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국소 진행성 위암에서 2제, 3제 선행항암화학 요법의 임상 결과

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Clinical Outcome of Doublet and Triplet Neoadjuvant Chemotherapy for Locally Advanced Gastric Cancer

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Background/Aims: In gastric cancer, the rate of recurrence and metastasis following radical resection is high, necessitating improvement in survival and cure rates. Neoadjuvant chemotherapy (NAC) has potential benefits for locally advanced gastric cancer; however, the surgical benefits and effects on survival are unclear. This study evaluates the effectiveness of NAC in locally advanced gastric cancer and compares clinical outcomes of doublet and triplet regimens.
Methods: We reviewed patient medical records of 383 patients who underwent NAC (n=41) or surgery only (n=342) for treatment of locally advanced gastric cancer. The baseline characteristics and clinical outcomes were compared between the groups. Chemotherapy patients were classified according to regimen, doublet (n=28) and triplet (n=13), and NAC-related clinical response, safety, and toxicity were analyzed.
Results: The baseline characteristics did not differ significantly between groups. After NAC, the tumor downstage rate was 51.2% (21/41); however, overall survival (p=0.205) and disease-free survival (p=0.415) were not significantly different between the groups. On subgroup analysis, no significant differences in drug toxicity (p=0.604) or clinical response (p=0.374) were found between outcomes of doublet and triplet chemotherapy regimens.
Conclusions: In patients with locally advanced gastric cancer, NAC showed tolerable drug toxicity and increased tumor downstage, but NAC failed to increase the survival rate, which may be caused by a high D2-lymphadenectomy rate. Therefore, NAC was found to be a therapeutic option for select gastric cancer patients. (Korean J Gastroenterol 2016;68:245-252)

Key Words: Neoadjuvant therapy; Drug therapy; Stomach; Adenocarcinoma

INTRODUCTION

Gastric cancer is the most frequently occurring cancer in Korea.[1] In a phase III study involving patients with stage 2 or higher resectable stomach cancer, patients treated with adjuvant chemotherapy demonstrated a 15% increase in the disease-free survival (DFS) rate and a 10% increase in the overall survival (OS) rate, compared with those treated with only surgery.[2] Adjuvant chemotherapy after D2 lymphadenectomy is considered standard treatment for gastric cancers.[2,3] Despite these efforts, compared with early stage gastric cancer with 5-year survival rates over 90%, locally advanced gastric cancer entails a high risk of lymph node metastasis, and even with complete resection, the prognosis is

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poor due to relapse.[4] Thus, several methods to increase treatment effectiveness have been attempted, including radiation therapy after D2 lymphadenectomy or consolidation adjuvant chemotherapy. However, none of these methods reduce relapse or increase survival, and they are no longer recommended for treatment.[5,6]

Neoadjuvant chemotherapy (NAC) is a potential treatment regimen for locally advanced gastric cancer. NAC can reduce tumor size, decrease clinical stage, enhance drug sensitivity, and reduce micrometastasis.[7,8] However, it is not effective for all patients, which may delay treatment, so ideal surgery timing may be missed due to disease progression. Many studies evaluating the effects of NAC report that it reduces the clinical stage and increases the curative resection (R0) rate when compared to surgery alone. However, there is no clear evidence that NAC increases the OS rate, the ultimate goal of treatment; therefore, it is a controversial treatment method.[9,10] In addition, several of these studies do not use a consistent NAC regimen, so it is unclear which chemotherapy agent should be used in NAC treatment.[11] Thus, this study evaluates the effectiveness of NAC in locally advanced gastric cancer, and compares a doublet regimen with a triplet regimen to propose criteria for the selection of a chemotherapy agent.

SUBJECTS AND METHODS

1. Study design and patient selection

Charts were reviewed for patients who were histologically diagnosed with gastric adenocarcinoma at the Chungnam National University School of Medicine between January 2008 and June 2014. The subjects were patients who received ongoing care for at least for one year after treatment for gastric cancer in this hospital.

The majority of cases were gastric cancer, although cases of gastroesophageal junction cancer were included. Patients were 18 years or older, with a World Health Organization (WHO) performance status score of 0 or 1. In order to target patients with locally advanced gastric cancer, those with clinical stage higher than T3 or lymph node metastasis were enrolled. Patients who received cancer treatment previously or those with distant metastasis, secondary malignancy, and inadequate cardiac or renal function (serum creatinine clearance rate ≤60 mL/min) were excluded. Pretreatment clin-

ical evaluation included a complete blood cell count with differential and serum multichannel chemical analysis. For clinical staging, upper gastrointestinal endoscopy with biopsy, abdominal CT, and chest radiography were conducted.

2. Neoadjuvant chemotherapy

Preoperative chemotherapy was administered over three cycles, with changes to dosage or time dictated by tumor response or safety. Chemotherapy regimens were classified into doublet and triplet regimens according to the number of the cytotoxic agents used. The doublet regimen was FOLFOX (oxaliplatin [100 mg/m^2], leucovorin [200 mg/m^2 of body surface area], intravenously on day 1; and 5-fluorouracil [5-FU, 2,400 mg/m^2] continuous infusion over 48 hours, repeated every two weeks), while the triplet regimen was DCF (docetaxel [75 mg/m^2], cisplatin [60 mg/m^2] of body surface area, intravenously on day 1; and 5-FU [750 mg/m^2] continuous infusion on each day 1-5, repeated every three weeks). Before each cycle of chemotherapy, a complete blood count and liver function test were performed, and electrolyte and serum creatinine levels were determined. DCF was reduced in patients with myelosuppression or thrombocytopenia, and 5-FU dosage was adjusted if mucositis or diarrhea occurred. In addition, if serum creatinine increased, cisplatin dosage was reduced or suspended according to the degree of renal function. The severity of toxicity or adverse effects was defined according to the National Cancer Institute Common Toxicity Criteria version 4.0.

Assessment of response to neoadjuvant therapy was based on reduction of primary tumor size as measured by endoscopy and abdominal CT. Complete disappearance of lesions on endoscopy and CT was considered a clinically complete response (CR). A tumor size reduction of greater than 50% compared with the initial findings was defined as a partial response (PR). Patients with a minor response or no change in the condition were defined as having stable disease (SD). The presence of new lesions or an increase of 25% or more in primary tumor size was considered progressive disease (PD). CR and PR were designated as responders, while SD and PD were designated as non-responders. Changed stage was defined if either T or N stage was up or down.

3. Surgery

Surgery was scheduled two to four weeks after completion

of the last cycle of chemotherapy in the NAC group, while operations for the surgery only group were performed immediately after diagnosis. For patients with curative resection, total or distal subtotal gastrectomy was performed depending on the location and macroscopic type of the gastric cancer. An extended D2 lymphadenectomy was performed, according to the rules of the Japanese Research Society for Gastric Cancer. *En bloc* resection of adjacent organs was performed when their involvement was questionable. All resected specimens were examined at local pathology laboratories according to the standard protocol. The pathological tumor, lymph node, metastasis (pTNM) stage were assessed according to the guidelines of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC). R0 resection was defined as the removal of all gross tumor material and a histopathological examination of proximal, distal, and circumferential margins that revealed the absence of malignant cells more than 2 mm from the edge.

4. Ongoing care

Each patient was assessed via a complete physical examination, routine lab work, chest radiography, abdominal CT, and tumor marker analysis, every six months for five years, then annually or until death. Twenty-seven patients were lost, and 199 patients (52.0%) died while under continuing care.

5. Statistical analysis

DFS was calculated from diagnosis to the first event (local recurrence or progression, or distant recurrence), and OS was calculated from diagnosis to death. Kaplan-Meier curves for DFS and OS were compared with the log-rank test on an intention-to-treat basis. Categorical variables were analyzed using chi-square or Fisher's exact tests. All analyses were conducted using IBM SPSS Statistics for Windows, version 19.0 (Released 2010., IBM Corp., Armonk, NY, USA). Two-sided null hypotheses of no difference were rejected if p-values were less than 0.05.

RESULTS

1. Patient characteristics

Three hundred and eighty-three patients were enrolled in this study. Forty-one of the 383 patients were administered preoperative chemotherapy followed by surgery, while 342 received only surgery. There were 289 men (75.5%), and the mean patient age was 63.40 years (standard deviation [SD]= 9.61 years). The baseline characteristics of the two groups are shown in Table 1, which illustrates that the patient distribution according to age, gender, WHO performance status, tumor location, and pretreatment M status was well balanced between treatment groups. However, pretreatment clinical T stage (p=0.012) and N status (p=0.000) were significantly higher in the NAC group than in the surgery only group.

2. Clinical outcome of neoadjuvant chemotherapy

Forty-one patients received NAC and were further classified according to the chemotherapy regimen. The doublet group consisted of 28 patients (68.3%) and the triplet group consisted of 13 patients (31.7%). The mean age (SD) of the doublet group was 64.96 years (9.67 years), while that of the triplet group was 55.31 years (7.75 years). The triplet group patients were younger than those in the doublet group, but not significantly different (p=0.602). The sex distribution of the two groups was similar (p=0.659). The NAC group was an-

Table 1. Patiens Baseline Characteristics

Characteristic	NAC group (n=41)	Surgery only group (n=342)	p-value
Age (yr)	61.90±10.09	63.59±9.16	0.270
Gender (male)	36 (87.8)	253 (74.0)	0.079
WHO performance status			0.671
0	30 (73.2)	265 (77.5)	
1	11 (26.8)	77 (22.5)	
Tumor location			0.425
Upper third	8 (19.5)	58 (17.0)	
Middle third	14 (34.1)	121 (35.4)	
Lower third	19 (46.3)	163 (47.7)	
Pretreatment T stage			0.012
T1	0 (0)	0 (0)	
T2	1 (2.4)	32 (9.4)	
T3	13 (31.7)	174 (50.9)	
T4	27 (65.9)	136 (39.8)	
Pretreatment N status			0.000
N0	1 (2.4)	72 (21.1)	
N1	2 (4.9)	82 (24.0)	
N2	26 (63.4)	123 (36.0)	
N3	12 (29.3)	65 (19.0)	
Pretreatment M status			0.254
M0	38 (92.7)	331 (96.8)	
M1	0 (0)	0 (0)	
Mx	3 (7.3)	11 (3.2)	

Values are presented as mean±SD or n (%).
NAC, neoadjuvant chemotherapy; WHO, World Health Organization.

alyzed for drug toxicities, and clinical responses were evaluated with endoscopy and CT after cancer treatment. These results are shown in Table 2. Fifteen patients (36.6%) experienced grade 3 or 4 toxicity (nine patients [32.1%] in the doublet group and six patients [46.2%] in the triplet group), but there was no significant difference in toxicity according to the NAC regimen (p=0.604). The most common chemotherapy toxicity was neutropenia (12.2%), followed by thrombocytopenia, anemia, nausea/vomiting, and mucositis. Twelve patients (29.3%) stopped cancer treatment or reduced the chemotherapy agent dosage due to the drug's side effects (seven patients [25.0%] in the doublet group and five patients [38.5%] in the triplet group), although these differences were not statistically significant (p=0.608).

Of the 41 NAC group patients, five patients achieved CR, and the doublet and triplet regimens did not differ significantly in clinical response rate (p=0.374). According to the response categories mentioned earlier, 19 patients (46.3%) were responders, 22 patients (53.7%) were non-responders, and the two groups showed similar results (p=0.749).

3. Surgical findings and surgical pathology

The surgical and pathological results were compared between the NAC and surgery-only groups, and the results are in Table 3. All 383 patients in the study received surgery, with 41 patients (10.7%) receiving preoperative chemotherapy and 342 patients (89.3%) receiving surgery only. There were no significant differences in surgery type (p=0.726), post-

operative complications (p=0.770), and R0 resection rate (p=0.829) between groups. Three hundred and fifty-nine patients (93.7%) had R0 resection (92.7% in the NAC group, and 93.9% in the surgery only group), a high R0 resection rate in both groups. Massive peritoneal seeding was found in one patient in the NAC group, which resulted in the termination of the operation without gastric resection.

Based on postoperative pathological results, pathologic stage was re-evaluated in all patients and compared with the preoperative clinical stage. The results showed no difference in M status between groups (p=0.127), but T stage (p=0.001) and N status (p=0.000) were significantly lower in the NAC group than in the surgery only group, in contrast to the pretreatment clinical stage under the influence of downstaging after chemotherapy. In the NAC group only, preoperative clinical stage was compared with postoperative pathologic stage, and the difference was analyzed (Table 4). Both tumor stage and nodal status significantly decreased in pathologic stage after NAC, as compared to the pretreatment clinical stage (p=0.000). In overall staging, 21 patients (51.2%) were downstaged, nine patients (22.0%) upstaged, and 11 pa-

Table 2. Grade 3 or 4 Toxicity and Clinical Response Assessment during Neoadjuvant Chemotherapy

Variable	Total (n=41)	Doublet (n=28)	Triplet (n=13)	p-value
Toxicity (total)	15 (36.6)	9 (32.1)	6 (46.2)	0.604
Neutropenia	5 (12.2)	4 (14.3)	1 (7.7)	
Thrombocytopenia	3 (7.3)	1 (3.6)	2 (15.4)	
Anemia	2 (4.9)	1 (3.6)	1 (7.7)	
Nausea/vomiting	2 (4.9)	2 (7.1)	0 (0)	
Mucositis	1 (2.4)	0 (0)	1 (7.7)	
Fever	1 (2.4)	0 (0)	1 (7.7)	
Nephrotoxicity	1 (2.4)	1 (3.6)	0 (0)	
Clinical response				0.374
Complete response	5 (12.2)	3 (10.7)	2 (15.4)	
Partial response	14 (34.1)	9 (32.1)	5 (38.5)	
Stable disease	19 (46.3)	15 (53.6)	4 (30.8)	
Progressive disease	3 (7.3)	1 (3.6)	2 (15.4)	

Values are presented as n (%).

Table 3. Surgical and Pathologic Results

Characteristic	NAC group (n=41)	Surgery only group (n=342)	p-value
Type of surgery			0.726
Total gastrectomy	6 (14.6)	39 (11.4)	
Distal gastrectomy	35 (85.4)	303 (88.6)	
Resection margin			0.829
R0	38 (92.7)	321 (93.9)	
R1	2 (4.9)	20 (5.8)	
R2	0 (0)	1 (0.3)	
Open & closure	1 (2.4)	0 (0)	
Postoperative complication	6 (14.6)	61 (17.8)	0.770
Pathologic results			
Tumor stage			0.001
T1	6 (14.6)	0 (0)	
T2	4 (9.8)	8 (2.3)	
T3	3 (7.3)	128 (37.4)	
T4	28 (68.3)	206 (60.2)	
Nodal status			0.000
N0	12 (29.3)	4 (1.2)	
N1	8 (19.5)	72 (21.1)	
N2	5 (12.2)	96 (28.1)	
N3	16 (39.0)	170 (49.7)	
Metastasis status			0.127
M0	39 (95.1)	338 (98.8)	
M1	2 (4.9)	4 (1.2)	

Values are presented as n (%).
NAC, neoadjuvant chemotherapy.

Table 4. Stage Change of the Pretreatment *vs.* Post Neoadjuvant Chemotherapy

Characteristic	Pretreatment (clinical stage)	Post NAC (pathologic stage)	p-value
Tumor stage			0.000
T1	0 (0)	6 (14.6)	
T2	1 (2.4)	4 (9.8)	
T3	13 (31.7)	3 (7.3)	
T4	27 (65.9)	28 (68.3)	
Nodal status			0.000
N0	1 (2.4)	12 (29.3)	
N1	2 (4.9)	8 (19.5)	
N2	26 (63.4)	5 (12.2)	
N3	12 (29.3)	16 (39.1)	
Change of overall stage			
Downstage		21 (51.2)	
Upstage		9 (22.0)	
No change		11 (26.8)	

Values are presented as n (%).
NAC, neoadjuvant chemotherapy.

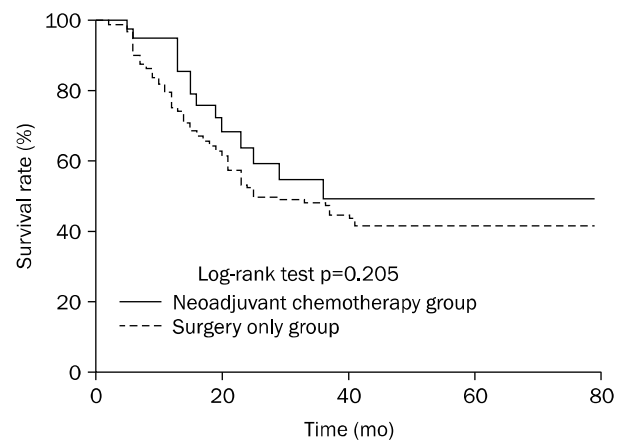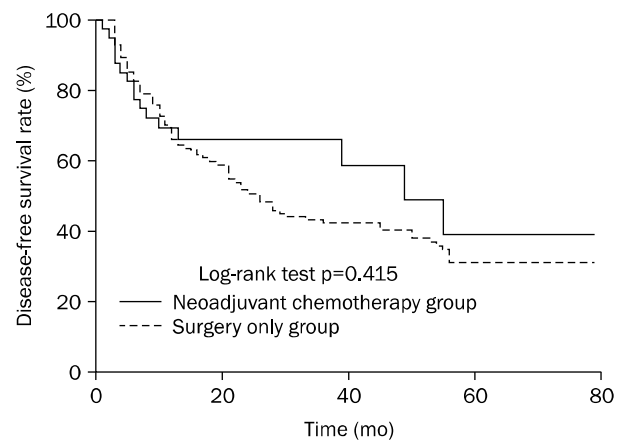**Table 5.** Pattern of Recurrence, Survival Status, and Cause of Death

Characteristic	NAC group (n=41)	Surgery only group (n=342)	p-value
Recurrence	20 (48.8)	218 (63.7)	0.119
Locoregional only	1 (2.4)	30 (8.8)	
Distant only	5 (12.2)	36 (10.5)	
Both	14 (34.1)	152 (44.4)	
Death	17 (41.5)	182 (53.2)	0.209
Cancer related	13 (31.7)	161 (47.1)	
Surgery related	2 (4.9)	12 (3.5)	
Others	2 (4.9)	9 (2.6)	

Values are presented as n (%).
NAC, neoadjuvant chemotherapy.

Fig. 1. Kaplan-Meier estimates of overall survival rate.

Fig. 2. Kaplan-Meier estimates of disease-free survival rate.

tients (26.8%) were unchanged.

4. DFS and OFS

The median follow-up (SD) period was 32.03 months (14.91 months) for all patients, 33.39 months (19.63 months) for the NAC group, and 31.86 (17.14) months for the surgery only group. The survival and recurrence during the observation period were analyzed, as shown in Table 5. One hundred and ninety-nine patients (52.0%) died (17 patients [41.5%] in the NAC group and 182 patients [53.2%] in the surgery only group); there was no difference in the OS between the two groups (p=0.209). The deaths of 174 (87.4%) of the 199 patients were cancer-related. A recurrence was observed in 238 patients (62.1%), with the most recurrence occurring in locoregional and distant regions simultaneously,

as seen in 166 patients (69.7%). There was no significant difference in the recurrence rate between the NAC group and the surgery only group (p=0.119).

The estimated median OS was 48.84 months (95% CI, 37.22 to 60.45) in the NAC group versus 42.76 months (95% CI, 38.37 to 47.15) in the surgery only group (Fig. 1). The OS rate at two years was 61.2% in the NAC group and 52.4% in the surgery only group. On a log-rank test, there was no difference in the OS between groups (p=0.205). The estimated median DFS was 46.08 months (95% CI, 34.32 to 57.84) in the NAC group versus 38.32 months (95% CI, 33.79 to 42.85) in the surgery only group (Fig. 2). There was no difference in DFS between groups (p=0.415).

DISCUSSION

In this study, NAC significantly decreased clinical T stage

and N stage, and 51.2% of patients treated with NAC experienced downstaging. In addition, NAC treatment did not increase postoperative complications, and the side effects of the chemotherapy agent were tolerable. However, in stomach cancer cases, the operation range cannot be reduced even with a decrease in tumor size or clinical stage after NAC, as the operation range is determined by the location of the primary lesion.[12] In addition, the determination of clinical stage through imaging examination is inaccurate. It is reported that CT has an accuracy of approximately 77-89% for T stage and approximately 59-78% for N stage.[13,14] Thus, the effect of NAC in locally advanced gastric cancer is meaningful only when the OS improves, which is the ultimate goal of treatment. However, in this study, the observed decrease in stage did not lead to an improvement in OS (p=0.205) or DFS (p=0.415). In the Medical Research Council (MRC) Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial that compared a group with preoperative ECF administration to a surgery only group with 503 patients, preoperative chemotherapy decreased T stage and N stage, which led to an improvement in survival (hazard ratio [HR], 0.75; 95% CI, 0.60 to 0.93; p=0.009).[15] However, there are several differences between our study and the MAGIC trial. Our study conducted D2 lymphadenectomy with all patients except one who did not have resection due to peritoneal seeding, while the MAGIC trial conducted D2 lymphadenectomy in just 43% of the patients. Therefore, we hypothesize that the effect of NAC was less because of the more extensive lymphadenectomy. In addition, there was a difference in the clinical stage of the enrolled patients, and the patient group of the MAGIC trial was in an earlier clinical stage.

In a randomized trial that showed a high D2 lymphadenectomy rate of 92%, similar to that reported in our study, there was no increase in postoperative complications after NAC. The R0 resection rate improved (81.9% *vs.* 66.7%; p=0.035), but the OS did not improve compared to the surgery only group (HR, 0.84; 95% CI, 0.52 to 1.35; p=0.466).[16] Similar to our study, in this trial, tumor downstaging was caused by NAC, but there was a question about whether this led to the increase in survival. In a meta-analysis with 1,249 patients, there was tumor downstaging after NAC (OR, 1.77; 95% CI, 1.27 to 2.49; p=0.0009), which led to an increase in the R0 resection rate (OR, 1.38; 95% CI, 1.03 to 1.85; p=0.03) and eventually significant increases in the OS rate (OR, 1.40; 95%

CI, 1.11 to 1.76; p=0.005) and progression-free survival (OR, 1.62; 95% CI, 1.21 to 2.15; p=0.001).[17] However, in a subgroup analysis, Western countries favored NAC more than Asian countries (OR, 1.40; 95% CI, 1.07 to 1.83), indicating that treatment results differ by region, most likely caused by the differences in D2 lymphadenectomy rate and location of the gastric cancer.[18]

In NAC, the selection of chemotherapy regimen is an important consideration, but a standard regimen is not established. The response rate of the doublet regimen in metastatic gastric cancer is approximately 40%, and the possibility of tumor progression within two months is approximately 20%, considered high. However, the response rate of the triplet regimen is 50-70% and the possibility of progression within two months was approximately 5%.[19,20] In a phase II trial with DOS triplet therapy as the NAC regimen, 54% patients responded with no drug side effects, and the two-year DFS rate was high (89.7%).[21]

The effect of NAC on surgical complications was also considered, as it is important that the risk not be higher than with surgery alone. This study compared the doublet and triplet regimens, and found no difference in drug toxicity (p=0.604) or postoperative complications (p=0.770) between groups. Seven patients (25.0%) in the doublet regimen and five patients (38.5%) in the triplet regimen stopped cancer treatment or reduced anti-cancer drug dosage due to intolerable drug side effects, yet there was no statistical difference between groups (p=0.608). In the analysis of clinical responses, the response rate was higher in the triplet regimen, with a rate of 53.9% in the triplet and 42.8% in the doublet regimen, but there was no statistically significant difference between the two (p=0.749). This may be a result of small sample size, especially in the triplet group, which had only 13 patients. The triplet regimen showed similar toxicity to the doublet regimen, but as it had a higher response rate, the triplet regimen was determined to be the preferred NAC treatment.

In NAC, cisplatin- or 5-FU-based regimens have been widely used with favorable results. According to multicenter randomized studies, the response rate of cisplatin, leucovorin, and 5-FU was 35.2% (95% CI, 23.7% to 45.7%).[22] The results of treatment with more modern cytotoxic agents, such as capecitabine, oxaliplatin, or docetaxel, were similar in several studies.[23,24] In addition, targeted therapies, such as epi-

dermal growth factor receptor inhibitors or anti-angiogenetic agents, have been attempted as alternative therapy. However, further studies are needed for a proper characterization of these therapies.[25,26]

Our study has a few limitations. First, it was a retrospective, single center study, so it is difficult to generalize the results of this study. Second, the sample size was small, especially for the triplet regimen subgroup in the larger NAC group, which may create a selection bias. In addition, endoscopic ultrasound was not conducted in all patients in pretreatment clinical staging. As we only evaluated the clinical staging using CT, the T or N stage may be inaccurate, which is likely to have influenced the change in stage after NAC. It is a limitation of a retrospective study, but in many other studies, only CT evaluation was performed for the clinical stage.

NAC has clear effects on some cancers, but its effects on gastric cancer are still controversial, and results differ between Eastern countries and Western countries. In the treatment of locally advanced gastric cancer, preoperative chemotherapy is preferred in Europe, while adjuvant chemotherapy after D2 lymphadenectomy is recommended in East Asia, including South Korea and Japan.[27] It was reported that NAC and D2 lymphadenectomy increase survival, but this trend was not supported by our study, so combined NAC and D2 surgery therapy is not yet recommended.[28] In this study, NAC decreased clinical stage in patients, but this did not lead to an increase in the OS, which may be a result of the high D2 lymphadenectomy rate.

In conclusion, our study demonstrated that NAC treatment successfully downstaged tumors, did not increase post-operative complications, and showed a tolerable toxicity. Moreover, it can be considered a therapeutic option in locally advanced gastric cancer. Additionally, the higher response rate of the triplet NAC regimen, despite similar side effects to the doublet regimen, may be important in NAC treatment determination. However, NAC treatments should be chosen with consideration of patient characteristics or operation condition. Although these results have provided new insights into NAC treatment regimens, additional studies are still needed to provide further insights into NAC treatment.

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