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Original Article

Phase II trial of preoperative sequential chemotherapy followed by chemoradiotherapy for high-risk gastric cancer

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ABSTRACT

Background and purpose: To evaluate the safety and efficacy of preoperative chemotherapy (CTx) followed by chemoradiotherapy (CCRT) for high-risk gastric cancer (GC).

Methods and materials: The inclusion criteria were as follows: (1) Borrmann type 4; (2) large Borrmann type 3 (≥8 cm); (3) single bulky (≥3 cm × 1) or multiple lymph nodes (≥1.5 cm × 3). Patients received two 21-day courses of induction CTx of TS-1 (35 mg/m^2, p.o, twice daily on days 1–14), docetaxel (30 mg/m^2, i.v., days 1 and 8), and cisplatin (30 mg/m^2, i.v., days 1 and 8) followed by CCRT (two courses of TS-1 and cisplatin in combination with 45 Gy radiation).

Results: Forty-two patients were enrolled between March 2014 and February 2016, and 39 of these completed sequential CTx and CCRT. Among the 33 patients who underwent R0 resection, the pathologic response rate was 39.4% [no residual carcinoma (n = 5, 15.2%), with 1–10% residual carcinoma (n = 8, 24.2%)]. Overall, 4 patients (12.1%) were pathologic stage 0, 7 (21.2%) were stage I, 10 (30.3%) were stage II, and 12 (36.4%) were stage III. The overall survival rate at 3 years was 77.9% for stages 0 and I, 66.8% for stages II–III, and 33.3% for unresectable cases (P = 0.001). Toxicity was mild to moderate with grade 4 neutropenia (n = 1) and neutropenic fever (n = 1) as the most prominent side-effects.

Conclusions: Sequential CTx and CCRT prior to surgery are feasible and effective for high-risk GC.

Trial registration number: NCT02495493.

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Despite adjuvant chemotherapy (CTx) after surgery, 25–40% of stage II–III gastric cancer (GC) patients still experience relapse [1,2]. Based on the better tolerability with preoperative treatment rather than the postoperative setting [3–5], active preoperative strategies have been widely studied [6–8].

As both preoperative CTx and chemoradiotherapy (CCRT) provide moderate benefits, combined treatment of CTx followed by CCRT was performed to further strengthen treatment strategies. The combination treatment resulted in a substantial pathologic response (20–30%), and patients achieving a pathologic response survived significantly longer [6,9]. Based on these studies, a randomized phase III trial of perioperative epirubicin/cisplatin/5-fluor ouracil CTx with or without CCRT for resectable GC (TOPGEAR) is ongoing [10]. Furthermore, the CRITICS-II trial, the aim of which is to determine the most promising preoperative modalities (CTx *vs* CCRT alone *vs* CT plus CCRT), is also ongoing [11].

However, despite the improved outcomes with preoperative trials, several drawbacks remain. The inclusion criteria of localized GC were not well-defined. Because of insufficient pretreatment staging, up to half the cases were clinical stage N0 or T1/2 [3,5]. Considering the high rate of grade 4 toxicities (about 20%), a uniform preoperative strategy for the heterogeneous stages is not feasible. As the remaining non-responders experienced a risk of toxicity without apparent

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benefits, it is extremely important to enroll high-risk patients and identify good responders to the preoperative treatment.

Based on this background, this study was designed to delineate the efficacy of preoperative sequential CTx followed by CCRT for GC with a high risk for recurrence. Moreover, the safety of an effective weekly triplet regimen as a preoperative treatment was analyzed.

Methods and materials

Patient selection and evaluation

Patients with histologically confirmed, high-risk gastric or gastroesophageal adenocarcinoma with the following characteristics were eligible: (1) Borrmann type 4; (2) large Borrmann type 3 ($\geq$8 cm); (3) single bulky ($\geq$3 cm $\times$ 1) or multiple regional lymph nodes ($\geq$1.5 cm $\times$ 3). Patients were required to be $\geq$20 years of age, with an Eastern Cooperative Oncology Group performance status of 0–1, and have normal liver, renal, and bone marrow functions. Patients with peritoneal carcinoma or distant metastasis, or those who were human epidermal growth factor receptor 2-positive were not eligible.

As part of the screening work-up, all patients underwent the following investigations: chest radiography, computed tomography (CT) of the abdomen and pelvis, esophagogastroduodenoscopy with endoscopic ultrasonography, electrocardiography, serum chemistry panel, complete blood count, and analysis of electrolytes. Laparoscopic staging was mandatory for all patients during screening. The study was approved by the institutional review board (IRB 4-2013-0548).

Study design

Patients received 2 cycles of induction CTx followed by CCRT (Supplementary Fig. 1). CCRT was administered in the absence of cancer progression just after CTx. The response was judged using radiographic evaluation. In the case of occurrence of less than R0 resection, palliative care was administered in the form of xeloda/oxaliplatin combination.

Step 1: Chemotherapy

During each 3-week cycle, patients received 2 cycles of oral TS-1, docetaxel, and cisplatin combination. TS-1 was administered orally twice daily on days 1–14 (35 mg/m^2). Cisplatin was administered by intravenous infusion for 2 h (30 mg/m^2), followed by docetaxel (30 mg/m^2) on days 1 and 8 of each cycle. The prophylactic administration of antiemetic medication was started following the institutional protocol.

Step 2: Chemoradiotherapy

Within 35 days of the final CTx, patients were treated with a 5-week course of CCRT. We delivered a dose of 1.8 Gy per day up to a total of 45 Gy (25 fractions) delivered 5 days per week. CT simulation with four-dimensional CT scan-based radiotherapy planning was mandatory. The radiation target included gross tumor of the primary site and involved nodal regions without elective lymph node irradiation. Internal target volume was generated to reflect internal organ movement. Clinical target volume was defined as internal target volume plus 1.5 cm additional margin in all directions. Three-dimensional conformal planning with multiport beam arrangements was used with the following general prescription and dose constraints to organ-at-risk: the volume of the duodenum exceeding 45 Gy was limited to less than 2 ml, the kidney and liver were limited to <15 Gy and <30 Gy for 50% or more of the total kidney volume and liver volume, respectively, and the maximum point dose within the planning target volume was allowed to receive doses <105%. A 5-cm margin of the esophagus was included for lesions involving the cardia or gastroesophageal junction and a 5-cm margin of the duodenum was included for distal lesions near the gastroduodenal junction. The concurrent CTx regimen comprised 2 cycles of a combination of cisplatin and TS-1 starting on days 1 and 22. TS-1 was orally administered twice daily for 14 days at a dose of 40 mg/m^2, and cisplatin was infused intravenously for 2 h at 30 mg/m^2 on days 1 and 8.

Step 3: Surgery

Within 4–6 weeks of the completion of CCRT, if restaging confirmed no evidence of distant metastasis or inoperable disease, patients underwent gastrectomy. To perform R0 resection [12], resection extent was determined by the tumor location and the types of reconstruction were determined according to the resection extent and surgeon's discretion. Distal subtotal or total gastrectomy with D2 lymph node dissection was performed according to the Korean gastric cancer treatment guidelines [12]. After resection, adjuvant chemotherapy was used following the standard regimens for stage II (with TS-1) and III (with a xeloda/oxaliplatin combination) cases [13,14].

Response assessment, toxicity criteria, and management

Tumor response using a CT scan and esophagogastroduodenoscopy was evaluated at baseline, after induction CTx, and just prior to surgery. Toxicity was graded according to the Common Terminology Criteria for Adverse Events criteria (CTCAE version 4.0). CTx dose modification was planned for both hematologic and non-hematologic toxicity. Briefly, the drug dose was to be decreased by 20% if grade 3 non-hematologic toxicity or grade 4 hematologic toxicity occurred. After resection, the patients were followed-up every 3 months up to 2 years; subsequent follow-up was planned every 6 months for 5 years. Operative mortality was defined as death from any cause within 30 days of surgery or during hospitalization associated with resection.

Statistical analysis

The primary objective of the study was to observe a 35% pathologic response (residual tumor $\leq$10%) [6]. Previously described evaluation criteria were used to assess the pathologic response [9,15]. A two-stage minimax design was used. Based on the α level of 5% and a power of 90% for P_0 = 15% and P_1 = 75%, 23 subjects were required to be enrolled in the first stage of the study and the trial would have been terminated if 3 or fewer responders were found. If the trial was continued to the second stage, a total of 38 subjects were to be enrolled. Allowing a 10% loss to follow-up rate, a total of 42 patients were anticipated.

The analysis of all end points was on per-protocol basis, except for survival outcomes which were based on all enrolled patients. Survival curves were plotted by employing the Kaplan–Meier method and compared using the log-rank test. Time to treatment failure (TTF) and overall survival (OS) were calculated from initiation of treatment to treatment failure (i.e., local/distant recurrence after curative resection, progression after neoadjuvant treatment for unresectable cases, or death), and death. All tests were two-sided, with P values of <0.05 considered to indicate statistical significance using SPSS version 18.0 (IBM, Chicago, IL).

Results

Characteristics of the patients

A total of 52 patients were screened between March 2014 and February 2016. After the assessment of eligibility, 10 patients were excluded: peritoneal seeding on diagnostic laparoscopy (n = 5),

distant metastasis ($n = 3$), and human epidermal growth factor receptor 2-positive cases ($n = 2$); thus, a total of 42 patients were enrolled (Fig. 1). Patients were enrolled for the following reasons: large Borrmann type 3 ($n = 19$, 45.2%), Borrmann type 4 ($n = 13$, 31%), bulky lymph node ($n = 6$, 14.3%), and multiple lymph nodes ($n = 4$, 9.5%, Table 1).

Delivery and toxic effects of neoadjuvant treatment

During induction CTx, grade 3 toxicities were observed in 14 of 42 patients (33.3%) and grade 4 toxicities in 2 patients (4.8%; neutropenia and neutropenic fever, 1 patient each). Three patients received only 1 cycle of induction CTx: 2 patients experienced tumor-related complications including tumor bleeding ($n = 1$) and hemophagocytic syndrome ($n = 1$), and 1 patient experienced CTx-related toxicity. In the final analysis, a total of 39 (92.9%) patients who completed 2 cycles of induction CTx proceeded to CCRT. One case of dose reduction (−1 dose level) was noted among 16 cases for all 3 agents (TS-1, cisplatin, and docetaxel). Average relative dose-intensity for TS-1, cisplatin, and docetaxel was 94.1%, 94.2%, and 94.0%, respectively.

All 39 patients completed CCRT and 7 grade 3 toxicities occurred; anorexia ($n = 2$), neutropenia ($n = 2$), thrombocytopenia ($n = 1$), nausea ($n = 1$), and diarrhea ($n = 1$). The dose of TS-1 and cisplatin was reduced once (−1 dose level) in 1 (2.6%) patient owing to grade 2 vomiting and grade 3 thrombocytopenia. No treatment-related deaths were observed. Details of the toxicities of each treatment are listed in Table 2.

Surgical findings and pathologic assessment

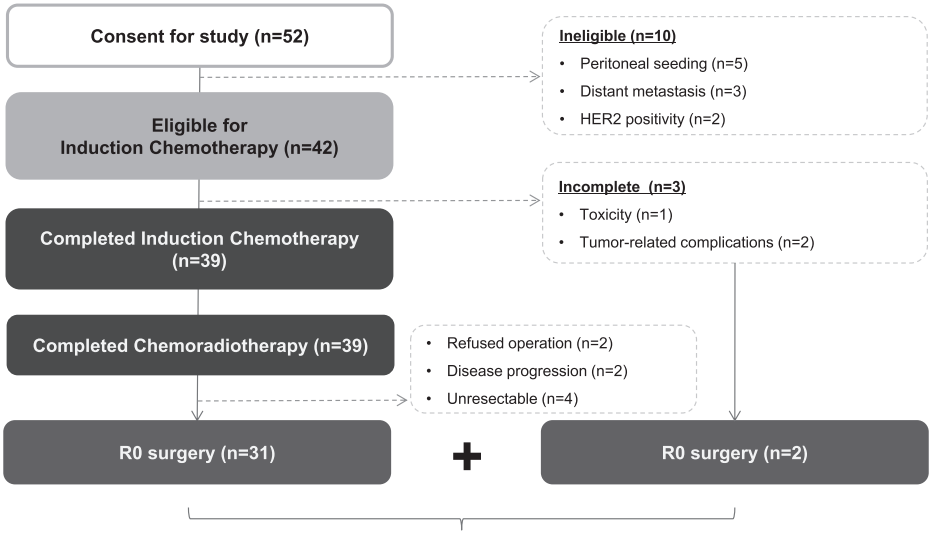
Among the 39 patients who completed full treatment of induction CTx and CCRT, 8 (20.5%) patients did not receive curative surgery owing to the following reasons: disease progression ($n = 2$), refused operation ($n = 2$), and unresectable tumor owing to persistent invasion of adjacent organ ($n = 4$). Of the 3 patients who received only induction CTx, 1 patient did not receive surgery owing to unresectable tumor and 2 received curative surgery. In total, R0 resection was achieved in 33 of 42 patients (78.6%) and the remaining cases were not resectable. The median time between the end of CCRT and surgery was 42 days (range 37–54). One patient had anastomosis site leakage but recovered after primary repair.

Among the 33 patients who underwent R0 resection, 5 (15.2%) had no residual carcinoma, 8 (24.2%) had 1–10% residual carcinoma, 10 (30.3%) had 11–50% residual carcinoma, and 10 (30.3%) had >50% residual carcinoma. Therefore, overall pathologic response (residual tumor ≤10%) was 39.4% (Table 3). Regarding the no residual carcinoma cases ($n = 5$), 4 were classified as stage 0 (ypT0N0M0), and 1 was classified as stage IA (ypT0N1M0, 1/57 positive lymph node). Overall, 4 patients (12.1%) had pathologic stage 0, 7 (21.2%) had stage I disease, 10 (30.3%) had stage II disease, and 12 (36.4%) had stage III disease. Finally, 24.3% of clinical stage III cases at baseline attained pathologic stage 0 or I (9 of 37). Pathologic nodal response was not different according to clinical N-stage and the correlation between residual tumor and pathologic stage is shown in Supplementary Fig. 2. None of the clinical factors (sex, location, Lauren classification, and pretreatment stage) were significantly associated with the achievement of pathologic response (data not shown).

Survival outcome and clinical predictive factors

At a median follow-up of 3.8 years (range 2.9–4.8), the 3-year OS rates were 75.5%. The median TTF was not reached for stages 0 and I, was at 25.9 months for stages II–III, and at 7.8 months for unresectable cases ($P < 0.001$, Fig. 2A). The OS rate at 3 years was 77.9% for stages 0 and I, 66.8% for stages II–III, and 33.3% for unresectable cases ($P = 0.001$, Fig. 2B). The TTF and OS did not differ significantly by residual carcinoma (data not shown).

Among the 33 patients with R0 resection, 12 had recurrences (local recurrence in 1 patient, distant lymph node in 2 patients,



Pathologic stage	Large B III	B IV	Bulky LN	Multiple LNs	P=0.48
0	2 (10.5%)	1 (7.7%)	0	1 (25.0%)	4 (9.5%)
I	4 (21.1%)	1 (7.7%)	1 (16.7%)	1 (25.0%)	7 (16.7%)
II	1 (5.3%)	5 (38.5%)	3 (50.5%)	1 (25.0%)	10 (23.8%)
III	6 (31.6%)	3 (23.1%)	2 (33.3%)	1 (25.0%)	12 (28.6%)
Unresectable	6 (31.6%)	3 (23.1%)	0	0	9 (21.4%)

Fig. 1. Consort diagram of patients.

Table 1
Patient demographics and tumor characteristics.

Characteristics	N (%)
Total	42 (100%)
Age, years	
Median	55
Range	27–75
Gender	
Male	32 (76.2)
Female	10 (23.8)
Performance status	
0	36 (85.7)
1	6 (14.3)
Differentiation	
Well	1 (2.4)
Moderate	12 (28.6)
Poorly	14 (33.3)
Signet ring cell	15 (35.7)
Tumor location	
Gastroesophageal junction	9 (21.4)
Body	7 (16.7)
Antrum	14 (33.3)
Entire	12 (28.6)
Borrmann type	
2	3 (7.1)
3	26 (61.9)
4	13 (31.0)
Clinical T stage	
T3	1 (2.4)
T4a	30 (71.4)
T4b	11 (26.2)
Clinical N stage	
N0	7 (16.7)
N1	15 (35.7)
N2	15 (35.7)
N3	5 (11.9)
Clinical TNM stage	
IIA	1 (2.4)
IIB	4 (9.5)
IIIA	9 (21.4)
IIIB	18 (42.9)
IIIC	10 (23.8)

liver in 1 patient, and peritoneal carcinomatosis in 8 patients). One (25%) of 4 patients with pathologic stage 0 cancer developed peritoneal recurrence, as did 1 (14.3%) of 7 patients with stage I. The median time to recurrence was 17.1 months (range 8.1–25.8).

A multivariate analysis using logistic regression was performed on the clinical factors to predict the probability of treatment failure defined as progression or recurrence. Among those cases, higher baseline T stage [cT4b rather than cT4a, odds ratio (OR) 5.9, 95% confidence interval (CI), 1.2–30.1, $P = 0.03$] and Borrmann type [Borrmann type 4, OR 5.6, 95% CI, 1.3–25.1, $P = 0.02$] were predictive of treatment failure (data not shown).

Discussion

The results of this phase II trial of induction CTx and CCRT prior to surgery indicate a promising clinical outcome with high pathologic responses. In addition, toxicities were acceptable without a significant increase in perioperative morbidity.

Based on convincing results with combination treatment in locally advanced esophageal carcinoma [16,17], the role of preoperative CCRT was tested in GC cancer. Significantly better local progression-free survival was reported in the CCRT group, than that with preoperative CTx, whereas distant metastases occurred equally [18]. Therefore, to further decrease distant recurrence, the concept of sequential CTx and CCRT was studied, and a substantial pathologic response was noted with durable survival times [6,9].

In patients with unresectable locally advanced or high-risk GC, the R0 resection rate was reported to be 45–69% of cases [19–21]. However, the various criteria for staging and pathologic complete response (CR) were observed in less than 10% of cases [19]. Our data demonstrated a higher R0 resection rate (78%) with 15.2% of pathologic CR. Furthermore, compared with other studies using preoperative treatment, we enrolled patients with advanced stages of cancer: T4a (71%) and T4b (26%) cases compared to only 8% T4 cases in the FLOT4 trial [22]. Although its superiority was not compared directly, our data provided evidence that sequential treatment with a triplet regimen may improve survival and warrant further investigation for high-risk patients.

Table 2
Toxicity grade per patient according to treatment sequence.

CTCAE grade	Induction chemotherapy ($n = 42$)				Chemoradiotherapy ($n = 39$)			
	1	2	3	4	1	2	3	4
Hematologic								
Neutropenia	–	6 (14.3%)	1 (2.4%)	1 (2.4%)	–	3 (7.7%)	2 (5.1%)	–
Neutropenic fever	–	–	1 (2.4%)	1 (2.4%)	–	–	–	–
Anemia	–	2 (4.8%)	1 (2.4%)	–	–	–	–	–
Thrombocytopenia		–	–	–	1 (2.6%)	–	1 (2.6%)	–
Non-hematologic								
ALT increased	5 (11.9%)	–	–	–	1 (2.6%)	1 (2.6%)	–	–
AST increased	2 (4.8%)	–	–	–	2 (5.1%)	–	–	–
Creatinine increased	1 (2.4%)	–	–	–	–	–	–	–
Hyponatremia	1 (2.4%)	–	2 (4.8%)	–	–	–	–	–
Hyperkalemia	–	1 (2.4%)	–	–	–	–	–	–
Hypomagnesemia	1 (2.4%)	–	–	–	–	–	–	–
Anorexia	6 (14.3%)	17 (40.4%)	–	–	4 (10.3%)	6 (15.4%)	2 (5.1%)	–
Nausea	7 (16.7%)	5 (11.9%)	3 (7.1%)	–	7 (17.9%)	4 (10.3%)	1 (2.6%)	–
Vomiting	4 (9.5%)	2 (4.8%)	3 (7.1%)	–	–	1 (2.6%)	–	–
Diarrhea	7 (16.7%)	6 (14.3%)	1 (2.4%)	–	–	–	1 (2.6%)	–
Abdominal pain	3 (7.1%)	7 (16.7%)	1 (2.4%)	–	–	9 (23.1%)	–	–
Stomatitis	–	3 (7.1%)	1 (2.4%)	–	1 (2.6%)	1 (2.6%)	–	–
Constipation	–	4 (9.5%)	–	–	2 (5.1%)	1 (2.6%)	–	–
Fatigue	2 (4.8%)	2 (4.8%)	–	–	1 (2.6%)	3 (7.7%)	–	–

Toxicity was graded according to the Common Terminology Criteria for Adverse Events criteria (CTCAE version 4.0).

Table 3
Correlation of clinical and pathologic assessment (n = 33).

		IIA	IIB	IIIA	IIIB	IIIC	n (%)
*Pathologic stage	0	1		2	1		4 (12.1%)
	IA			1			1 (3.0%)
	IB		1	1	3	1	6 (18.2%)
	IIA		1	1	1		3 (9.1%)
	IIB		1	2	1	3	7 (21.2%)
	IIIA		1	1	2	2	6 (18.2%)
	IIIB				4	1	5 (15.2%)
	IIIC				1		1 (3.0%)
Residual tumor (%)	0	1		2	2		5 (15.2%)
	1–10		2	3	1	2	8 (24.2%)
	11–50			3	4	3	10(30.3%)
	>50		2		6	2	10(30.3%)
		1 (3.0%)	4 (12.1%)	8 (24.2%)	13 (39.4%)	7 (21.2%)	Total n = 33 (%)

* Standard pathologic staging was determined using guidelines from the 7th edition of the American Joint Committee on Cancer tumor, node, and metastasis classification.

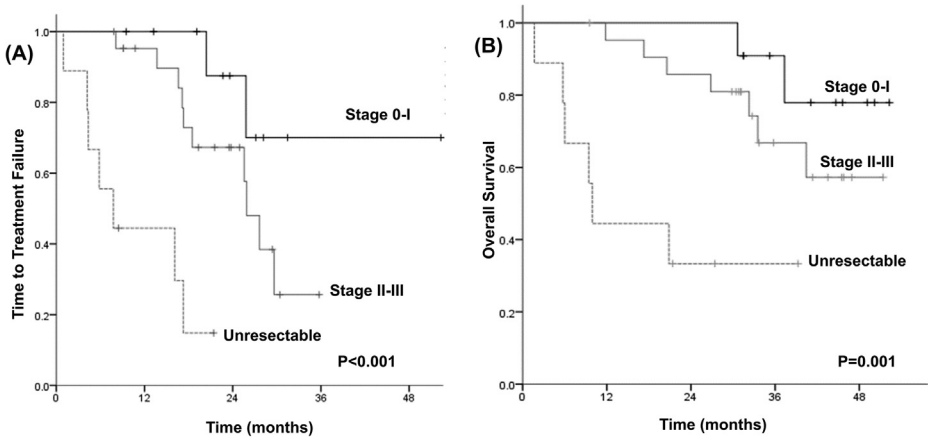


Fig. 2. Kaplan–Meier estimates of time to treatment failure (A) and overall survival (B) according to the treatment outcome.

Traditionally, combinations of 5-fluorouracil (5-FU) and cisplatin have been widely used as standard perioperative combinations [5,9]. The substitution of oral 5-FU derivatives, such as capecitabine or TS-1 for continuous infusion of 5-FU, has improved treatment outcomes without the inconvenience of continuous infusion [23,24]. Recently, the triplet regimen of docetaxel, 5-FU, and cisplatin significantly improved survival, response, and clinical benefits in advanced GC [25,26]. Meta-analysis also suggested taxane-based triplet regimen offers the best opportunity with better survival and responses [27]. In a recent phase II/III FLOT study, docetaxel-based triplet regimen achieved higher responses than epirubicin-based triplet regimens by 10% [22]. However, triplet combination inevitably produced a high rate of grade 3–4 neutropenia (52%), and non-hematologic toxicities offset the value of higher response. This led us to consider the application of weekly dosing. Therefore, based on reports of weekly regimen alleviating toxicities without compromising efficacy [28,29]; we combined TS-1 with a weekly docetaxel and cisplatin regimen. We found that all toxicities or grade 3–4 toxicities were considerably less frequent in our study than in other trials with triplet regimens [25,26]. Weekly-split and daily oral administration during induction CTx resulted in significantly lower rates of grade 3–4 neutropenia (4.8%) and anemia (2.4%) in our study.

A major concern of radiotherapy in GC is its perceived toxicity. In a study by Stahl [30,31], patients with locally advanced GC who were treated with doublet-regimen CTx followed by 30 Gy CCRT had a postoperative mortality of 10–16%. The traditional radiotherapy field covers a large drainage area surrounding several lymph nodes, which results in significant toxicity and low completion rate. One of the reassuring findings in our trial was that CCRT is well tolerated with 100% completion rates, and perioperative surgical complications are minimal. With the aid of CT-based conformal delivery, the clinical utility and safety of a reduced radiotherapy field were well validated [32–35]. These results support the continued use of radiotherapy target encompassing high-risk nodal areas, such as para-aortic, aortocaval, retrocaval, and retropancreatic lymph nodes rather than all lymphatic drainage. The absolute completion rate of CCRT in the present study was also higher than that in the ARTIST trial (100% vs 81.7%), which implies the significance of perioperative radiotherapy delivery for more adherence to treatment. With recent improvements in radiotherapy, preoperative 45-Gy-CCRT was safe and tolerable in our study.

Surgery with adjuvant chemotherapy is the standard treatment for potentially curable GC [13,14]. In our study, TS-1 monotherapy (n = 27) or xeloda/oxaliplatin combination (n = 3) was introduced for 30 patients. The remaining 3 patients did not receive adjuvant chemotherapy because of the pathologic CR (n = 2) and patient's refusal (pathologic stage III, n = 1); however, no recurrence occurred in any of the cases. TTF and OS were not statistically different and only pathologic stage was the best predictor of survival outcome consistent with other studies [21,36].

Given the potential efficacy of neoadjuvant treatment for resectable GC, appropriate selection of patients based on accurate staging who experience greater benefits than toxicity is important. In this context, a preoperative strategy may be an acceptable and effective option for these high-risk patients. Macroscopic

Borrmann type III and IV tumors with aggressive features, including serosa invasion and higher lymph node metastasis, are known to have poor OS [37]. In addition, large tumor size (>8 cm) and bulky lymph nodes were poor prognostic factors after survival, which act as a guide for more effective therapy [38,39]. Therefore, a clinical trial with neoadjuvant CTx for high-risk, resectable GC is ongoing [38]. In addition, for optimal preoperative treatment, we established a complex staging procedure, including endoscopic ultrasonography and diagnostic laparoscopy. Because peritoneal metastases were noted in 20% of cases [40], we performed a mandatory laparoscopy and uncovered 10% of peritoneal seeding not detected in the baseline CT scan. Therefore, we selected the most high-risk group of patients with locally advanced GC that would have the maximum benefit from a more effective neoadjuvant treatment.

In our study, a complex preoperative strategy requiring laparoscopy as part of initial staging, followed by induction CTx and CCRT, was adopted. An intensive, weekly-split, triplet regimen could represent a therapeutic option for locally advanced, high-risk GC. Collectively, our data suggested that preoperative sequential treatment was tolerable and had substantial pathologic responses that led to prolonged survival time, worthy of investigation via future randomized trials.

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Declaration of Competing Interest

The authors have no potential conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.06.029.

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