

Original Article



OPEN ACCESS

Received: Jul 28, 2020

Revised: Nov 1, 2020

Accepted: Nov 14, 2020

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Trial Registration

ClinicalTrials.gov Identifier: [NCT02949258](https://clinicaltrials.gov/ct2/show/study/NCT02949258)

Phase II Study of Preoperative Intra-Arterial Epirubicin, Etoposide, and Oxaliplatin Combined with Oral S-1 Chemotherapy for the Treatment of Borrmann Type 4 Gastric Cancer

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ABSTRACT

Purpose: A phase II study was conducted to evaluate the safety and efficacy of preoperative, intra-arterial perfusion of epirubicin, etoposide, and oxaliplatin combined with oral chemotherapy S-1 (SEEOX) for the treatment of type 4 gastric cancer.

Materials and Methods: A single-center, single-arm phase II trial was conducted on 36 patients with histologically proven type 4 gastric cancer without distant peritoneal or organ metastasis. Patients received 3, 21-day courses of SEEOX preoperative chemotherapy. The primary endpoint was overall survival (OS) and the secondary outcomes assessed were chemotherapeutic response, radical resection rate, pathological regression, toxicities, postoperative morbidity, and mortality.

Results: All patients were at an advanced stage of cancer (stage III or IV) and completed the entire course of treatment. Based on changes in tumor volume and peritoneal metastasis, the objective response rate was 55.6% (20/36; 95% confidence interval [CI], 38.5%–72.6%) and the disease control rate was 69.4% (25/36; 95% CI, 53.6%–85.3%). The radical resection rate was 75% (27/36; 95% CI, 60.1%–89.9%) and the proportion of R0 resections was 66.7% (21/36; 95% CI, 50.5%–82.8%). The pathological response rate was 33.3%, of which 13.9% showed complete pathological regression. The median survival was 27.1 months (95% CI, 22.24–31.97 months), and the 2-year OS was 48.5% (95% CI, 30.86%–66.1%).

Conclusions: Preoperative SEEOX is a safe and effective treatment for type 4 gastric cancer. Based on these preliminary data, a phase III study will be conducted to confirm the superiority of this regimen over standard treatment.

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Keywords: Gastric cancer; Neoadjuvant chemotherapy; Linitis plastica

Author Contributions

Conceptualization: G.L.L.; Data curation: X.X.S., S.Y., M.L., Z.C.S., M.R.F.; Formal analysis: L.G.L., X.X.S.; Investigation: S.Y., M.L.; Methodology: X.X.S., Z.C.S.; Project administration: L.G.L.; Software: X.X.S.; Supervision: L.G.L.; Writing - original draft: X.X.S., S.Y.; Writing - review & editing: X.X.S., L.G.L.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Despite a decrease in the incidence of gastric cancer during recent years, it remains the fifth most commonly diagnosed malignancy and the third most frequent cause of cancer-related deaths worldwide [1]. Approximately 10%–15% of gastric adenocarcinomas are classified as Borrmann type 4, which is characterized by thickening and stiffening of the gastric wall due to tumor cell infiltration. Furthermore, the absence of mucosal ulceration, or mucosal elevation during the early stages, creates challenges for endoscopic detection. Since a large proportion of patients are diagnosed at advanced stages, most type 4 gastric tumors are unresectable or only marginally resectable at initial diagnosis, resulting in a very short overall survival (OS) and poor prognosis [2,3]. In contrast, the survival rates of resectable type 4 and other types of gastric cancer are similar [4]. Furthermore, type 4 gastric cancers have also been associated with a high rate of peritoneal metastasis, including peritoneal dissemination (P1) and positive peritoneal cytology (CY1). The latter is a predictive factor of distant metastasis (M1), which is classified as stage IV by the Union for International Cancer Control (UICC), the American Joint Committee on Cancer (AJCC), and the Japanese classification systems of gastric carcinoma [5-8].

Several studies have reported that perioperative chemotherapy, especially neoadjuvant chemotherapy (NAC), can significantly improve the prognosis of advanced gastric cancer patients. However, the recent FLOT series of studies have not specifically described the effects of this treatment on type 4 gastric cancer [9,10]. The Japan Clinical Oncology Group (JCOG)-0501 study also did not observe a positive impact of the use of cisplatin and S1 on the prognosis of patients with type 4 gastric cancer [11]. Therefore, an effective chemotherapeutic regimen must be established to improve the radical resection rate and OS of patients with type 4 gastric cancer.

Transcatheter arterial infusion of chemotherapy drugs can increase their intra-tumoral concentration to therapeutically significant levels and improve treatment outcomes. We developed a S-1, etoposide, oxaliplatin and epirubicin (SEEOX) preoperative chemotherapy regimen by combining the intra-arterial perfusion of epirubicin, etoposide, and oxaliplatin, with oral S-1 chemotherapy for the treatment of advanced gastric cancer. The local perfusion of oxaliplatin and epirubicin in a concentration-dependent manner and the time-dependent release of S-1 increased their retention at the target site, resulting in greater therapeutic efficacy. The SEEOX regimen significantly improved the outcomes of patients diagnosed with type 4 gastric cancer [12,13]. To further evaluate these observations, we initiated a phase II study in October 2016 (NCT-B4) and present the final results in this report.

MATERIALS AND METHODS

Patients

The patients were enrolled in this study based on the following inclusion criteria: i) histologically-proven gastric adenocarcinoma, ii) macroscopic type 4 tumors characterized by a lack of marked ulcerations or raised margins, gastric wall thickening and induration, and unclear margins as diagnosed using gastroscopy or computed tomography (CT), iii) no distant peritoneal, or liver/lung metastasis, or a large volume of ascites, except localized peritoneal seeding around the stomach or positive peritoneal lavage cytology with laparoscopic confirmation, iv) age 20–75 years with an Eastern Cooperative Oncology

Group performance status of 0–2, v) no prior history of chemotherapy, radiation therapy, or surgery for gastric cancer, vi) sufficient organ function (white blood cell [WBC] count $3\text{--}12 \times 10^9/\text{L}$; platelet [PLT] count $>100 \times 10^9/\text{L}$; alanine aminotransferase [ALT] and aspartate aminotransferase [AST] ≤ 2.5 times the upper limit of the normal range [ULN], creatinine $45\text{--}110 \mu\text{mol}/\text{L}$), and vii) willingness to provide written informed consent.

Patients with i) synchronous or metachronous (within 5 years) malignancies other than in situ carcinoma or ii) severe heart, liver, kidney, hematopoietic, central nervous system diseases or epilepsy, or pregnant/lactating patients were excluded.

Exploratory laparoscopy

All patients underwent exploratory laparoscopy to determine the presence or absence of peritoneal metastasis, and peritoneal lavage cytology was performed to determine the cytological characteristics of the fluid. The disease was characterized as CY0 or CY1 based on the absence or presence of cancer cells in the peritoneal fluid, respectively. Peritoneal metastasis was classified according to the Japanese Classification of Gastric Carcinoma 12th edition guidelines [14]: P0, no peritoneal metastasis; P1, dissemination to the peritoneum adjacent to the gastric cancer; P2, few metastatic masses in the peritoneum; and P3, numerous metastatic masses in the peritoneum. Based on the above-mentioned criteria, patients who were diagnosed with P2–3 and CY0–1 were excluded.

Preoperative chemotherapy

All patients included in this study received 3 cycles of preoperative chemotherapy, with each cycle lasting 3 weeks. Intra-arterial etoposide ($80 \text{ mg}/\text{m}^2$), oxaliplatin ($100 \text{ mg}/\text{m}^2$), and epirubicin ($30 \text{ mg}/\text{m}^2$) were administered on day 1. The specific procedure was as follows: the 5F vascular sheath was inserted percutaneously into the femoral artery using the Seldinger technique, then hooked onto the celiac axis and linked to an external high-pressure injector to perform high-pressure angiography. If the diameter of the target vessel was smaller than the 5F catheter, or if it was too difficult to superselect with the 5F catheter, a micro godet was used to achieve intubation. The feeding artery of the tumor was identified according to the results of angiography, and the chemotherapy drugs were slowly injected over 10 minutes. The feeding artery of most lower gastric cancers is the right gastroepiploic artery, while the feeding artery of middle and upper gastric cancers is the left gastric artery. All patients also received oral S-1, ($40\text{--}60 \text{ mg}$, twice a day; the total dose depending on the patient's body surface area as follows: $<1.25 \text{ m}^2$, 80 mg ; $1.25\text{--}1.5 \text{ m}^2$, 100 mg ; and $>1.5 \text{ m}^2$, 120 mg ; on days 1–14 of every 3-week cycle. The drug doses were decreased to 75% of the initial dosage and thereafter to 50%, if any of the following were observed: WBC count $<2.0 \times 10^9/\text{L}$, PLT count $<50 \times 10^9/\text{L}$, neutrophil count $<1.0 \times 10^9/\text{L}$, neuropathy score ≥ 2 (creatinine $\geq \text{ULN}$), edema ≥ 2 or hepatorenal dysfunction ≥ 2 AST/ALT $\geq 2.5 \times \text{ULN}$ or total bilirubin $\geq 1.5 \times \text{ULN}$).

Surgery

The response to chemotherapy was evaluated using a CT scan taken 7–10 days after the last dose. The presence of an increasing amount of ascites or distant metastases in the liver and lung were indicative of disease progression and were not followed by exploratory laparoscopy. If there were no changes in the primary tumor and R0 resection was still impossible, laparoscopy was not performed and the patient received systemic chemotherapy. If R0 resection was deemed possible with D2 or D3 lymph node dissection, as determined through gastrectomy, laparoscopy was performed prior to the surgery. Gastrectomy was not performed if the patient was diagnosed with P2–3, or CY1 disease; instead, systemic

chemotherapy was initiated. If the patient was diagnosed with PO-1 and CY0 disease gastrectomy and radical lymphadenectomy were performed for R0 resection.

Adjuvant chemotherapy and follow-up

Three to four cycles of adjuvant chemotherapy of S-1 and oxaliplatin were administered for 6 weeks following radical surgery. Patients received oral S-1 twice a day at a body surface area-dependent dosage on days 1-14 of each 3-week cycle. Oxaliplatin was administered as an intravenous infusion of 100 mg/m² on day 1 of each course. During follow-up, abdominal CT scans were performed every 6 months, and the circulating levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were measured every 3 months over a period of 2 years.

Objectives, evaluation, and study design

This study was a single-center, single-arm phase II trial. The primary endpoint was OS, defined as the time from enrollment to death resulting from any cause or the last date of contact with a surviving patient. The secondary endpoints were: chemotherapeutic response, radical resection rate, pathological regression, toxicities, postoperative morbidity, and mortality. The response to chemotherapy was evaluated in terms of the change in tumor volume, peritoneal metastasis, and lavage cytology. The tumor response to chemotherapy was assessed using an enhanced CT scan and exploratory laparoscopy. An objective response was defined using the RECIST 1.1 criteria, which includes complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR, PR, and SD with no changes in PO → P1-3 and no changes in CY0 → CY1 were indicative of controlled disease. Progression of initial tumor, peritoneal metastasis progression (PO → P1-3 or P1 → P2-3) and positive peritoneal lavage cytology (CY0 → CY1) were all indicative of PD. The pathological response of the primary tumor was graded according to Becker regression criteria [15], which is based on the percentage of vital tumor cells within the macroscopically identifiable tumor bed: TRG1a, equivalent to complete pathological regression without any residual tumor cells; TRG1b, subtotal regression <10% residual tumor cells, TRG2, partial regression with 10%–50% residual tumor cells, and TRG3, minor or no regression >50% residual tumor cells. Adverse events (AEs) associated with either gastrectomy or chemotherapy were separately evaluated according to the Common Terminology Criteria for AEs (version 5.0).

In the JCOG-0210 study, the 2- and 3-year survival rates of patients with resectable gastric cancer were 35% and 24.5%, respectively [16]. Consistent with this finding, Blackham et al. [8] retrospectively found that the median survival duration of type 4 gastric cancer was only 11.6 months and the 2-year survival rate was less than 30%. Since many patients in our cohort were initially determined to be unresectable, we expected their 2-year survival rate to increase to above 30% after treatment. Therefore, after excluding patients with distant peritoneal metastasis, 35 patients were selected to receive the SEEOX regimen. As an exploratory phase II study, the number of patients required was calculated based on an expected 2-year OS of over 30%, with a one-sided α of 5% and 80% statistical power.

The survival curve was estimated using the Kaplan-Meier method, and the 95% confidence interval (CI) of yearly survival was calculated using Greenwood's formula, and the log-rank test was used to determine statistical differences between groups. Statistical analyses were performed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk NY, USA). The study protocol was approved by the Ethics Committee of Jinling Hospital, Nanjing University (2014ZFYJ-012). This study was conducted in accordance with the international ethical

recommendations stated in the Declaration of Helsinki. This study is registered with ClinicalTrials.gov under the following reference: NCT02949258.

RESULTS

A total of 36 patients were enrolled between October 2016 and March 2018, and the study flowchart is shown in Fig. 1. All patients received preoperative chemotherapy, and the average follow-up duration was 22.3 months (range, 6–41 months). Patient demographics and tumor characteristics are summarized in Table 1. The majority of patients suffered from late-stage disease. Laparoscopic exploration revealed positive peritoneal lavage cytology (CY1) in 17 patients classified as stage IV. Ten patients (27.8%) were stage IIIc and 19 (52.8%) were stage IV disease, while the tumors were unresectable or marginally resectable in all of these 29 patients (80.6%).

Preoperative chemotherapy and clinical response

As shown in Fig. 2, the primary tumors of 25 patients significantly decreased in size ($\geq 30\%$) and that of 3 patients receded completely after 3 cycles of preoperative treatment. Typical CT images of patients who received SEEOX preoperative chemotherapy were also shown in Fig. 2. We did not observe large metastatic growths in the liver or lung after chemotherapy in any of the patients. One patient initially determined as P1CY1 developed a large volume of ascites, and the progressed tumor was unresectable in 3 patients initially determined as P1CY1. Thus, 32 patients underwent re-exploratory laparoscopy, which did not show peritoneal metastasis or cancer cells in the peritoneal lavage of 12 patients initially determined to be POCY0. Ten of the 17 patients initially determined to be CY1 patients retrogressed to CY0 after preoperative treatment (58.8%; 95% CI, 32.7%–84.9%), whereas 3 patients initially determined to be P1CY1 patients progressed to P2–3. Thus, based on both tumor volume and peritoneal metastasis, 20 patients were found to be responders, including 3 patients with CR

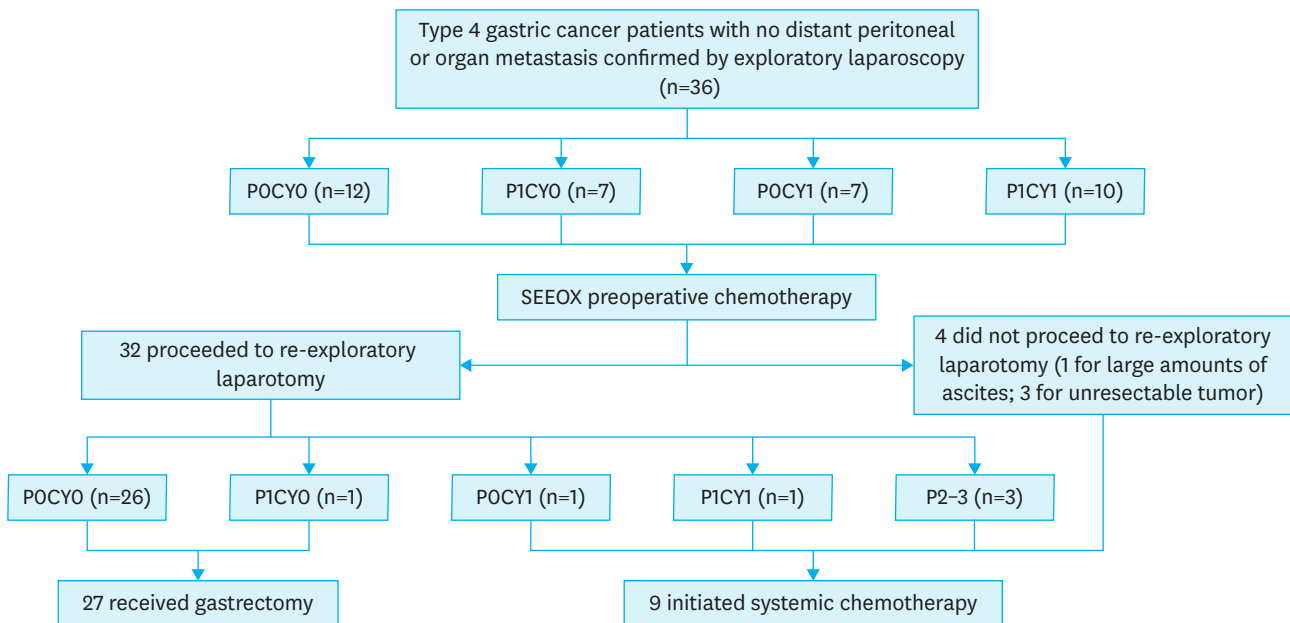


Fig. 1. The CONSORT flow chart.

Table 1. Patient demographics and tumor characteristics

Variable	Patients (n=36)
Age (yr)	5 (29–72)
Sex	
Male	19 (52.8)
Female	17 (47.2)
Extent of the tumor	
Distal	12 (33.3)
Total	24 (66.6)
Tumor invasion	
cT4a	28 (77.8)
cT4b	8 (22.2)
Lymph node metastasis	
cN0–1	3 (8.3)
cN2	12 (33.3)
cN3	21 (58.3)
Peritoneal metastasis and peritoneal cytology	
POCYO	12 (33.3)
PICYO	7 (19.4)
POCY1	8 (22.2)
PICY1	9 (25.0)
cStage	
IIIa	3 (8.3)
IIIb	4 (11.1)
IIIc	10 (27.8)
IV	19 (52.8)

Values are presented as median (interquartile range) or number (%).
cStage = clinical stage.

and 17 patients with PR. Among the non-responders, 5 showed SD and eleven showed PD. Accordingly, the objective response rate was 55.6% (20/36; 95% CI, 38.5%–72.6%) and the disease control rate was 69.4% (25/36; 95% CI, 53.6%–85.3%).

Surgical and pathological findings

The surgery and pathological findings are shown in **Table 2**. All patients were re-evaluated for the possibility of radical resection after completion of preoperative chemotherapy. Three patients were found to have unresectable primary tumors, whereas another showed extensive ascites. Thirty-two patients underwent surgery, while 5 patients did not undergo radical resection due to peritoneal and mesenteric metastasis or positive peritoneal lavage cytology. Twenty-seven patients underwent radical gastrectomy, including 22 patients who underwent total gastrectomy and 5 patients who underwent distal gastrectomy. The radical resection rate was 75% (27/36; 95% CI, 60.1%–90.0%). R0 resection was performed in 24 patients, and R1 resection was performed on 3 patients who presented with positive margins. Thus, the frequency of R0 resections among all 36 patients was 66.7% (21/36; 95% CI, 50.5%–82.8%).

Histopathological assessment revealed poorly differentiated adenocarcinoma as the predominant histological type. Furthermore, signet ring cells were detected in 11 patients. We observed complete pathological remission in 5 patients, while 7 patients presented with some residual tumor cells (TRG1b and TRG2). Therefore, the pathological CR rate of preoperative chemotherapy was 13.9% (5/36; 95% CI, 2.0%–25.8%) and the pathological response rate was 33.3% (12/36; 95% CI, 17.2%–49.5%).

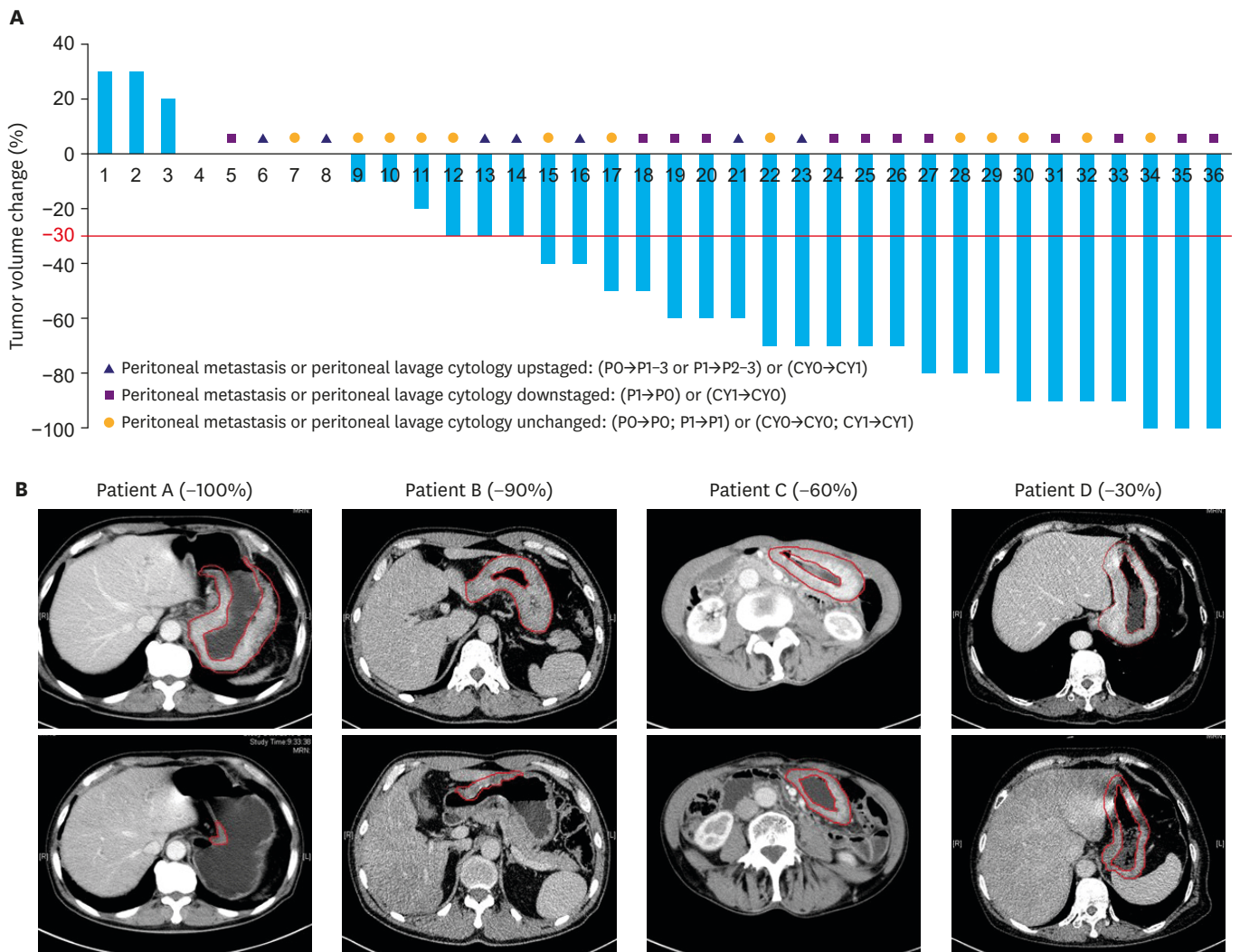


Fig. 2. Waterfall plot of tumor volume changes and typical CT graphs. (A) Waterfall plot showing changes in tumor volume, peritoneal metastasis and peritoneal lavage cytology. Patients 1–3 did not undergo laparoscopy due to disease progression, and patient 4 due to the large amount of ascites. (B) Typical CT images of patients who received SEEOX preoperative chemotherapy. Patient A is a 71-year-old surviving male diagnosed with POCY1. After preoperative treatment, CT evaluation indicated CR, re-laparoscopy revealed POCY0 and histological examination showed complete pathological regression. Patient B was a 45-year-old male diagnosed with POCY1. CT evaluation and re-laparoscopy respectively indicated PR (–90%) and POCY0. The histological subtype of this tumor was signet ring cell carcinoma, T4aN2M0, TRG3. The patient passed away 17 months post-surgery due to peritoneal metastasis. Patient C is a surviving 67-year-old male diagnosed with P1CY0. CT evaluation showed PR (–60%), re-laparoscopy indicated POCY0 and the histological subtype indicated poorly differentiated adenocarcinoma, T4bN3M0, TRG3. Patient D is a surviving 65-year-old female diagnosed with POCY1. CT evaluation showed PR (–30%), re-laparoscopy revealed POCY0 and a complete pathological regression was seen. CT = computed tomography; SEEOX = S-1, etoposide, oxaliplatin and epirubicin; CR = complete response; PR = partial response.

AEs and surgical complications

The types and frequencies of AEs encountered during chemotherapy are summarized in **Table 3**. Grade 3 toxicities were observed in 7 patients (19.4%), whereas grade 4 AEs were not observed. The major AEs included leucopenia, anemia, nausea, vomiting, and diarrhea. No specific complications were observed due to intra-arterial chemotherapy. Surgical complications were assessed in all 32 patients who underwent surgery. As shown in **Table 4**, surgical complications included anastomotic leakage in one patient, a pancreatic fistula in 2 patients, and wound infection and pneumonia in one patient each. There were no incidences of surgical mortality or reoperation, while surgical morbidity was 15.6% (5/32).

Table 2. Surgery and pathological findings in all resected patients (n=27)

Variables	Values
Type of resection	
Total gastrectomy	22
Distal gastrectomy	5
Curability	
R0	24
R1	3
Histology	
Poorly differentiated	15
Moderately-poorly differentiated	5
Well-differentiated	1
Signet ring cell carcinoma	1
No obvious cancer cells	5
Signet ring cell (exists)	
Negative	16
Positive	11
Tumor invasion	
T0	5
T1a	1
T2	3
T3	2
T4a	13
T4b	3
Lymph node metastasis	
N0	14
N1	3
N2	5
N3	5
ypTNM stage	
I	3
IIB	9
IIIA	2
IIIB	3
IIIC	5
Unevaluated	5
Pathological response	
TRG1a	5
TRG1b	1
TRG2	6
TRG3	15
Resection of adjacent organs	
No	24
Yes	3
Gallbladder	1
Spleen	1
Colon	1

ypTNM = yield pathologic Tumor-Node-Metastasis.

OS

All 36 patients were followed over a period of 2 years, during which 17 patients died. As shown in **Fig. 3A**, the 2-year OS rate was 48.5% (95% CI, 30.86%–66.1%), and the lower limit of the 95% CI was higher than the predicted threshold (30%). The median survival time was 27.1 months (95% CI, 22.24–31.97 months). Furthermore, the mean survival duration of patients who did not undergo resection was only 9.67 months (95% CI, 8.28–11.05 months) compared to 32.95 months (95% CI, 28.21–37.70 months) among patients who underwent radical resection ($P < 0.001$). Although the OS was not significantly different between patients initially diagnosed with P0CY0, P1CY0, P0CY1, and P1CY1, patients initially diagnosed with CY0 showed significantly better prognosis compared to those diagnosed as CY1's (median

Table 3. Adverse events during chemotherapy in all eligible patients (n=36)

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytes	7	4	1	0
Hemoglobin	2	1	2	0
Platelets	9	4	0	0
Total bilirubin	3	0	0	0
AST	2	1	0	0
ALT	2	0	0	0
Creatinine	1	0	0	0
Nausea	11	5	2	0
Vomiting	12	3	1	0
Anorexia	4	2	0	0
Diarrhea	4	1	1	0
Stomatitis	6	1	0	0
Fatigue	3	1	0	0

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 4. Surgical complications in operated patients (n=32)

Surgical complications	Number of patients (%)
Anastomotic leakage	1 (3.1)
Pancreatic fistula	2 (6.2)
Wound infection	1 (3.1)
Pneumonia	1 (3.1)

survival, 32.17 months; 95% CI, 26.14–38.21 months vs. 21.38 months; 95% CI, 14.58–28.18 months; P=0.049).

DISCUSSION

This phase II study is the first to demonstrate the efficacy and safety of the use of SEEEX, a combination of intra-arterial chemotherapy and oral chemotherapy, for type 4 gastric cancer.

Type 4 gastric cancer is characterized by severe malignancy, occult onset, and rapid but insidious progression that makes early diagnosis challenging [3]. Not surprisingly, many patients in our study were diagnosed at the late stages of disease through radiological examination and exploratory laparoscopy. This is consistent with a retrospective Korean study in which 73.9% of type 4 gastric cancer patients were diagnosed at stage III or IV of the disease [2]. Furthermore, Blackham et al. [8] reviewed data on 869 gastric cancer patients from the U.S. Gastric Cancer Collaborative Database and found that 90% of type 4 gastric cancer patients were diagnosed with stage III or IV cancers. Type 4 gastric cancers also present with a high frequency of peritoneal metastasis, including peritoneal dissemination and positive peritoneal cytology (CY1) [4]. The latter is a risk factor for distant metastasis (M1) and is classified as stage IV by the UICC and AJCC. In the present study, the prognosis of patients initially diagnosed with CY1 disease was also found to be significantly worse than that of patients with no cancer cells in the peritoneal fluid (CY0).

At present, the only effective treatment for gastric cancer is radical tumor resection. Nazli et al. [17] analyzed the postoperative survival of 121 patients at varying stages of type 4 gastric cancer and found that R0 resection was the most crucial factor affecting the survival rate of patients at the same stage. Blackham et al. [8] also observed no differences between the survival rates of type 4 and other gastric cancer patients after radical R0 resection. However, most type 4 gastric tumors are unresectable or only partially resectable due to positive

Preoperative Chemotherapy for 4 Gastric Cancer

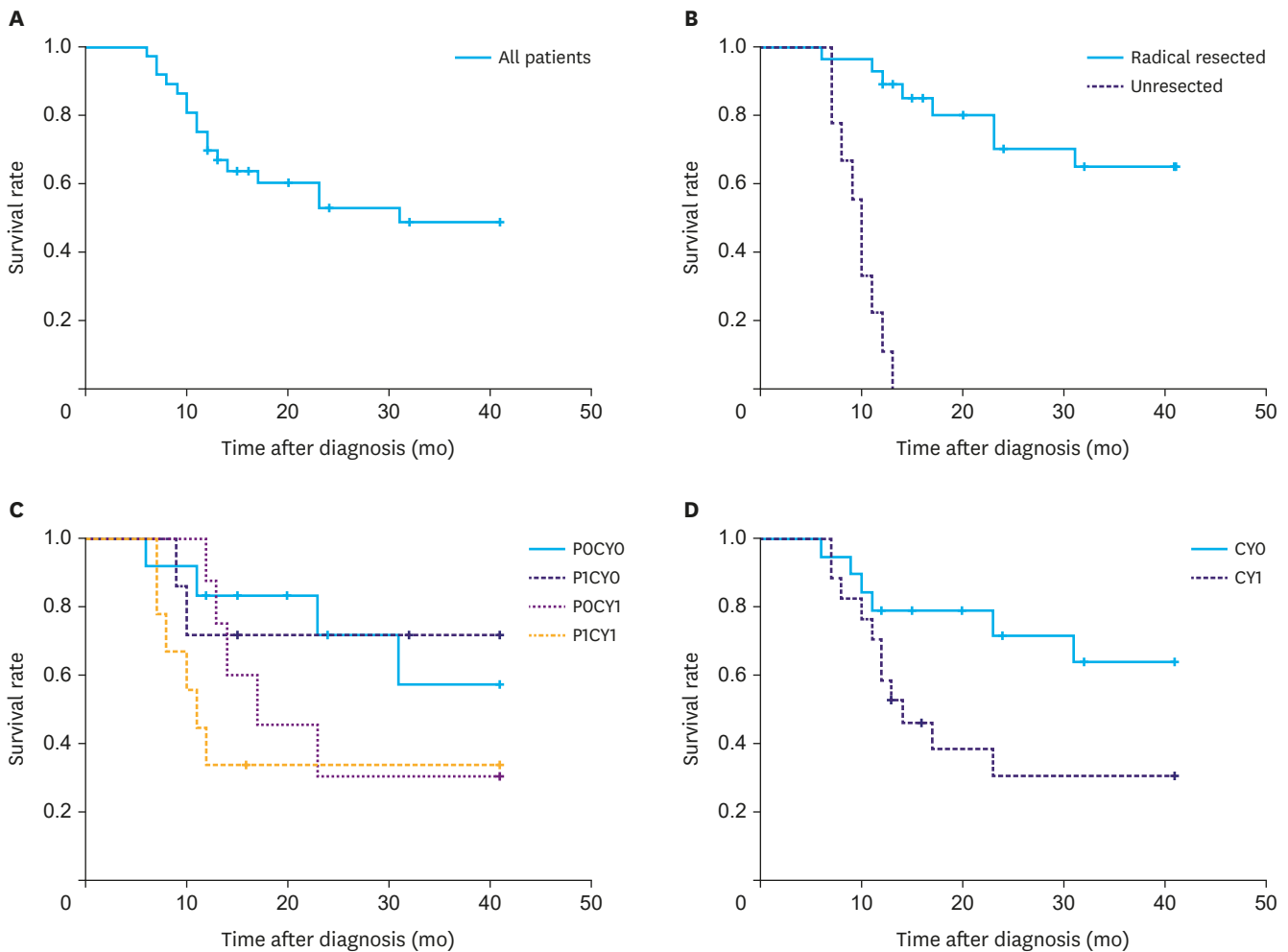


Fig. 3. (A) Kaplan-Meier OS curve of 36 enrolled patients. (B) Kaplan-Meier OS curves of resected (n=27) and unresected (n=9) patients ($P < 0.001$). (C) Kaplan-Meier OS curve of patients demarcated on the basis of peritoneal metastasis (P) and peritoneal lavage cytology (CY) ($P = 0.167$). (D) Kaplan-Meier OS curve of patients on the basis of CY ($P = 0.049$). OS = overall survival.

margins, peritoneal metastasis, or adjacent organ invasion. Liang et al. [18] reviewed data of 469 type 4 gastric cancer patients, of which only 146 (31%) had received curative resection. Since positive margins are more common in type 4 gastric tumors, the median survival time of patients is poor and ranges from 5.7 to 13.8 months [19,20]. In our study, however, the mean survival duration of the 36 type 4 gastric cancer patients was extended to 27.1 months after SEEEX treatment, which is significantly longer than the rates reported in other studies. Thus, the preoperative administration of SEEEX may improve the conditions for radical tumor resection.

The multicenter MAGIC and FLOT clinical studies have also confirmed that preoperative neoadjuvant chemotherapy (NAC) can significantly decrease the progression of gastric cancer [9,10]. However, these trials were conducted on a general gastric cancer population, and the response of type 4 gastric cancer was not assessed. The JCOG-0210 and JCOG-0501 studies conducted by the Japan Clinical Oncology Association also confirmed the safety of the use of cisplatin + S1 preoperative chemotherapy for resectable Borrmann type 4 and large type 3 (>8 cm) gastric cancers, although the procedure did not result in a survival benefit [11,16].

Furthermore, both the ARTIST trial and the 10-year update of the INT-0116 trial showed that adjuvant radiotherapy was significantly less effective in diffuse tumors [21,22]. The Checkmate-032 and Keynote-062 studies showed that immune checkpoint inhibitors did not provide a superior therapeutic effect against gastric cancer and were particularly ineffective against advanced stages of the disease [23,24].

The poor efficacy of these strategies for type 4 gastric cancer can be attributed to the abundance of desmoplastic stroma found in type 4 gastric cancer, which not only enhances tumor cell growth and invasiveness but also promotes immune escape and chemoresistance [25]. Drugs commonly used for preoperative chemotherapy of gastric cancer include platinum drugs and taxanes, whose therapeutic effects are related to the drug concentration in tumor tissues [26]. This drug concentration is limited due to the redistribution of drugs via the systemic circulation. However, it is impossible to elevate the local drug concentration by infinitely increasing the drug dosage due to its toxicity. Selective arterial administration of drugs into the feeding vessels of tumors can significantly increase the local drug concentration without increasing the total drug dose and can decrease the first-pass loss of drug. Moreover, it may reduce the incidence of adverse drug reactions [27]. In previous studies, we showed that local intra-arterial perfusion with varying doses of oxaliplatin and epirubicin along with the oral administration of the time-dependent release drug S-1 significantly improved the therapeutic outcomes of gastric cancer patients. The SEEEX regimen also improved the prognosis of several patients with type 4 gastric cancer [12,13]. In the present study, most patients showed a significant cessation of primary tumor growth after preoperative SEEEX. Ten of the 17 patients initially diagnosed with CY1 were restaged as CY0 after chemotherapy. In addition, preoperative chemotherapy improved the radical resection rate to 75% and the R0 resection rate to 58.3%, whereas 80.6% of tumors were deemed unresectable or challenging for resection prior to chemotherapy. The median survival duration of the 27 patients who underwent radical resection after SEEEX treatment was 32.95 months, which is longer than that observed in the atypical type of advanced gastric cancer at the same stage.

The 2-year OS in our study was 48.5%, which is different from the 3-year OS of the NAC group in JCOG-0501 (62.4%), probably because of the different characteristics of the patients in the 2 studies. The JCOG-0501 reported 149 patients with gastric cancer largely types 3 and 4. Among them, 61.1% (91/149) cases were type 4, the positive rate of peritoneal cytology was 18.8% (28/149), only one patient had peritoneal metastases P1, and clinical staged IIIa–IV patients accounted for 63.1% (94/149) of cases. On the contrary, all patients in our study were type 4, and the positive rate of peritoneal cytology was 27.7% (17/36). 44.4% patients (16/36) had P1 peritoneal metastases, the clinical stage III accounted for 100.0% of cases. P1 and CY1 are reported to be poor prognostic factors. In the use of conversion therapy for peritoneal lavage cytology-positive type 4 and large type 3 gastric cancer patients, the average survival time was only 24.1 months, and the 3-year OS was 35.5% [28]. In the study by Blackham et al. [8], the 3-year survival rate of type 4 patients was only 24%, whose patient characteristics were similar to our study. In summary, our results suggest that SEEEX can improve the survival and prognosis of type 4 gastric cancer patients.

There are several limitations to our study that ought to be considered. Given the limited therapeutic efficacy observed in type 4 gastric cancer, we conducted a single-arm exploratory phase II study without a control group. In addition, since the median survival duration of type 4 gastric cancer patients is relatively short, we evaluated OS as the primary endpoint, and the

shortest follow-up time that could be used to accurately determine this was 2 years. However, given the encouraging results obtained using the SEEEX method we are investigating further its underlying mechanism of action and have initiated a multicenter phase III study on type 4 gastric cancer patients.

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