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ORIGINAL ARTICLE

Concurrent versus sandwich treatment in adjuvant treatment in high risk operated gastric cancer: A single center experience

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Summary

Purpose: *In this study we compared postoperative early vs sandwich chemoradiotherapy in operated stage IIA-IIIC gastric cancer patients in terms of effectiveness and outcome.*

Methods: *The data of 201 gastric cancer patients treated in the same center between December 2006 and June 2017 were retrospectively evaluated. One hundred forty nine patients who were eligible for the study criteria were divided into two groups according to the postoperative treatment modality. The first group included 85 patients who were given chemoradiotherapy simultaneously (ETG) and the second group icluded 64 patients who received sandwich (chemotherapy-chemoradiotherapy-chemotherapy) (STG) treatment. Overall survival (OS) and disease-free survival (DFS) were evaluated as primary endpoints.*

Results: *The median follow-up time for all patient groups was 26.7 months (1.3 -136.5 months). Adjuvant chemotherapy and radiotherapy were initiated concurrently in patients receiving concomitant therapy. Half of the planned chemotherapy, then chemoradiotherapy and then the remaining chemotherapy treatments were given to the sandwich treatment group. A total of 50.4 Gy radiotherapy was given to the concurrent chemoradiotherapy group and a total of 45 Gy radiotherapy to the group receiving the sandwich treatment. OS was 30.6 months (23.7-37.5) in all groups, 30.4 months (23.7-35.0) in concurrent therapy (ETG) and 35.6 months (26.3-45) in sandwich therapy (STG) (p=0.73). DFS was 26.6 months (21.3-32.0) in all groups and 24.5 months (18.1-31.0) in the group receiving ETG, 32.5 months (22.2-42.8) in STG. (p=0.46). The most common grade 3 and above toxicities were; acute upper gastrointestinal toxicity (19.1% in ETG vs. 9.0% in STG, p=0.01) and hematological toxicity (31.8% in ETG vs. 13.9% in STG; p=0.002). Early cessation of treatment was similar in both groups. In multivariate analysis, female gender (p=0.01), stage III disease, grade III disease were seen as negative predictive factors for overall survival. In DFS multivariate analysis, there was no difference between the groups in terms of gender, T stage, N stage, and AJCC stage.*

Conclusion: *In this study, superiority of sandwich treatment over concurrent treatment was observed in patients with operated stage IIB-IIIC gastric cancer, but the difference was not statistically significant. If this study is performed in larger patient series, the difference of sandwich treatment may become meaningful.*

Key words: *gastric cancer, adjuvant treatment, sandwitch chemoradiotherapy*

Introduction

Gastric cancer (GC) is the fourth most common cancer in the world and the second most common cause of overall cancer-related death [1]. Generally, patients are diagnosed at a locally advanced stage and their prognosis is poor. Five-year OS rates are 5-20% [2]. The best survival rates for non-metastatic GC have been reported in patients who can undergo curative surgery, yet distant metastases and/or locoregional recurrence are observed during the follow-up of 23-38% of patients [3]. For this reason, the need for postoperative adjuvant treatment emerged. In the Intergroup 0116 (INT0116) trial,

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which is one of the most important studies in the literature, adjuvant radiotherapy and simultaneous FU/FA (fluorouracil and folinic acid) (chemoradiotherapy-chemotherapy) treatment was applied, yet 17% of patients stopped treatment due to acute toxicity [4]. Despite this, chemoradiotherapy (CRT) has been shown to contribute to both DFS and OS compared surgery (p=0.005) [4]. Although many different treatment schemes have been tried to reduce the side effects of adjuvant therapy in high-risk patients, it is not yet known which is the most appropriate treatment approach [5]. At the same time, the optimal timing of chemotherapy (CT) and radiotherapy (RT) is still controversial. For this reason, we aimed to evaluate immediate versus sandwich CRT applications in the adjuvant therapy in terms of treatment effectiveness and side effects

Methods

Patient population

The records of 201 high-risk operated patients who were followed-up and treated at our center between December 2006 and June 2017 were retrospectively evaluated. Patients over 18 years old with pathological stage IIA-IIIC, ECOG PS 0-1, with no distant metastasis and who were treated with adjuvant therapy were included in the evaluation. All patients underwent subtotal or total gastectomy and lymph node dissection at baseline. Pathologically, adenocarcinoma was found in 129 (87%) patients and ring-cell carcinoma in 20 (13%). Patients who underwent preoperative-neoadjuvant CT / RT / CRT, R1 and R2 resection and inadequate lymph node dissection (<15) were excluded from the study, 150 patients were found eligible for the study and evaluated. Basic and treatment characteristics of 149 patients are shown in Table 1.

Treatment protocols

Surgical treatments of the patients

79 patients (53%) had total gastrectomy, 70 (47%) had subtotal gastrectomy, 54 (36%) underwent D1 dissection and 95 (64%) underwent D2 dissection. All patients were staged according to AJJC 7th Edition. Adjuvant treatments of all patients were performed according to the physician's preference. Simultaneous chemoradiotherapy was applied to 85 patients and sandwich CRT to 64 patients.

Chemotherapy regimens

The chemotherapy (CT) regimens were as follows: XELOX (oxaliplatin 130 mg/m^2 every 3 weeks and capecitabine 2000 mg/m^2 for 14 days every 3 weeks), cisplatin (75 mg/m^2 every 3 weeks) and 5-FU (750 mg/m^2 for 5 days every 3 weeks); FOLFOX (oxaliplatin 85 mg/m^2, FA 400 mg/m^2, 5-FU bolus 400 mg /m^2, and 5-FU 2400 mg/m^2 every 2 weeks); CFF (cisplatin 40 mg/m^2, FA 200 mg/m^2, 5-FU 200 mg/m^2 bolus, and 5-FU 2400 mg/m^2 every 2 weeks); and FUFA (FA 20 mg/m^2 for 5 days and fluorouracil 425 mg/m^2 for 5 days every 28 days). 5-FU-based CT was administered to 70 patients (47%) and platinum-based CT to 79 patients (53%). After selecting the CT regimen for patients in the concurrent therapy group (CTG), concurrent CRT was started, and the planned CT was continued after the end of RT. After half of the planned CT dose was administered in the sandwich therapy group (STG), CRT was administered in patients who did not exhibit signs of recurrence, and the initial CT regimen was resumed within 2 weeks after the completion of CRT. Simultaneous infusional 200 mg/m^2/day 5-FU (57%) or 1650 mg/m^2/day capecitabine (43%) treatment was administered to patients receiving CRT.

Radiotherapy

The patients had undergone a 2.5-mm slice thickness, free-breathing computed tomography (CT) scan for treatment planning purposes. The patients were positioned supine with arms above the head and immobilized using a semi-rigid patient head-positioning system. To better demonstrate vasculature and anastomosis, intravenous and oral contrast agents were during the planning CT. Target volumes and organs at risk (OAR) definitions in this study were in accordance with the International Commission on Radiation Units and Measurements 50 and 62 reports.

RT was applied to all patients with either 3DCRT (69 patients, 52%) or IMRT (64 patients, 48%) technique. A median dose of 50.4 Gy (range 41.4-50.4) was planned for the entire patient group, with an average of 50.4 Gy (range 41.4-50.4) in the concurrent treatment group (ETG) and 45.0 Gy (range 41.4-50.4) in the sandwich treatment group was applied.

The treatment plans were generated using 3DCRT, VMAT, and HT techniques. The 3DCRT plans consisted of five coplanar fields; the upper part of the planned treatment volume (PTV) comprising the gastric bed consisted of oblique fields with varying angles to reduce OAR doses. All plans were normalized to deliver 99% of clinical target volume (CTV) and 95% of PTV receiving at least 45 Gy. All 3DCRT plans were developed using an Eclipse version 7.5 (Varian Medical Systems, Palo Alto, CA, USA). The isocenter was positioned in the center of the PTV and beams were shaped with 1-cm multi-leaf collimators (MLC) using 6MV energy (MLC; Varian DHX 3323, Varian Medical Systems, Palo Alto, California, USA). The VMAT plans consisted of a double arc that included 179° as the starting angle, and 330° as the end angle. Gantry speed, MLC leaf position, and dose rate varied continuously during VMAT delivery [15]. The VMAT plans were calculated with a Monaco treatment planning system version 5 (CMS; Elekta, Crawley, UK) using the Monte Carlo algorithm. VMAT plans were performed for delivery with 6MV energy Axesse linear accelerator (Elekta AB, Stockholm, Sweden) with 5-mm MLC thickness. The HT plans were generated using a Hi-Art Tomotherapy system (TomoTherapy Inc., Madison, WI, USA), which is a helical fan-beam IMRT using 6-MV photon using inverse planning software. The HT plans were made for TomoEdge™ Dynamic Jaws system of the TomoHDA™ series. A collimator aperture of 2.5 cm,

Table 1. Baseline and treatment characteristics

Characteristics	*All patients (n=149)* *n (%)*	*Concurrent (n=85)* *n (%)*	*Sandwich (n=64)* *n (%)*	*p*
Median age, years (range)	61 (27-84)	59 (27-84)	62 (31-77)	0.27
Gender				
Male	97 (65)	40 (63)	57 (67)	0.61
Female	52 (35)	24 (37)	28 (33)	
Pathology				
Adenocarcinoma	129 (87)	54 (84)	75 (88)	0.50
Signet cell carcinoma	20 (13)	10 (16)	10 (12)	
Tumor location				
GEJ	18 (12)	6 (9)	12 (14)	0.32
Corpus	53 (36)	28 (44)	25 (29)	
Antrum	64 (43)	25 (39)	39 (46)	
Pylorus	14 (9)	5 (8)	9 (11)	
Operation technique				
Total gastrectomy	79 (53)	36 (56)	43 (51)	0.51
Subtotal gastrectomy	70 (47)	28 (44)	42 (49)	
Lymph node dissection				
D1	54 (36)	19 (30)	35 (41)	0.17
D2	95 (64)	45 (70)	50 (59)	
T stage				
T1	6 (4)	3 (5)	3 (4)	0.005
T2	21 (14)	3 (5)	18 (21)	
T3	65 (44)	25 (39)	40 (47)	
T4	57 (38)	33 (51)	24 (28)	
N stage				
N0	20 (13)	6 (9)	14 (17)	0.01
N1	45 (30)	14 (22)	31 (37)	
N2	35 (24)	14 (22)	21 (24)	
N3	49 (33)	30 (47)	19 (22)	
AJCC stage				
IIA	35 (24)	11 (17)	24 (28)	0.007
IIB	24 (16)	5 (8)	19 (22)	
IIIA	42 (28)	18 (28)	24 (29)	
IIIB	16 (11)	10 (16)	6 (7)	
IIIC	32 (21)	20 (31)	12 (14)	
LVSI				
Negative	19 (13)	9 (14)	10 (12)	0.16
Positive	109 (73)	50 (78)	59 (69)	
Unknown	21 (14)	5 (8)	16 (19)	
PNI				
Negative	15 (10)	7 (11)	8 (9)	0.68
Positive	106 (71)	47 (73)	59 (69)	
Unknown	28 (19)	10 (16)	18 (21)	
Grade				
I	7 (5)	2 (3)	5 (6)	0.63
II	42 (28)	16 (25)	26 (31)	
III	100 (67)	46 (72)	54 (64)	

GEJ= gastroesophageal junction, AJCC= American Joint Committee on Cancer, LVSI= lymphovascular space invasion, PNI= perineural invasion

pitch of 0.287, and modulation factor of 2.5 were used. Dose calculations were performed using the fine-dose calculation grid (3 mm in the craniocaudal direction over a 256 × 256 matrix in the axial plane from the original CT scan).

Statistics

All statistical analyses were performed using SPSS 20 software (SPSS, Chicago, IL, USA). The results are presented as mean ± standard deviation. Student's t-test and x^2 test were used to analyze the clinical and pathological differences between ETG or STG patients. The primary results of the study were OS and DFS. Time of death or progressions were calculated as the period from the date of diagnosis to the date of death or the date of the first clinical or radiological recurrence. Both OS and DFS were estimated using the Kaplan-Meier method with log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazard model (p value <0.1). Toxicities were scored using CTCAE (common terminoloy criteria for adverse events, version 4.0). All p values were two-sided and p<0.05 was considered statistically significant.

Results

The median follow-up time was 26.7 months (1.3-136.5) and the mean age of the patients was 61 (27-84). There was no difference between the two groups in terms of patient characteristics, except for T stages, N stages, and AJJC stages. While T2, T3 and stage IIA-IIB disease were more common in STG, T4, N3 and stage IIIB-IIIC disease were more common in ETG. Radiotherapy dose and duration (50.4 Gy and 5.4 weeks) were higher in the co-treated group than the sandwich treatment group (45.0 Gy and 5.1 weeks) (Table 2).

Treatment results

OS in both groups (median 30.6 months in the ETG group vs 35.6 months in the STG group; p=0.73) and DFS (median 26.6 months in the ETG group vs STG group 32.5 months; p=0.46) were similar. OS and DFS rates at 2 and 5 years were also similar (Table 2). Disease progression occurred in 91 (61%) of 149 patients (ETG 52 patients 61%; STG 39 patients 60%, p=0.52). Progressions consisted of local metastases in 40 patients (26%), local recurrence in 7 patients (4.6%), and both local recurrence and distant metastasis in 44 patients (29.5%).

Prognostic factors for overall survival and disease-free survival

In the univariate analysis, males were compared to females (42,6 months vs 24,5 months; p=0.006), N0 disease was compared to N1 disease (112.9 months vs 49.1 months; p=0.002), Stage II disease was compared to Stage III disease (60.5 months vs 26.9 months; p=0.002), grade 1-2 disease was compared to grade 3 disease (113.0 vs 28.4 months; p=0.004). All these were significant prognostic factors for OS (Table 3). Similarly, the

Table 2. Treatment characteristics and treatment outcomes

Characteristics	*All patients (n=149)*	*Concurrent (n=85)*	*Sandwich (n=64)*	*p*
Median RT dose, Gy (range)	50.4 (41.4-50.4)	50.4 (41.4-50.4)	45.0 (41.4-50.4)	0.002
RT duration, week (range)	5.3 (4.5-9.7)	5.4 (4.5-9.7)	5.1 (4.5-6.9)	0.004
Concurrent chemotherapy, n (%)				
5-FU	85 (57)	75 (88)	51 (80)	0.17
Capecitabine	64 (43)	10 (12)	13 (20)	
Pre- and/or post-RT chemotherapy, n (%)				
5-FU	69 (47)	55 (65)	14 (22)	0.007
FOLFOX	17 (11)	2 (2)	15 (23)	
XELOX	6 (4)	3 (4)	3 (5)	
CFF	57 (38)	25 (29)	32 (50)	
Median follow-up (months), range	26.7 (1.3-136.5)	24.7 (1.3-65.1)	27.5 (5.2-136.5)	0.25
OS				
Median (months, 95%CI)	30.6 (23.7-37.5)	30.4 (23.7-35.0)	35.6 (26.3-45.0)	0.73
2-year (%)	65.1	64.1	66.4	
5-year (%)	35.7	35.6	35.5	
PFS				
Median (months, 95%CI)	26.6 (21.3-32.0)	24.5 (18.1-31.0)	32.5 (22.2-42.8)	0.46
2-year (%)	53.4	52.4	54.6	
5-year (%)	31.5	31.8	33.1	

same features were also significant factors for DFS (Table 3). There was no significant difference in OS and DFS between the 2 groups (Figure 1 and 2).

In multivariate analysis, female gender (1.76 (1.13-2.76); p=0.01) both stage III and grade 3 disease (2.13 (1.31-3.45; p=0.002) and only grade III disease (2.08 (1.26-3.44; p=0.004) remained significant as negative prognostic factors for OS, In the multivariate assessment for DFS, no significance was found (Table 4).

Toxicity

Overall, 118 patients (87.9%) were able to complete the chemoradiotherapy and adjuvant systemic chemotherapy as planned. There was no significant difference in the treatment compliance between two groups (89.4% in the concurrent arm and 85.9% in the sandwich arm, p=0.41). The median RT dose was significantly higher in the concurrent arm compared to patients treated with sandwich ChT and RT [50.4 Gy (range, 41.4-

Table 3. Results of univariate analysis for overall and progression free survival

Variables	*Median OS (months)*	*p*	*Median PFS (months)*	*p*
Age, years				
>60	44.0	0.12	29.6	0.33
≤60	28.5		24.4	
Gender				
Male	42.6	0.006	32.5	0.009
Female	24.5		21.1	
Tumor location				
GEJ	30.4	0.82	23.3	0.48
Distal of GEJ	44.0		27.8	
Gastrectomy				
Total	31.4	0.47	23.8	0.33
Subtotal	30.6		27.8	
Pathology				
Adenocarcinoma			26.6	0.57
Signet cell carcinoma			23.6	
LN dissection				
D1	28.8	0.50	23.8	0.52
D2	35.8		29.6	
T stage				
T1-2	49.1	0.19	35.4	0.16
T3-4	30.3		23.8	
N stage				
N0	112.9	0.002	60.5	0.01
N1	49.1		42.6	
N2	26.7		23.8	
N3	26.1		19.0	
AJCC stage				
II	60.5	0.002	46.6	0.001
III	26.9		19.3	
PNI				
Negative	36.1	0.13	24.5	0.14
Positive	28.5		23.8	
Grade				
I-II	113.0	0.004	46.6	0.001
III	28.4		19.3	
Concurrent chemotherapy				
5-FU	31.4	0.72	29.6	0.05
Capecitabine	30.4		17.8	

GEJ: gastroesophageal junction

50.4 Gy) vs. 45.0 Gy (range, 41.4-50.4 Gy); p=0.002] (Table 2). Due to higher RT doses delivered in the concurrent arm, the RT duration was also significantly longer compared to sandwich arm [5.4 weeks (range, 4.5-9.7 weeks) vs. 5.1.weeks (range, 4.1-6.9 weeks); p=0.004]. A treatment break due to toxicity was observed in 18 patients (12%) [10 in the concurrent arm (11.7%) and 8 in the sandwich arm (12.3%]. The median treatment break duration was 7 days (range 3-12) in the concurrent arm and 8 days (range 4-11) in the sandwich group.

Acute upper gastrointestinal and hematological toxicity were the most common in both groups. However, grade 3 and above acute upper gastrointestinal and hematological toxicity were more common in ETG (acute upper gastrointestinal toxicity was 19.1% ETG vs 9.0% STG, p=0.01; hematological toxicity 31% in ETG, respectively, 8 vs 13.9% in STG, p=0.002). Grade 4 side effects (thrombocytopenia) were seen in 2.1% of patients. Grade 5 side effects were not reported.

Discussion

In our study, no difference was observed between the two and all treatment methods of both immediate and sandwich patients for the timing of CRT in patients with operated high-risk gastric cancer. However, high grade and advanced stages of the patients were found to have a negative prognostic effect on OS. As the planned treatment schedule for all patients, it was observed that ETG was significantly more toxic in hematological and gastrointestinal system toxicity, but the rates of stopping treatment were similar in both groups. The patients were able to tolerate both treatment modalities easily and 87.9% of the patients were able to complete their treatment. The most effective curative treatment approach for gastric cancer today is surgery [6]. Due to the high recurrence rates and poor prognosis, chemotherapy and chemoradiotherapy have been used in both neoadjuvant and adjuvant periods to improve prognosis and en-

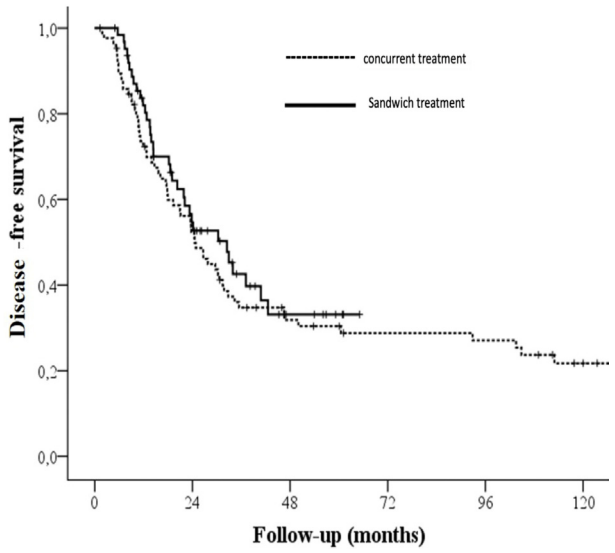

Figure 1. Disease-free survival in the treatment arms (p>0.05).

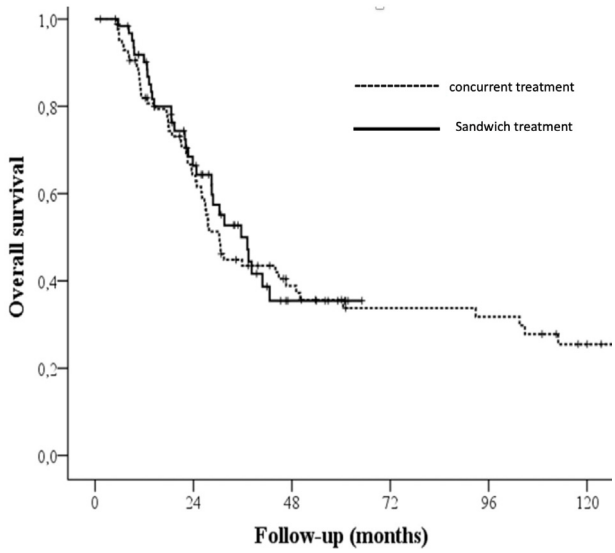

Figure 2. Overall survival for treatment arms (p>0.05).

Table 4. Multivariate analysis

Variables	*Risk factors*	*HR (95% CI)*	*p*
Overall survival			
Gender	Female vs. male	1.76 (1.13-2.76)	0.01
N stage	N(+) vs. N(-)	1.21 (0.58-2.51)	0.42
AJCC stage	III vs. II	2.13 (1.31-3.45)	0.002
Grade	III vs I-II	2.08 (1.26-3.44)	0.004
Progression-free survival			
Gender	Female vs. male	2.86 (0.70-11.6)	0.14
T stage	T3-T4 vs. T1-T2	2.99 (0.63-14.1)	0.17
N stage	N(+) vs. N(-)	2.59 (0.43-15.6)	0.30
AJCC stage	III vs. II	2.13 (0.56-8.1)	0.27

sure long survival in the last 30 years [7-11]. Local recurrence of up to 80% in patients with operated gastric cancer has been the basis for the idea of using radiotherapy in these patients [12]. However, today there is no clarity regarding the timing of radiotherapy in the treatment of gastric cancer. In our study, it was shown that the application of the CRT timing by the immediate or sandwich method did not cause any difference between the groups in OS and DFS (p=0.73). However, when the groups were analyzed in more detail, it was seen that immediate CRT patients group included more T4, N3 and more advanced disease. Therefore, it was thought that there could be no survival difference between groups in these patients.

Intergroup 0116 (INT0116) study is a landmark study, investigating the effect of adding chemoradiotherapy to postoperative chemotherapy in operated gastric cancer patients [4,13]. In this study simultaneous chemoradiotherapy against surgery was compared in 556 stage IB-IV, M0 patients. The median OS in the surgery group was 27 months and 36 months in the postoperative chemoradiotherapy group and the difference was statistically significant. In this study, the third year OS (50% vs 41%) and recurrence-free survival rates (48% vs 31%) were found better in the STG. While distant metastasis rates were similar, regional recurrence was less common in the chemoradiotherapy arm. There was also a 10% reduction in local recurrence [13]. In our study, DFS was 26.6 months in all patient groups, while it was 24.5 months in the concurrent treatment group and 32.5 months in the sandwich treatment group, but the difference was not statistically significant (p=0.46). Median OS was 30.6 months, which is similar to the literature data. This period was calculated as 35.4 months in the sandwich treatment group and 30.4 months in the OS group. Despite the 5-month advantage, the difference was not statistically significant. We think that in a series where the number of patients is higher, the difference will be more likely to be significant. In univariate analysis, male gender, stage II disease, lymph node negative disease and grade 1-2 disease were seen as significant factors in terms of OS. Despite the promising results of chemoradiotherapy, negative consequences such as high toxicity and high early termination of treatment have also been reported [4,14,15]. In some retrospective studies, high toxicity rates of up to 46.4% have been reported [16]. In a study from Brazil, the proportion of patients who completed adjuvant chemoradiotherapy was only 51% [17]. In this study, there was a significant difference in survival compared to the group who could not complete the treatment. Therefore, the need to reduce treatment-related toxicity has emerged. In the INT0116 study, 17% of the patients could not complete their treatments due to grade 3-4 toxicity (hematological 54%, gastrointestinal 33%). In our study, the most common toxicities were acute upper gastrointestinal and hematological. Gastrointestinal toxicity was statistically significantly higher in ETG than STG (18% vs 8.6%, p=0.01, respectively), and hematological toxicity was similarly detected in ETG (32.2% vs 13%, p=0.002). However, due to toxicity, 10 patients in ETG and 8 patients from STG had to discontinue treatment. It was thought that the reason for the higher toxicity in ETG may be due to higher median RT doses than ETG (50.4 Gy vs 45 Gy; p=0.002). However, both treatment schemes were tolerable by the patients. It was found that only 12.1% of patients had to stop the treatment during the treatment period and the rate of early cessation was higher in ETG (13% vs 9%, p=0.59). Therefore, it was thought that the sandwich treatment may be a more tolerable treatment for patients. Based on the INT0116 study, while postoperative chemoradiotherapy is considered as the standard treatment in the USA, this idea has not been widely accepted in Europe due to its high toxicity [4,18]. The European's negative opinion regarding chemoradiotherapy was supported in the Dutch D1D2 study based on the fact that chemoradiotherapy could not be demonstrated in patients with D2 dissection [19]. In the Phase 3 ARTIST study, postoperative chemotherapy after D2 dissection and chemoradiotherapy were not different in terms of recurrence [20,21]. In a retrospective analysis investigating surgical and postoperative fluoroprimidine-based chemoradiotherapy treatments alone, the recurrence rate was only 8% in patients who received D1 dissection, whereas D1 was found to be 2% in the group treated after dissection (p=0.001). However, the same effect was not seen in patients undergoing D2 dissection [19]. In our study, 26% (n=40) distant metastases, 29.5% (n=44) both local recurrence and distant metastasis were observed in the entire patient group. Local recurrence and distant metastasis were observed in 18% in the simultaneous treatment group and 17.2% in the sandwich treatment group. There was no difference between the two treatments in terms of distant metastasis and local recurrence. In our study, D2 dissection had an advantage in terms of OS and DFS, but the difference did not reach statistical significance. Adjuvant chemoradiotherapy with or without chemotherapy has been compared with chemotherapy alone in many studies [20,22-28]. Only one of these studies demonstrated significant OS benefit of adding radiotherapy to chemotherapy [25]. In the meta-analysis of 6 studies comparing direct chemoradiotherapy and chemotherapy,

chemoradiotherapy was significantly associated with higher 5-year DFS and lower locoregional recurrence [22,23]. However, there was no significant difference in terms of OS. Other randomized and non-randomized data suggest that postoperative chemoradiotherapy can potentially benefit even after optimal D2 dissection [20,21,24,29]. There are many publications demonstrating the advantage of postoperative chemoradiotherapy over surgery alone after D2 dissection. Kim and colleagues demonstrated the survival advantage of simultaneous chemoradiotherapy in the study in which they evaluated the role of postoperative chemoradiotherapy compared to surgery alone after D2 dissection [29]. It is recommended to consider chemoradiotherapy rather than chemotherapy in the adjuvant period in certain patient groups with operated gastric cancer [30].

To the best of our knowledge there is no study comparing different chemoradiotherapy schemes. There is a study comparing chemotherapy and sandwich chemoradiotherapy in patients with unresectable locally advanced gastric cancer which reported that there was a significant increase in OS with sandwich therapy [14]. In a phase 2 study in which sequential chemotherapy and chemoradiotherapy were used as neoadjuvant, 40% pathological complete response was obtained [15].

In the present study, we compared 2 different chemoradiotherapy applications and shared their results which is a gap field in the treatment of gastric cancer.

The negative aspects and limitations of our study are that this was a retrospective study, differences due to the radiotherapy applications with two different techniques (3DRT,IMRT), late toxicity data couldn't be obtained, different chemotherapy schemes were applied, it was a single center experience and the number of patients was not sufficient. In conclusion, adjuvant chemoradiotherapy is an effective strategy compared to surgery alone in patients with locally advanced gastric cancer. Although more advanced stage patients were included in the ETG, similar survival results were obtained with STG. However, according to the data of our study, it was thought that sandwich therapy may still be a more appropriate choice for less toxicity and better DFS and OS results. Larger patient series and prospective studies are needed to confirm this claim.

Ethics

The study protocol was reviewed and approved by our Institutional Ethics Committee before collection of patients' data.

Conflict of interests

The authors declare no conflict of interests.

References

1. .Siegel RL, Miller KD, Jemal A. Cancer statistics,2018. CA Cancer J Clin 2018;68:7-30.
2. Ochenduszko S, Puskulluoglu M, Konopka K et al. Clinical effectiveness and toxicity of second line irinotecan in advanced gastric and gastroesophageal junction adenocarcinoma: a single center observational study. Ther Adv Med Oncol 2017;9:223-33.
3. Gunderson LL. Gastric cancer patterns of relapse after surgical resection. Semin Radiat Oncol 2002;12:150-61.
4. McDonald JS, Smalley SR, Benedetti Ji et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001:345:725-30.
5. Benevento I, Bulzonetti N, De Felice F, Musio D, Vergine M, Tombolini V. The role of different adjuvant therapies in locally advanced gastric adenocarcinoma. Oncotarget 2018;9:34022-29.
6. Norero E, Vargas C, Achurra P et al. Survival and perioperative morbidity of totally laparoscopic versus open gastrectomy for early gastric cancer: analysis from a single latin american centre. Arq Bras Cir Dig 2019;32:e1413.
7. Choi YY, Noh SH, Cheong JH. Evolution of Gastric Cancer Treatment: From the Golden Age of Surgery to an Era of Precision Medicine. Yonsei Med J 2015;56:1177-85.- doi: 10.3349/ymj.2015.56.5.1177.
8. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean Practice Guideline for Gastric Cancer 2018: an Evidence-based, Multi-disciplinary Approach. J Gastric Cancer 2019;19:1-48.
9. van Hagen P, Hulshof MC, van Lanschot JJ et al. CROSS Group. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
10. Orditura M, Galizia G, Sforza V et al. Treatment of gastric cancer. World J Gastroenterol 2014;20:1635-49.- doi: 10.3748/wjg.v20.i7.1635.
11. Xu J, Zhu J, Wei Q. Adjuvant radiochemotherapy versus chemotherapy alone for gastric cancer: Implications for target definition. J Cancer 2019;10:458-66.

12. Gunderson LL, Sosin H. Adenocarcinoma of the stomach areas of failure in a reoperation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1982;8:1-11.
13. Smalley SR, Benedetti JK, Haller DG et al. Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 2012;30:2327-33.
14. Wei-Bin Z, Xin-Sheng Z, Zhen F, Yun-Fei W, Chun-Yu Q, Bin Z. Comparison of clinical efficacy between two treatments in locally advanced gastric cancer with unresectable factors: chemotherapy and sequential chemoradiotherapy combined with radiotherapy and chemotherapy. Int J Clin Exp Med 2019;12:6140-5.
15. Hyo Song K, Woong Sub K, Song-Ee B, Hyoung-Il K, Minkyu J, Seung-Hoon B. Phase II trial of preoperative sequential chemotherapy followed by chemoradiotherapy for high-risk gastric cancer. Radiother Oncol 2019:140:143-49.
16. Kundel Y, Purim O, Idelewich E et al. Postoperative chemoradiation for resected gastric cancer: is MacDonald regimen tolerable? A retrospective multi-istitutional study. Radiat Oncol 2011;6:127.
17. Andreollo NA, Drizlionoks E, Tercioti-Junior V et al. Adjuvant chemoradiotherapy after subtotal or total gastrectomy and D2 lympadenectomy increases survival in advanced gastric cancer ? Arq Bras Cir Dig 2019;32:e1464.
18. Smyth EC, Verheij M , Allum W et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27 (Suppl 5):v38-v49.
19. Dikken JL, Jansen EP, Cats A et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. J Clin Oncol 2010;28:2430-6.
20. Park SH, Sohn TS, Lee J et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. J Clin Oncol 2015;33:3130-6.
21. Lee J, Lim DH, Kim S et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012;30:268-73.
22. Cats A, Jansen EPM, van Grieken NCT et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018;19:616-28.
23. Verheij M, Janhsen PM, Cats A, et al.. A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer. First result from the CRITICS study. J Clin Oncol 2016;34 (suppl, abstr 4000).
24. Zhu WG, Xua DF, Pu J et al. A randomized controlled multicenter study comparing intensity-modulated radiotherapy plus concurrent chemoradiotherapy alone in gastric cancer patients with D2 resection. Radiother Oncol 2012;104:361-6.
25. Yu C, Yu R, Zhu W et al. Intensity modulated radiotherapy combined with chemotherapy for the treatment of gastric cancer patients after standard D1/D2 surgery. J Cancer Res Clin Oncol 2021;138:255-59.
26. Kim TH, Park SR, Ryu KW et al. Phase 3 trial of postoperative chemotherapy alone versus chemoradiation therapy in stage III-IV gastric cancer treated with RO gastrectomy and D2 lymph node dissection. Int J Radiat Oncol Biol Phys 2012;84:e585-92.
27. Kwon HC, Kim MC, Kim KH et al. Adjuvant chemoradiation versus chemotherapy in completely resected advanced gastric cancer with D2 nodal dissestion. Asian Pas J Clin Oncol 2010:6:278-85.
28. Bamias A, Karina M, Papakostas P et al. A randomized phase III study of adjuvant platinum/docetaxel chemotherapy with or without radiation therapy in patients with gastric cancer. Cancer Chemother Pharmacol 2010:65:1009-21.
29. Kim S, Lim DH, Lee J et al. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 2005;63:1279-85.
30. Cainap C, Vlad C, Seican A et al. Gastric cancer: adjuvant chemotherapy versus chemoradiation. A clinical point of view. JBUON 2019;24(6):2209-2219.