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Comparison of neoadjuvant versus upfront surgery for treatment of locally advanced gastric cancer

OBJECTIVE: *In this study, we aimed to compare long term oncological outcomes of upfront surgery versus neoadjuvant treatment in patients with locally advanced gastric cancer.*
METHODS: *A total of 183 patients who were operated for gastric cancer were retrospectively analyzed. The patients received either standard gastrectomy or preoperative NACT + gastrectomy. Neoadjuvant therapy was administered with FLOT regimen (docetaxel, oxaliplatin, fluorouracil, and leucovorin) or DCF regimen (docetaxel, cisplatin, and 5-fluorouracil).*
RESULTS: *Of the patients receiving NACT, 33 received FLOT regimen and 14 received DCF regimen. The number of male patients was higher in both standard gastrectomy and NACT + gastrectomy groups (p=0.385). Leukopenia and neutropenia were the most common hematological toxicities, while anemia and nausea were the most frequent non-hematological side effects in the both of NACT group. The outcomes of the grades of postoperative complications according to the Clavien-Dindo classification is similar between groups. There was no statistically significant difference in the length of hospital stay after surgery between the groups (p=0,001). According to the disease stage, it was found no statistically significant difference in the OS and DFS between the NACT and standard gastrectomy groups.*
CONCLUSION: *Although we found no significant difference between the patients undergoing standard gastrectomy and those undergoing NACT before gastrectomy, we believe that NACT may contribute to the favorable prognosis of patients with locally advanced disease with improved OS and DFS and this should be examined in future studies.*

KEY WORDS: FLOT, Gastric Cancer, Neoadjuvant Treatment

Introduction

Gastric cancer is the fifth most common cancer and is the third leading cause of cancer-related mortality worldwide [1]. Nearly one million individuals are newly diagnosed with gastric cancer worldwide annually and it is two-fold higher in men than women [1,2]. Despite diagnostic and therapeutic developments, the five-year overall survival (OS) is 20 to 30% in resectable gastric cancer [3]. However, survival rate increases up to 70% in Japan and Far Eastern countries, which can be attributed to thorough screening programs, early diagnosis, and the utilization of extended D2 lymph node dissection combined with gastrectomy in these countries [3]. In recent years, D2 lymph node dissection has been shown to decrease local recurrence and reduce cancer-related mortality in Europe [4]. In two studies conducted in Italy, gastrectomy combined with D2 lymph node dissection significantly improved the OS in patients with gastric cancer [5,6].
Although there is a number of genetic and histological subtypes of gastric cancer, radical gastrectomy is still the

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only curative treatment method for all types [7]. Nearly one-third of all gastric cancers are reported as locally advanced in European studies [8]. Therefore, neoadjuvant chemotherapy (NACT), either preoperatively or perioperatively, has been recently recommended by many referral centers [9]. The initial findings of NACT in locally advanced, unresectable gastric cancer were first reported by Wilke et al [10] in 1989. The authors found NACT consisting of etoposide, doxorubicin, and cisplatin to be highly effective in this group of patients. The main goals of preoperative NACT are to reduce disease stage, increase the chance for surgery with curative intention, remove micrometastatic tumor cells, evaluate treatment response, and improve the OS rate. Based on the favorable results of randomized-controlled studies, the NACT has become a standard treatment modality in locally advanced gastric cancer in the Western and Far Eastern countries [11-15].

In the present study, we aimed to compare long-term oncological outcomes of gastric cancer patients undergoing gastrectomy receiving and not receiving preoperative NACT.

Materials and Methods

This retrospective study was conducted in the single-center at the Department of General Surgery between January 2011 and December 2020. A total of 222 patients who were operated for gastric cancer were evaluated. Of these patients, 16 who had short-follow-up data and 23 who received NACT using different protocols were excluded. Of a total of 183 patients included in this study, 136 underwent standard gastrectomy and 47 underwent preoperative NACT and gastrectomy. Thirty-three patients received FLOT regimen, while 14 patients received DCF regimen. The study flow chart is shown in (Fig. 1).

Data including demographic and clinical characteristics of the patients, type of medical and surgical treatment, pathological examination results, and early- and long-term survival data (OS and disease-free survival [DFS]) were retrieved from the hospital database. Diagnosis and staging were performed in all patients preoperatively. The diagnosis was initially made based on endoscopic findings and then confirmed by pathological examination. Staging was performed using endoscopic ultrasound (EUS), computed tomography (CT), or magnetic resonance imaging (MRI). In selected cases, positron emission tomography (PET)/CT was used. Staging was made based on the 3rd English Edition of the Japanese Classification of Gastric Carcinoma [16].

The upfront surgery was administered for gastric cancer without locally and distant metastasis. Neoadjuvant therapy was administered with FLOT regimen consisting of docetaxel, oxaliplatin, fluorouracil, and leucovorin or DCF regimen consisting of docetaxel, cisplatin, and 5-fluorouracil.

Neoadjuvant therapy was given to the patients with clinical ≥T2 stage with pathological lymph node positivity without distant metastasis (liver, lung or bone). Following neoadjuvant therapy, the treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [17]. Pathological examination of the treatment response was performed using the gastrectomy specimens using the Japanese

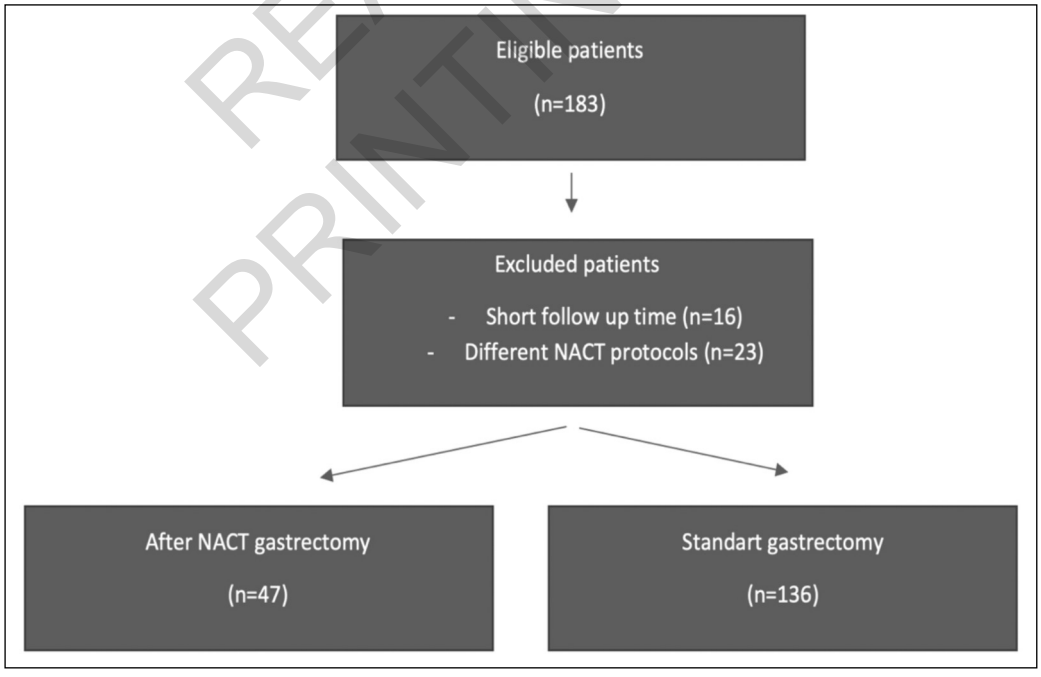

Fig. 1: Study flow chart.

Classification of Gastric Carcinoma criteria [18] and graded between 0 and 3 according to the necrosis in the tumor mass and treatment response. In our study, pathological complete response was graded as 0-1a, while treatment response was graded as 1b, 2 and 3.
Treatment-related side effects were classified into two main groups as hematological and non-hematological toxicities and assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [19]. Depending on the location of the gastric tumor, total or subtotal gastrectomy combined with D2 lymph node dissection was performed in accordance with the 5th Edition of the Japanese Gastric Cancer Treatment Guidelines [20].
Roux-en-Y reconstruction was employed in all cases. The Clavien-Dindo classification [19] was used to assess postoperative complications. After discharge, all patients were scheduled for follow-up every two weeks for the first month and every month thereafter. All patients underwent intravenous contrast-enhanced abdominal CT every three months. The patients with a suspicion of recurrence or distant metastasis underwent upper gastrointestinal endoscopy and PET/CT.
A written informed consent was obtained from each patient. The study protocol was approved by the Institutional Review Board (2021.058.IRB2.008). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows version 25.0 software (IBM Corp, Armonk,

Table I - *Demographic and clinical data of patients.*

Variable	Standard gastrectomy n (%)	NACT + gastrectomy FLOT regimen n (%)	NACT + gastrectomy DCF regimen n (%)	*P*-value
Sex, n (%)				0,385
Male	91 (66,9)	25 (75,7)	10 (71,4)	
Female	45 (33,08)	8 (24,2)	4 (28,5)	
Age, year				0,009
median	63,0	63,0	52,0	
range (min-max)	31-90	37-83	29-73	
BMI, kg/m^2				0,031
median	26,29	25,9	23,9	
range (min-max)	15,2-52,03	15,05-55,51	16,0-34,6	
Histological subtype, n (%)				0,257
Differentiated adenocarcinoma	121 (88,9)	30 (90,9)	13 (92,85)	
Signet-ring cell carcinoma	15 (11,02)	3 (9,09)	1 (7,14)	
Tumor stage, n (%)				0,054
T3	42 (30,88)	16 (48,48)	8 (57,1)	
T4	26 (19,11)	17 (51,51)	6 (42,8)	
Lymph node involvement, n (%)				0,235
N0	102 (75)	4 (12,12)	1 (7,1)	
N1	34 (25)	24 (72,72)	12 (85,7)	
N2	0	5 (15,1)	1 (7,1)	
TNM stage, n (%)				0,012
3	70 (51,4)	30 (90,9)	10 (71,4)	
4	5 (3,67)	3 (9,09)	4 (28,5)	

NACT: neoadjuvant chemotherapy; FLOT: docetaxel, oxaliplatin, fluorouracil, and leucovorin; DCF: docetaxel, cisplatin, and 5-fluorouracil; BMI: body mass index; TNM: Tumor, Node, Metastasis.

TABLE II - *Clinical and pathological results of gastrectomy.*

Variable	Standard gastrectomy n (%)	NACT + gastrectomy FLOT regimen n (%)	NACT + gastrectomy DCF regimen n (%)	*P*-value
Tumor location, n (%)				0,225
Cardia	36 (26,47)	5 (15,1)	4 (28,5)	
Proximal	25 (18,38)	11 (33,3)	5 (35,7)	
Distal	74 (54,41)	15 (45,4)	5 (35,7)	
Linitis plastica	1 (0,73)	2 (6,06)	0	
Type of gastrectomy, n (%)				0,755
Total	102 (75)	30 (90,9)	12 (85,7)	
Subtotal	34 (25)	3 (9,09)	2 (14,2)	
T stage, n (%)				0,357
T0	5 (3,67)	4 (12,1)	0	
T1	33 (24,26)	4 (12,1)	2 (14,2)	
T2	15 (11,02)	5 (15,1)	1 (7,14)	
T3	26 (19,11)	10 (30,3)	5 (35,7)	
T4	57 (41,91)	10 (30,3)	3 (21,4)	
Lymph node involvement, n (%)				0,287
N0	44 (32,35)	17 (51,5)	4 (28,5)	
N1	26 (19,11)	5 (15,1)	2 (14,2)	
N2	24 (17,64)	4 (12,1)	4 (28,5)	
N3	42 (30,88)	7 (21,2)	4 (28,5)	
Number of lymph nodes dissected, n, median (range)	34 (9-94)	37 (21-75)	31 (16-52)	0,541
Treatment response				0,843
Grade 0		4 (12,1)	0	
Grade 1		6 (18,1)	1 (7,14)	
Grade 2		10 (30,3)	3 (21,4)	
Grade 3		13 (39,3)	10 (71,4)	

NACT: neoadjuvant chemotherapy; FLOT: docetaxel, oxaliplatin, fluorouracil, and leucovorin; DCF: docetaxel, cisplatin, and 5-fluorouracil.

TABLE III - *Postoperative complications.*

Complication	Standard gastrectomy n (%)	NACT + gastrectomy FLOT regimen n (%)	NACT + gastrectomy DCF regimen n (%)
Intraabdominal bleeding	2 (1,47)	2 (6,06)	2 (14,28)
Wound infection	6 (4,41)	0	1 (7,14)
Pulmonary infection	15 (11,02)	6 (18,1)	2 (14,28)
Intraabdominal infection	8 (5,88)	1 (3,03)	0
Anastomotic leak	3 (2,2)	4 (12,1)	0
Pancreatic fistula	1 (0,73)	1 (3,03)	0
Renal failure	0	0	0
Heart/respiratory failure	2 (1,47)	1 (3,03)	0
Redo surgery	5 (3,67)	5 (15,1)	1 (7,14)
Mortality	0	1 (3,03)	0

NACT: neoadjuvant chemotherapy; FLOT: docetaxel, oxaliplatin, fluorouracil, and leucovorin; DCF: docetaxel, cisplatin, and 5-fluorouracil.

TABLE IV - *Grades of postoperative complications according to the Clavien-Dindo classification*

Clavien-Dindo Classification	Standard gastrectomy n (%)	NACT + gastrectomy FLOT regimen n (%)	NACT + gastrectomy DCF regimen n (%)
Grade 1	34 (25)	1 (3,03)	1 (7,1)
Grade 2	12 (8,82)	7 (21,2)	3 (21,4)
Grade 3	9 (6,61)	7 (21,2)	2 (14,2)
Grade 4	0	0	0
Grade 5	0	0	0

NACT: neoadjuvant chemotherapy; FLOT: docetaxel, oxaliplatin, fluorouracil, and leucovorin; DCF: docetaxel, cisplatin, and 5-fluorouracil.

TABLE V - *Side effects related to FLOT regimen.*

Side effect	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)
Leukopenia	3	3	0	2	0	24,2%
Neutropenia	2	2	0	3	0	21,21%
Febrile neutropenia	0	1	0	0	0	3,03%
Anemia	1	3	1	3	0	24,2%
Thrombocytopenia	1	0	0	1	0	6,06%
Nausea	0	3	1	5	1	30,3%
Cachexia	0	0	0	2	0	6,06%

Data are given in number and percentage, unless otherwise stated.

TABLE VI - *Side effects related to DCF regimen.*

Side effect	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total (%)
Leukopenia	3	1	0	1	0	35,7%
Neutropenia	1	0	0	1	0	14,2%
Febrile neutropenia	0	0	0	0	0	0%
Anemia	0	2	2	0	1	35,7%
Thrombocytopenia	1	0	0	0	0	7,14%
Nausea	1	0	1	2	1	35,71%
Cachexia	0	0	0	0	0	0%

Data are given in number and percentage, unless otherwise stated.

NY, USA). Descriptive data were expressed in median (min-max) for continuous variables and in number and frequency for categorical variables. The Shapiro-Wilk test was used to assess the distribution of continuous variables. For comparison of two normally distributed variables, the Student *t*-test was used. The Mann-Whitney U test was used to compare between two non-normally distributed cotinuous variables. The Kaplan-Meier analysis was performed to analyze OS and DFS rates. A *p* value of <0.05 was considered statistically significant.

Results

Demographic And Clinical Characteristics Of The Patients

The number of male patients was higher in both standard gastrectomy and NACT + gastrectomy groups (p=0.385). The median age were 63,0 (31-90), 63,0 (37-83) and 52 (29-73) in upfront gastrectomy, NACT+ gastrectomy (FLOT regimen), NACT +gastrectomy (DCF regimen) respectively (p=0.009). There was no observed a statistically significant difference in clinical data. Demographic and clinical data of all patients are summarized in (Table I).

Clinical And Pathological Results Of Gastrectomy

The number of patients with distal tumors was higher in both patient groups receiving standard gastrectomy and preoperative NACT + gastrectomy (p= 0,225). No distal or proximal margin involvement was observed in any of the patients after surgery.
There was no observed a statistically significant difference in the clinical and pathological results of gastrectomy. Clinical and pathological results of gastrectomy are presented in (Table II).

Postoperative Complications

In the standard gastrectomy group, anastomotic leak was seen in three patients (2.2%) and intraabdominal bleeding in the early postoperative period in two patients (1.47%). In the FLOT group, anastomotic leak was seen in four (12.1%), intraabdominal bleeding in two (6,06), subdural hematoma in one (3.03%), and pleural bleeding in one patient (3.03%). In the DCF group, intraabdominal bleeding was seen in two patients (14.8%). Data on postoperative complications are listed in (Table III). Grades of postoperative complications according to the Clavien-Dindo classification are shown in (Table IV).
The median day on length of hospital stay were 9,7 (5-34), 12,5 (6-45) and 8,1 (5-15) in upfront gastrectomy, NACT+ gastrectomy (FLOT regimen), NACT +gastrectomy (DCF regimen) respectively (p=0.001).

Side Effects

Side effects related to FLOT and DCF regimens are shown in (Table II and Table III), respectively. Leukopenia and neutropenia were the most common hematological toxicities (Grade 0,1,2,3,4) in the patients receiving FLOT regimen (24.2% *vs.* 21.21%, respectively). Among these patients, only one patient (3.03%) had Grade 1 febrile neutropenia treated with antibiotherapy. This patient was unable to complete preoperative NACT. Anemia and nausea were the most frequent non-hematological side effects in the patients receiving FLOT regimen (24.2% and 30.3%, respectively). In the DCF group, leukopenia and neutropenia were the most common hematological toxicities (grade 0,1,2,3,4) 35.7% and 14.2%, respectively. Anemia and nausea were seen in 35.7% and 35.71%, respectively of the patients receiving DCF regimen. All patients in this group completed treatment. No treatment-related mortality was observed in any of the patients. The side effects of NACT are shown in (Tables VI).

Table VII - *Pathological grades after gastrectomy.*

pTNM stage	Standard gastrectomy n (%)	NACT + gastrectomy FLOT regimen n (%)	NACT + gastrectomy DCF regimen n (%)
0	5 (3,67)	3 (9,09)	0
1 (1a+1b)	33 (24,26)	9 (27,27)	2 (14,28)
2 (2a+2b)	14 (10,29)	5 (15,15)	3 (21,42)
3 (3a+3b+3c)	84 (61,76)	16 (48,48)	9 (64,2)

pTNM: post-neoadjuvant pathological stage; NACT: neoadjuvant chemotherapy; FLOT: docetaxel, oxaliplatin, fluorouracil, and leucovorin; DCF: docetaxel, cisplatin, and 5-fluorouracil.

TABLE VIII - *OS rates according to disease stage.*

pTNM stage	Follow-up duration of standard gastrectomy group, month, median (range)	OS of standard gastrectomy group, (%)	Follow-up duration of NACT + FLOT group, month, median (range)	OS of NACT + FLOT group, %	p
0	36 (34-49)	100%	38 (37-40)	100%	-
1 (1a+1b)	55 (19-118)	90,3%	28 (12-40)	100%	0,514
2 (2a+2b)	47 (19-95)	78,6%	23 (13-37)	80,0%	0,546
3 (3a+3b+3c)	45 (10-117)	58,9%	20 (5-40)	77,8%	0,941

pTNM: pathological stage; NACT: neoadjuvant chemotherapy; FLOT: docetaxel, oxaliplatin, fluorouracil, and leucovorin; DCF: docetaxel, cisplatin, and 5-fluorouracil; OS: overall survival; DFS: disease-free survival.

TABLE IX - *DFS rates according to disease stage.*

pTNM stage	Follow-up duration of standard gastrectomy group, month, median (range)	DFS of standard gastrectomy group, (%)	Follow-up duration of NACT + FLOT group, month, median (range)	DFS of NACT + FLOT group, %	p
0	36 (34-49)	100%	38 (37-40)	100%	-
1 (1a+1b)	55 (19-118)	96,8%	28 (12-40)	100%	0,648
2 (2a+2b)	47 (19-95)	92,9%	23 (13-37)	100%	0,254
3 (3a+3b+3c)	45 (10-117)	89,0%	20 (5-40)	66,7%	<0,001

pTNM: pathological stage; NACT: neoadjuvant chemotherapy; FLOT: docetaxel, oxaliplatin, fluorouracil, and leucovorin; DCF: docetaxel, cisplatin, and 5-fluorouracil; OS: overall survival; DFS: disease-free survival.

Survival analysis

In the DCF group, survival analysis was unable to be performed due to the small sample size according to disease staging. The patients receiving FLOT regimen as NACT and those receiving standard gastrectomy were compared. The median follow-up was 45 (range, 10 to 117) months and 20 (range, 5 to 40) months in the patients with Stage 3 disease receiving standard gastrectomy and post-NACT gastrectomy, respectively. Accordingly, between groups, there was no statistically significant difference in the OS in stage 3 locally advanced gastric cancer. The OS rates varied from 58.9% to 77.8% in this group (p<0.941). The DFS rates varied from 89.0% to 66.7% in the patients with Stage 3 disease (p<0.001). Pathological grades after gastrectomy and OS and DFS rates according to disease stage are shown in (Table VII and IX) respectively.
Comparison of OS and DFS according to disease stage are depicted in (Figs. 2, 3), respectively.

Discussion

Treatment of gastric cancer requires a multidisciplinary approach considering the disease stage, surgical indica-

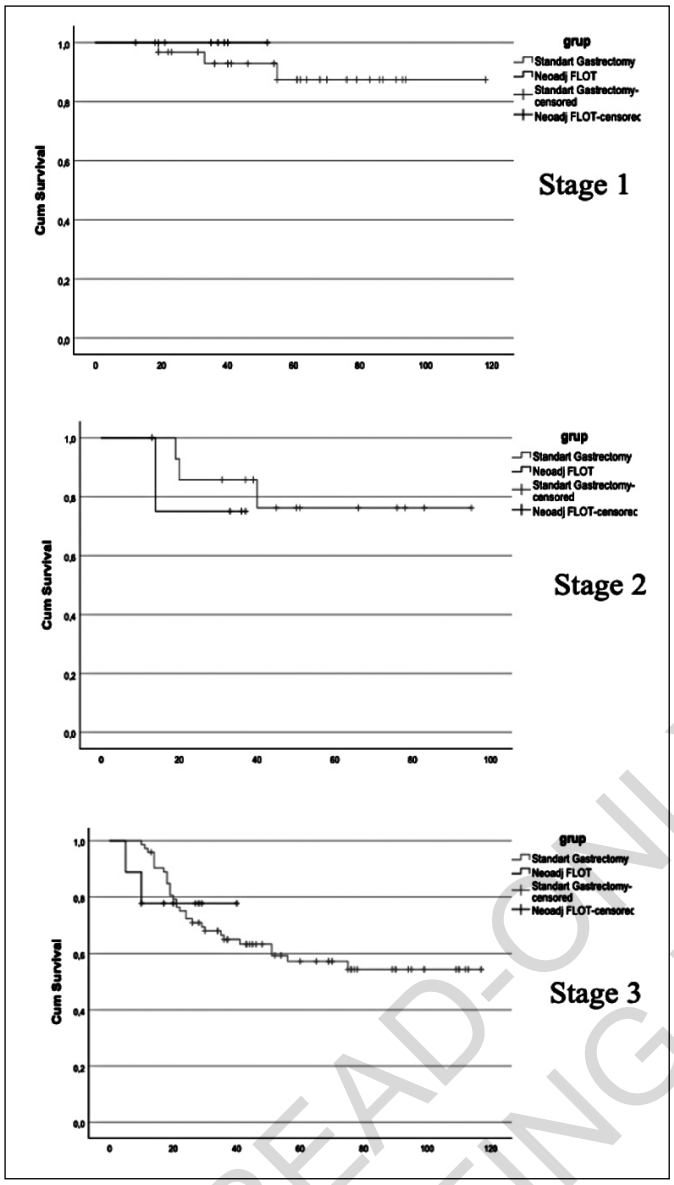

Fig. 2: Comparison of OS according to disease stage.

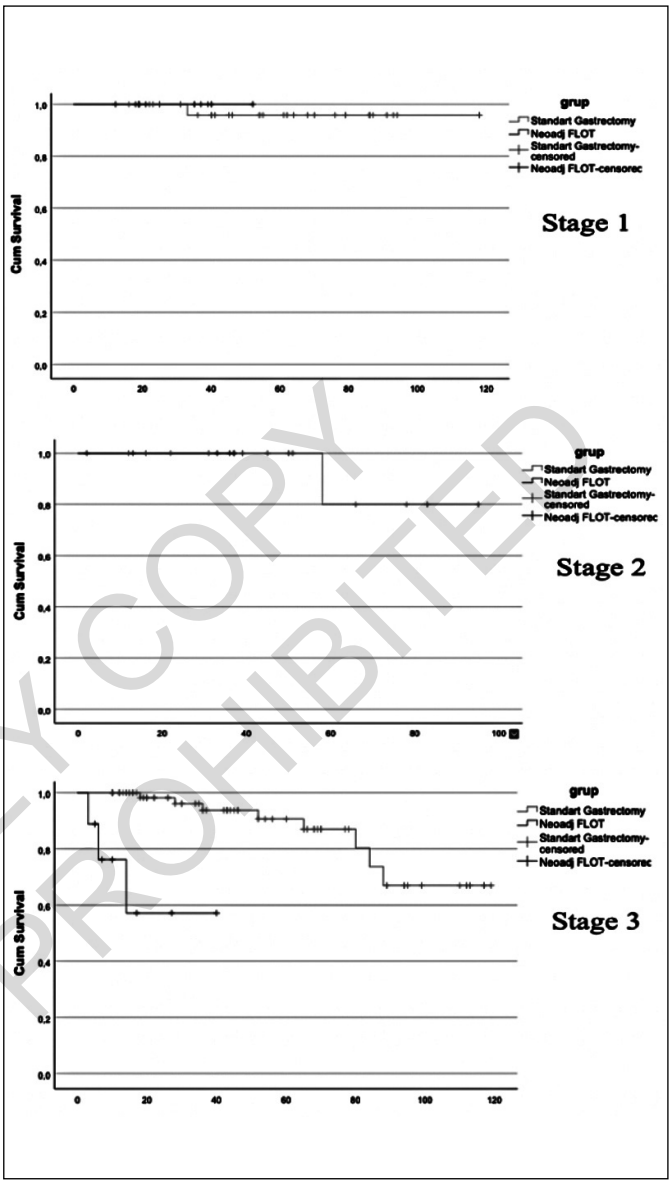

Fig. 3: Comparison of DFS according to disease stage.

tion, comorbidities, and patient preference. A study including 463 patients in Italy confirmed the dismal prognosis of GC and the need to increase the diagnosis of early gastric cancer [21]. In addition, irrespective of the disease stage, gastrectomy can be completed with minimally invasive techniques [22]. In advanced disease (Stage 1B-3C), gastrectomy can be performed after pre-/perioperative NACT or chemoradiotherapy (CRT). Adjuvant chemotherapy and CRT after gastrectomy have been shown to improve survival in patients receiving no NACT [23].

Previous studies have demonstrated that preoperative NACT has advantages compared to postoperative chemotherapy [24]. Patient compliance is higher with NACT than adjuvant chemotherapy, and NACT increases the chance of R0 resection, prevents early micrometastasis, and allows for evaluation of treatment response in the *in vivo* setting [13,23]. Similarly, in the present study, we observed that pathological stage was downstaged from T4 to T1 in four patients, and from T3 to T1-T0 in three patients in the patients receiving FLOT regimen. The pathological stage was downstaged from T3 to T1 in two patients receiving DCF regimen. Due to downstaging, R0 resection can be done in a safer fashion in patients with advanced stage disease.

On the other hand, NACT has several side effects similar to neoadjuvant chemotherapy. The most common hematological side effects are neutropenia (25 to 53%), leukopenia (16.9 to 30%), and febrile neutropenia (6.3 to 20%) with the DCS regimen consisting of docetaxel, cisplatin, and S-1 [25,26]. In patients receiving four cycles of FLOT regimen, leukopenia Grade 3, 4 in one

patient (3.2%), neutropenia Grade 3,4 in two patients (6.5%), and febrile neutropenia Grade 0,1,2 in 31 patients (100%), while leukopenia Grade 0,1,2 in 24 patients (100%), neutropenia grade 3,4 in two patients (8.3%), and febrile neutropenia grade 3,4 in one patient (4.2%) were the most common side effects of chemotherapy of oxaliplatin combined with S-1 (SOX) regimen consisting of tegafur, gimeracil, oteracil potassium capsules plus oxaliplatin [27]. Consistent with previous findings, the current study has acceptable side effects of NACT.

Standard gastrectomy combined with D2 lymph node dissection after NACT has been shown to be associated with the increased complication rate. In particular, the complication rate varies between 18.6 to 31.3% in patients receiving DCS regimen [25,26]. In our study, the complication rate according to the Clavien-Dindo classification Grade 3-5 was 6.61% after standard gastrectomy, 21.2% after FLOT regimen, and 14.2% after DCF regimen, indicating no statistically significant difference. Another study showed that according to the Clavien-Dindo classification Grade 3 or higher, the complication rate was 28% following standard gastrectomy [28]. The high complication rates can be attributed to the fact that all patients had a locally advanced disease in our study. Several studies have shown that DCS regimen as NACT has a high pathological response (71.2 to 87.5%) and three-year OS (88%) [25,26]. For NACT administration, SOX and XELOX (oxaliplatin plus capecitabine) have been also used in Japanese and Far Eastern Asian populations which allow for the chance of surgery with curative intention with favorable pathological and radiological responses in locally advanced cancer patients [29,30]. The pathological response rate has been reported as 67.7% after FLOT regimen (tumor regression grade [TRG] Grade 1+2) [27]. Similarly, the pathological response was achieved after FLOT regimen in 60.5% of the patients in our study (TRG: 0+1+2).

Thanks to its favorable effects, the NACT has been widely adopted as a standard treatment modality in locally advanced cancer in some Western and Far Eastern countries for many years (12,13,23,31,32). In the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, the five-year OS increased from 23% to 36% in patients with Stage 2-3 gastric cancer who received six cycles of ECF regimen consisting of epirubicin, cisplatin, and 5-fluorouracil (three cycles preoperative and three cycles postoperative), compared to chemotherapy-naïve patients who underwent isolated gastrectomy [23]. In addition, in a randomized-controlled study investigating the efficacy and safety of FLOT versus ECF/ECX (epirubicin, 5-fluorouracil, and capecitabine) in patients with locally advanced, resectable tumors, perioperative FLOT regimen yielded a higher pathological response with a higher chance of R0 resection and improved OS [33].

In this study, the OS increased in the FLOT group compared to the ECF/ECX group with a median OS of 50 months in the FLOT group (hazard ratio [HR]: 0.77, 95% confidence interval [CI]: 0.63-0.94) versus 35 months in the ECF/ECX group. In several studies conducted in China, the FLOT regimen has been shown to be effective and safe with improved OS in locally advanced gastric cancer [34-36].

Similarly, in our study, we used FLOT and DCF regimens for NACT. Due to the small sample, the effect of DCF on survival was unable to be evaluated. According to the disease stage, however, we found no statistically significant difference in the OS in the FLOT and standard gastrectomy groups. According to the disease stage, we found a statistically significant difference in the DFS just in stage 3.

The rates of DFS were lower in the FLOT group than in standard gastrectomy. As a result, we find no favorable effect of NACT for advanced gastric cancer in our study. The discrepancy in the results between our study and previous studies can be attributed to the relatively short follow-up with a small sample size in our study.

Limitations

Nonetheless, there are some limitations to this study to be taken into consideration. First, the study has a single-center, retrospective design. Second, the sample size is relatively small for NACT + gastrectomy than for standard gastrectomy. Third, the follow-up duration is relatively short in the NACT + gastrectomy group than the standard gastrectomy group. Therefore, further large-scale, long-term, prospective, clinical controlled studies are needed to gain a better understanding of the value of NACT before gastrectomy and compare the results with standard gastrectomy.

Conclusions

In conclusion, radical gastrectomy is the most effective and only curative treatment of gastric cancer. In the current study, we found no significant difference between the patients undergoing standard gastrectomy and those undergoing NACT before gastrectomy due to possible aforementioned limitations. In particular, NACT should be evaluated in further large-scale studies, as downstaging allows for resection in advanced stage cases. Therefore, in the light of literature data, we believe that NACT may contribute to the favorable prognosis of patients with locally advanced disease with improved OS and DFS.

Riassunto

Scopo di questo studio è di confrontare gli esiti oncologici a lungo termine della chirurgia ad inizio rispetto

al trattamento neoadiuvante in pazienti con carcinoma gastrico localmente avanzato.
Sono stati analizzati retrospettivamente 183 pazienti operati per cancro gastrico. I pazienti sono stati sottoposto ad una gastrectomia standard oppure ad un trattamento chemioterapico preoperatorio (NACT) e quindi una gastrectomia. La terapia neoadiuvante è stata somministrata con il regime FLOT (docetaxel, oxaliplatino, fluorouracile e leucovorin) o con il regime DCF (docetaxel, cisplatino e 5-fluorouracile).
Risultati: Dei pazienti con trattamento NACT, 33 sono stati trattati con il regime FLOT e 14 hanno con il regime DCF. Il numero dei pazienti maschi era maggiore sia nel gruppo dei gastrectomizzati ab initio che nel gruppo NACT + gastrectomia (p=0,385). Leucopenia e neutropenia sono state le tossicità ematologiche più comuni, mentre anemia e nausea sono stati gli effetti collaterali non ematologici più frequenti in entrambi i gruppi NACT. Gli esiti dei gradi di complicanze postoperatorie, secondo la classificazione Clavien-Dindo, sono simili tra i gruppi. Non è risultata alcuna differenza statisticamente significativa nella durata della degenza in ospedale dopo l'intervento chirurgico tra i vari gruppi (p=0,001). In base allo stadio della malattia, non è stata trovata alcuna differenza statisticamente significativa nell'OS e nella DFS tra i gruppi NACT e gastrectomia standard.
Conclusione: sebbene non abbiamo riscontrato differenze significative tra i pazienti sottoposti a gastrectomia standard e quelli sottoposti a NACT prima della gastrectomia, riteniamo che la NACT possa contribuire alla prognosi favorevole dei pazienti con malattia localmente avanzata con OS e DFS migliorati e questo dovrebbe essere esaminato in studi futuri .

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: *Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries*. Cancer J Clin, 2018; 68:394-424.

2. Russo A, Li P, Strong VE: *Differences in the multimodal treatment of gastric cancer: East versus west.* J Surg Oncol, 2017; 115:603-14.

3. Hartgrink HH, van de Velde CJ, Putter H, Songun I, Tesselaar ME, Kranenbarg EK, de Vries JE, Wils JA, van der Bijl J, van Krieken JH: *Cooperating investigators of the dutch gastric cancer group*: *Neo-adjuvant chemotherapy for operable gastric cancer: Long term results of the dutch randomised FAMTX trial*. Eur J Surg Oncol, 2004; 30(6):643-9.

4. Songun I, Putter H, Kranenbarg EM, Sasako M, and de Velde C: *Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial*. Lancet Oncol, 2010; 11:439-49.

5. Degiuli M, Sasako M, and Ponti A: *Morbidity and mortality in the İtalian gastric cancer study gruop randomized clinical trial of D1 versus D2 resection for gastric cancer*. Br J Surg, 2010; 97:643-49.

6. Degiuli M, Sasako M, Ponti A, et al: *Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer*. Br J Surg, 2014; 101:23-31.

7. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F: *Gactric Cancer*. Lancet, 2020; 29:396(10251):635-48, doi: 10.1016/S0140-6736(20)31288-5, PMID: 32861308, Review.

8. Greenlee RT, Howe HL: C*ounty-level poverty and distant stage cancer in the United States*. Cancer Causes Control, 2009; 20(6):989-1000.

9. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, Haag C, Mauer ME, Hasan B, Welch J, Ott K, Hoelscher A, Schneider PM, Bechstein W, Wilke H, Lutz MP, Nordlinger B, Van Cutsem E, Siewert JR, Schlag PM: *Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European organisation for research and treatment of cancer randomized trial 40954*. J Clin Oncol, 2010; 10: 28(35):5210-8.

10. Wilke H, Preusser P, Fink U, Gunzer U, Meyer HJ, Meyer J, et al: *Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: A phase II study with etoposide, doxorubicin, and cisplatin*. J Clin Oncol, 1989; 7:1318-26.

11. Cunningham D, Allum WH, Stenning SP, et al: *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer.* N Engl J Med, 2006; 355:11-20.

12. Schuhmacher C, Gretschel S, Lordick F, et al: *Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European organisation for research and treatment of cancer randomized trial 40954*. J Clin Oncol, 2010; 28:5210-18.

13. Ychou M, Boige V, Pignon JP, et al: *Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial.* J Clin Oncol, 2011; 29:1715-721.

14. Kang Y-K, Yook JH, Park Y-K, et al: *S-1 phase III randomized study of neoadjuvant chemotherapy (CT) with docetaxel (D), oxaliplatin (O) and S-1 (S) (DOS) followed by surgery and adjuvant S-1, vs surgery and adjuvant, for resectable advanced gastric cancer (GC) (PRODIGY).* Ann Oncol, 2019; 30 (suppl 5):v876-77.

15. Ji J, Shen L, Li Z, et al: *Perioperative chemotherapy of oxaliplatin combined with S-1 (SOX) versus postoperative chemotherapy of SOX or oxaliplatin with capecitabine (XELOX) in locally advanced gastric adenocarcinoma with d2 gastrectomy: A randomized phase III trial (RESOLVE Trial)*. Ann Oncol, 2019; 30:(suppl 5):v851-34.

16. *Japanese Gastric Cancer Association*. Gastric Cancer, 2017; 20(1):1-19, doi: 10.1007/s10120-016-0622-4, Epub 2016 Jun 24.

17. Eisenhauer EA, Therasse P, Boqaerts J, et al: *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).* Eur J Cancer, 2009; 45:228-47.

18. *Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition*. Gastric Cancer, 2011; 14:101-12.

19. Dindo D, Demartines N, Clavien PA. *Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey*. Ann Surg, 2004; 240:205-13.

20. *Japanese gastric cancer treatmant guidelines.* 2014; (ver. 5).

21. Viani L, Bertocchi E, Iapichino GG, Dell'Abate P, Sivelli R, Sianesi M, Del Rio P: *Experience of 463 cases of gastric cancer from a single surgical center*. Ann Ital Chir, 2015; 86:513-7, PMID: 26898669.

22. Omarov N, Uymaz D, Azamat IF, Ozoran E, Ozata IH, Bırıcık FS, Taskin OC, Balik E: *The role of minimally invasive surgery in gastric cancer*. Cureus, 2021; 14:13(11):e19563, doi: 10.7759/cureus.19563, PMID: 34796082, PMCID: PMC8590860.

23. Cunningham D, et al, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, *x*. N Engl J Med, 2006; PMID: 16822992, Clinical Trial.

24. Ott K, Lordick F, Herrmann K, Krause BJ, Schuhmacher C, Siewert JR: *The new credo: Induction chemotherapy in locally advanced gastric cancer: Consequences for surgical strategies*. Gastric Cancer, 2008; 11(1):1-9, doi: 10.1007/s10120-007-0448-1, Epub 2008; Mar 29, PMID: 18373171.

25. Oyama K, Fushida S, Kinoshita J, et al: *Efficacy of pre-operative chemotherapy with docetaxel, cisplatin, and S-1 (DCS therapy) and curative resection for gastric cancer with pathologically positive para-aortic lymph nodes.* J Surg Oncol, 2012; 105:535-41.

26. Migita K, Nashimoto A, Yabusaki H, et al: *Efficacy of neoadjuvant chemotherapy with docetaxel, cisplatin and S-1 for resectable locally advanced gastric cancer*. Int J Clin Oncol, 2016; 21:102-9.

27. Birendra Kumar Sah, Benyan Zhang Huan Zhang, Jian Li, Fei Yuan, Tao Ma, Min Shi, Wei Xu, Zhenglun Zhu, Wentao Liu, Chao Yan, Chen Li, Bingya Liu, Min Yan & Zhenggang Zhu: *Clinical trial neoadjuvant FLOT versus SOX phase II randomized clinical trial for patients with locally advanced gastric cancer*. 2020; 30:11(1):6093, doi: 10.1038/s41467-020-19965-6, Nat Commun.

28. Yalav O, Topal U: *Evaluation of factors related to Clavien Dindo* 3 and above *complications in patients undergoing gastrectomy due to gastric cancer*. Ann Ital Chir, 2020; 91:617-26, PMID: 33021242.

29. Kim GM, Jeung HC, Rha SY, Kim HS, Jung I, Nam BH, Lee KH, Chung HC: *A randomized phase II trial of S-1-oxaliplatin versus capecitabine-oxaliplatin in advanced gastric cancer*. Eur J Cancer, 2012; 48(4):518-26.

30. Satake H, Miki A, Kondo M, Kotake T, Okita Y, Hatachi Y, Yasui H, Imai Y, Ichikawa C, Murotani K, Hashida H, Kobayashi H, Kotaka M, Kato T, Kaihara S, Tsuji A: *Phase I study of neoadjuvant chemotherapy with S-1 and oxaliplatin for locally advanced gastric cancer (Neo G-SOX PI).* ESMO Open, 2017; 2(1):e000130.

31. Kang YK, Yook JH, Park YK, et al: *Phase III randomized study of neoadjuvant chemotherapy (CT) with docetaxel (D), oxaliplatin (O) and S1(S) (DOS) followed by surgery and adjuvant S1, vs surgery and adjuvant S1, for resectable advanced gastric cancer (GC) (PRODIGY).* Ann Oncol, 2019; 30:(suppl 5): v876-77.

32. Ji J, Shen L, Li Z, et al: *Perioperative chemotherapy of oxaliplatin combined with S1 (SOX) versus postoperative chemotherapy of SOX or oxaliplatin with capecitabine (XELOX) in locally advanced gastric adenocarcinoma with D2 gastrectomy: A randomized phase III trial (RESOLVE Trial).* Ann Oncol, 2019; 30:(suppl 5):v851-934.

33. Al-Batran SE, Homann N, Pauligk C et al: *Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro oesophageal junction adenocarcinoma (FLOT4): A randomised, phase 2/3 trial*. Lancet, 2019; 393:1948-57.

34. Zhou C, Ma T, Shi M, Xi W, Wu J, Yang C, Zhu Z, Zhang J: *Dose-finding study of modified FLOT (mFLOT) regimen as first-line treatment in chinese patients with metastatic adenocarcinoma of stomach*. Cancer Chemother Pharmacol, 2020; 85(1):113-19.

35. Sah BK, Xu W, Zhang B, Zhang H, Yuan F, Li J, Liu W, Yan C, Li C, Yan M, Zhu Z: *Feasibility and safety of perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel for locally advanced gastric cancer patients in china*. Front Oncol, 2021; 18; 10:567529, doi: 10.3389/fonc.2020.567529, PMID: 33537232, PMCID: PMC7848150.

36. Wang K, Ren Y, Ma Z, Li F, Cheng X, Xiao J, Zhang S, Yu Z, Yang H, Zhou H, Li Y, Liu H, Jiao ZY: *Docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil (FLOT) as preoperative and postoperative chemotherapy compared with surgery followed by chemotherapy for patients with locally advanced gastric cancer: A propensity score-based analysis.* Cancer Manag Res, 2019; 11( ):3009-20.