characteristics

Characteristics	n	(%)
Gender		
Female	32	(56.1)
Male	25	(43.9)
Median Age	62	(40-77)
Tumor Location		
Proximal+GEJ	20	(35.1)
Corpus	15	(26.3)
Distal	22	(38.6)
Stage at Diagnosis		
I	2	(3.5)
IIA	8	(14)
IIB	12	(21)
IIIA	6	(10.5)
IIIB	22	(38.6)
IIIC	78	(12.3)
Type of Operation		
Total Gastrectomy	26	(45.6)
Subtotal Gastrectomy	31	(54.4)
Resection		
R0	49	(86)
R1	8	(14)
Pathology		
Well differentiated	8	(14)
Moderately differentiated	15	(26.3)
Poorly differentiated	21	(36.8)
Signet ring cell	13	(22.8)
Her-2 Status		
Positive	7	(12.3)
Negative	21	(36.3)
Unknown	29	(53.4)

GEJ: Gastroesophageal junction.

Table 2. Baseline characteristics of Adjuvant Therapy and Recurrence

Characteristics	n	(%)
Chemotherapy		
Capecitabine	13	(22.8)
FUFA	19	(19.3)
FOLFOX	9	(15.8)
KAPEOX	20	(35.1)
Cisplatin+ 5-Fluorouracil	2	(3.5)
Not Received	2	(3.5)
Not Complete Adjuvant Chemotherapy	15	(26.3)
Complete Adjuvant Chemotherapy	40	(70.2)
Drug in Chemoradiotherapy		
Capecitabine	41	(71.9)
5-Fluorouracil	16	(28.1)
Not Complete Chemoradiotherapy	5	(8.77)
Complete Chemoradiotherapy	52	(91.23)
ECOG Scores Before Chemoradiotherapy		
0	5	(8.8)
1	52	(91.2)
ECOG Scores After Chemoradiotherapy		
0-1	31	(54.4)
2	19	(33.3)
3	7	(12.3)
Recurrence Sites		
Local	3	(13)
Peritoneum	18	(78.2)
Liver	6	(26)
Lung	4	(17.3)
Lymphe Nodes	5	(21.7)
Received Chemotherapy After Recurrence	14	(60.8)
Not Received Chemotherapy After Recurrence	9	(39.1)

FUFA: 5- FLUOROURACİL + FOLINIC ACID; FOLFOX: 5- FLUOROURACİL + FOLINIC ACID + OXALIPLATIN; CAPEOX: CAPECITABINE + OXALIPLATIN; ECOG: Eastern Cooperative Oncology Group.

with local or distant metastasis.

The median follow-up duration of the study was 27 (5-95) months. In the study, the 3-year OS was 62.5%. The estimated OS median was 95 months. Whereas the 3-year OS was 45.6% in total gastrectomies, it was 80% in subtotal gastrectomies, and it was statistically significant (p=0.03). While the 3-year OS was 80.4% in pathologically well and moderately differentiated tumors, and the median was 75 (45.41-104.58) months, it was 44.8% in poorly differentiated and signet-ring cell tumors, and the median was 34 (20.36-47.64) months; although there was a difference between them, it was not statistically significant (p=0.19). The 3-year DFS was 60%, the estimated median DFS was 52 (24.73-79.2) months (Table 3).

While the 3-year OS was 61.8% (estimated median was 95 months) in 50 patients who underwent R0 resection, all of them were exitus at 3rd year, and the median OS was 27 months (p=0.001) in 7 patients who underwent R1 resection. While the 3-year DFS in R0 resections was 56.5% and the estimated median was 60 (39.6-80.37), the estimated median in the third year was 14 (8.10-19.80) months in patients with R1 resection, and it was significant (p=0.029).

ECOG performance score of all patients before CRT was 0-1. Following CRT, the performance of 54.4% of the patients was 0-1, while the ECOG score of 33% of the patients were 2, and 12% of the patients' ECOG were 3 (p=0.005). 3-year OS was 53.3% for those with a performance score of 0-1 after CRT, while 3-year OS was 16 for those with a score of 2-3 (p=0.003). The 3-year DFS was 45% for those with 0-1 ECOG performance score after CRT, while 3-year DFS was 16% for those with 2-3, which was statistically significant (p=0.006). The estimated median OS and DFS were significantly shorter in 15 patients who could not complete adjuvant chemotherapy compared to patients who completed adjuvant chemotherapy (75 months vs. 22 months for OS; p<0.001), (87 vs. 17 months for DFS; p<0.001).

Table 3. OS and DFS

	OS (3-Year)	p
All patients	62.5%	
Total gastrectomy	45.6%	0.03
Subtotal gastrectomy	80%	
Well-moderately differentiated	80.4%	0.19
Poor differentiated-signet-ring Cell	44.8%	
RO Resection	61.8%	0.001
R1 Resection	0%	
ECOG 0-1 after KRT	53.3%	0.003
ECOG 2-3 after KRT	16%	
	DFS (3-Year)	**p**
All patients	60%	
RO Resection	56.5%	0.029
R1 Resection	0%	
ECOG 0-1 after KRT	45%	0.006
ECOG 2-3 after KRT	16%	

OS: Overall survival; DFS: Disease free survival; ECOG: Eastern Cooperative Oncology Group; CRT: Chemoradiotherapy.

The most common adverse effect related to adjuvant chemotherapy and CRT was fatigue (91%), 12.2% of which was severe, at grade 3. The most common hematological adverse effect was anemia (89.5%). While the rate of grade 3-4 neutropenia was 19.3%, Febril neutropenia (FEN) was detected at a rate of 17.5%. While 75% of the patients had nausea, 8.8% had severe vomiting. While 74% of the patients had anorexia, weight loss was around 74%. Dose modification was performed in adjuvant chemotherapy in 34 patients (59.6%) due to side effects. Side effects related to adjuvant therapy are summarized in Table 4.

Discussion

3-year OS was found to be 62.5% (estimated median 95 months) and 3-year DFS was 60% (estimated median 52 months) in this study, in which patients with operated gastric and GEJ adenocarcinoma who underwent D2 lymph node dissection, and who received adjuvant chemotherapy and CRT were retrospectively examined. In the pivotal ARTIST study, which examined the results of adding CRT to adjuvant chemotherapy in D2 dissected patients and published in 2012, the 3-year DFS was 78.2% in the CT/CRT/CT arm, and 74.2% in the arm receiving only CT, and there was no significant difference between them. In the final analysis of the study in 2015, there was no difference between the arms in terms of DFS and OS, and the 5-year OS in the CRT arm was 75%. In the subgroup analysis of the study, it was found out that CRT contributed to DFS in patients with positive pathological lymph nodes.[6,9] In the presented study, OS and DFS rates were determined to be lower than the pivotal study. The median age of the patients in this study

Table 4. Summary of advers events related adjuvant therapies

Characteristics	n	(%)
Anemia		
None	6	(10.5)
Grade 1-2	42	(73.7)
Grade 3-4	9	(15.8)
Neutropenia		
None	21	(36.8)
Grade 1-2	25	(43.9)
Grade 3-4	11	(19.3)
Febrile neutropenia	10	(17.5)
Thrombocytopenia		
None	32	(56.1)
Grade1-2	23	(40.4)
Grade 3-4	2	(3.5)
Mucositis		
None	42	(73.6)
Grade 1-2	12	(21)
Grade 3-4	3	(5.2)
Nausea		
None	14	(24.5)
Grade 1-2	28	(49.1)
Grade 3-4	15	(26.3)
Vomiting		
None	27	(47.4)
Grade 1-2	25	(43.9)
Grade 3-4	5	(8.8)
Diarrhea		
None	39	(68.4)
Grade 1-2	16	(28.1)
Grade 3-4	2	(3.5)
Constipation		
None	33	(57.9)
Grade 1-2	20	(35)
Grade 3-4	4	(7)
Weight Loss		
None	15	(26.3)
Grade 1	23	(40.4)
Grade 2	17	(29.8)
Grade 3	2	(3.5)
Anorexia		
None	15	(26.3)
Grade 1-2	31	(54)
Grade 3-4	11	(19.3)
Fatigue		
None	5	(8.7)
Grade 1	33	(57.8)
Grade 2	12	(21)
Grade 3	7	(12.2)
Neuropathy		
None	37	(64.9)
Grade 1-2	19	(33.3)
Grade 3-4	1	(1.8)

was 62 years, while it was 56 in the ARTIST. The rate of patients with early-stage (I-II) was 38.5% and 35.1% with GEJ and proximal stomach localization, while the early-stage rate was higher in the pivotal the ARTIST study (57.8%), and it was located proximally in 5.7% of the patients. Lower DFS and OS values might have been found out due to these differences between the patient population. Moreover, while in the presented study, 42% of the patients received single-agent adjuvant chemotherapy, in the pivotal study, all patients were administered with the combination regimen. It has been demonstrated in the ARTIST-2 study, which was published in 2020, that the adjuvant combination regimens are superior to a single agent (3-year DFS was 64.8% in the arm receiving adjuvant monotherapy and 74.3% in the combination arm).[10] It has been also demonstrated in the Dutch Gastric Cancer Group Trial (DGCT) study that adjuvant CRT does not contribute additionally to patients with D2 dissection, and it has been revealed that the main contribution of CRT was in D1 dissections (2% vs. 8%; p=0.001).[11] The only study showing the contribution of CRT to OS and DFS, compared to CT alone, is a Korean study with 68 patients, and the 3-year DFS and OS rates were 56% vs. 29%, and 68% vs. 44%, respectively.[12] In the presented study, R1 resected patients (n=7) had worse DFS and OS data compared to R0, in line with the literature. Despite adjuvant chemotherapy and CRT, all patients were lost in the 3rd year.

Although the treatment of 55 of the 57 patients, who were included in the study, was scheduled as a continuation of radiotherapy with capecitabine or 5-Fluorouracil (5-FU) for 5 weeks following adjuvant 1st cycle CT, 5 patients could not complete the started CRT, and fifteen patients could not complete adjuvant chemotherapy due to poor performance or adverse effects following CRT. While the rate of completing adjuvant chemotherapy was 70.2% in the presented study, it was 82.8% in the pivotal The ARTIST study.[6] Consistent with the presented study, in the CALGB 80101 study, one arm received radiotherapy with capecitabine or 5-FU, while a combination of chemotherapy consisting of epirubicin, cisplatin, and 5-FU was administered to the other arm. Despite the administration of multiple medications in the CT arm, the rate of treatment completion was higher than the CRT arm (68% vs. 63%).[13] In the presented study, DFS and OS were lower in patients who could not complete adjuvant therapy, in line with the literature. In the INT 0116 study, which demonstrated the need for postoperative adjuvant therapy and put it into daily practice, 556 patients with gastric or GEJ cancer were assigned to either observation alone or adjuvant CRT following resection. The 3-year DFS (48% vs. 31%) and OS rates (50% vs41%) were significantly better with adjuvant therapy.[4]

In the present study, while the ECOG performance score of all patients before CRT was 0-1, following CRT, the performance of almost half of them (45.6%) decreased to 2-3, which was statistically significant. It is well-known that the ECOG performance score is a prognostic factor in various cancers.[14] In line with the literature, DFS and OS of patients with lower ECOG performance scores was also shorter in the presented study (3-year DFS 16% and 3-year OS 16%). Based on these data, adding CRT to treatment might impact treatment success adversely through reducing total treatment completion rates and patients' overall performance score.

When the adverse effect profiles were examined, the most common side effect related to adjuvant chemotherapy and CRT was fatigue (91%). The most common hematological adverse effect was anemia (89.5%). While loss of appetite and weight were around 74%, the most common gastrointestinal system adverse effect was nausea (75.5%). In a single-centered Korean study, the most common adverse effects in the arm receiving CRT were grade I-II nausea and vomiting (82.4%) and grade I-II neutropenia (70.6%).[12] In the CALGB 80101 study, the rate of total adverse effects was higher in the CRT arm compared to the CT arm (98% vs. 94%), and the incidence of grade 4 and higher neutropenia was also detected to be higher compared to the CT arm (34% vs. 19%).[13] In the CALGB 80101 study, 57% of the dose was modified due to adverse effects, similarly, 59.6% of the patients had dose modifications in the presented study. It was determined in a meta-analysis, in which 6 randomized studies including a total of 1171 patients were examined, that neutropenia was more common among patients who received CRT compared to the CT arm (OR=1.47, 95% CI:1.11--1.96; p=0.008), and there was no significant difference in other adverse effects.[5] In the presented study, grade III-IV neutropenia was detected in 19.3% and FEN in 17.5%.

This study has some limitations. It was a retrospective study; hence, prospective multicenter study would be much better in terms of evaluating adjuvant CRT in D2 dissected gastric and GEJ cancer. In this study, there is a risk of bias in some results due to the low number of patients and missing data.

Conclusion

In the light of the above-mentioned data and current literature, adding CRT to adjuvant chemotherapy in operated gastric and GEJ cancer patients who underwent D2 lymph node dissection might lead to the risk of reducing the success of adjuvant treatment though reducing the overall treatment completion rate and the overall performance score of the patients, as well as by impacting the adverse

effect profiles. Large prospective studies on this subject will provide better information and could reduce the possibility of bias.

Disclosures

Ethics Committee Approval: This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the local Institutional Review Board (01.2021-113).

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