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ORIGINAL PAPER

Phase I study of neoadjuvant chemoradiotherapy with S-1 for clinically resectable type 4 or large type 3 gastric cancer in elderly patients aged 75 years and older (OGSG1303)

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Abstract

Purpose The prognosis for type 4 and large type 3 gastric cancer (GC) is extremely poor, especially in elderly patients (≥ 75 years). To improve the prognosis of these types of GC, we performed a phase I study to determine the recommended dose (RD) of S-1 combined with neoadjuvant radiotherapy. Methods Patients with clinically resectable type 4 and large type 3 GC were enrolled to successive cohorts in a conventional 3 + 3 design. Three dose levels were designed, as follows: level 0: S-1 60 mg/m^2/day on Days 1–14; level 1: S-1 80 mg/m^2/day on Days 1 –14; level 2: S-1 80 mg/m^2/day on Days 1–14 and Days 22–35. The starting dose was level 1. Radiotherapy was delivered at a total dose of 40 Gy in fractions for 4 weeks. Results Ten patients were enrolled from July 2014 to August 2018. Six patients were registered at level 1, and one patient developed a dose limiting toxicity as gastric stenosis (grade 3). Two of four patients enrolled at level 2 developed dose limiting toxicity (inability to receive S-1 for hematological reasons). Therefore, the RD was determined as level 1. All patients underwent the protocol surgery; one patient underwent R1 resection because of positive peritoneal washing cytology. There were no treatment-related deaths, and the pathological response rate was 80%. The 5-year overall- and progression-free survival rates were both 60.0%. Conclusion The RD was determined as level 1. A phase II trial using the RD should be initiated.

Keywords Gastric cancer · Chemoradiotherapy · Type 4 · Large Type 3 · S-1 · Elderly

Introduction

Cancer is the leading cause of death among Japanese people, and according to a report by the Cancer Control and Information Center of Japan's National Cancer Center, in particular, the percentage of patients over 75 years of age among the total number of newly diagnosed gastric cancer (GC) cases is increasing annually [1]. In January 2017, the Japan Gerontological Society and the Japan Geriatrics Society defined 75 years and older as elderly [2].

Among GC, type 4 GC has a particularly poor prognosis. The 5-year overall survival (OS) rate of patients with type 4 GC ranges from 12.5% to 27.6% [3, 4]. To improve the prognosis of type 4 GC, Furukawa et al. performed extended resection surgery (left upper abdominal exenteration plus the Appleby procedure) [5]. However, this extended surgery has not become common owing to the high incidence of pancreatic fistula.

The JCOG0002 trial using S-1 as neoadjuvant chemotherapy to improve the prognosis of scirrhous GC (also known as

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type 4 GC) showed a pathologic response rate (Grade > 1b) of 32% and no improvement in prognosis compared with historical controls [6]. Additionally, the JCOG0501 trial was performed to confirm the superiority of neoadjuvant S-1 plus cisplatin followed by D2 gastrectomy over upfront surgery, primarily in patients with type 4 GC. However, the 3-year overall survival rates were 62.4% in the upfront surgery group and 60.9% in the neoadjuvant group [7]. Because the JCOG0501 trial failed to demonstrate a survival advantage of neoadjuvant chemotherapy with a doublet regimen of S-1 plus cisplatin, the JCOG2204 trial is currently underway, aiming to assess the efficacy of a triple regimen of FLOT (5-fluorouracil/oxaliplatin/docetaxel) or DOS (docetaxel/oxaliplatin/S-1) as neoadjuvant chemotherapy for patients with clinically resectable type 4 and large type3 GC [8]. However, elderly patients have decreased renal function compared with younger patients [9]. Therefore, elderly patients are more likely to be unable to tolerate neoadjuvant chemotherapy with a triplet regimen, let alone a doublet regimen. Consequently, a new strategy is needed to improve the outcomes of type 4 GC in elderly patients.

Saikawa et al. investigated the efficacy of chemoradiotherapy (CRT) with S-1 plus low-dose cisplatin for unresectable GC and reported a high response rate (65.5%) [10]. Additionally, a phase I trial of neoadjuvant CRT consisting of S-1 and low-dose cisplatin for patients with resectable advanced GC reported no major surgical complications and a pathologic complete response rate of 10% [11]. Thus, CRT with S-1 and cisplatin may be a promising treatment for advanced GC. However, the feasibility, safety, and efficacy of neoadjuvant CRT for resectable type 4 GC, especially for elderly patients, remain unknown.

Considering these previous reports, we performed this prospective study to determine the feasibility, safety, and efficacy of neoadjuvant CRT for type 4 GC and large type 3 GC, which is considered to have the same biological behavior as type 4 GC, such as a high incidence of peritoneal dissemination [12]. Additionally, because this study included elderly GC patients aged ≥ 75 years, cisplatin was excluded from the chemotherapy regimen because of age-related declines in renal function [9]. This phase I study was designed to determine the dose-limiting toxicity (DLT) of S-1, with concurrent radiotherapy, and to define the recommended dose (RD) for a subsequent phase II study.

Materials and methods

Patients

The eligibility criteria for this study were as follows: (1) histologically proven and clinically resectable GC; (2) age ≥ 75 years; (3) macroscopic type of carcinoma as type 4 or type 3 GC; (4) in type 3 GC, tumor size ≥ 8 cm in diameter; (5) Eastern Cooperative Oncology Group performance status of 0 or 1; (6) tumor invasion of the esophagus ≤ 1 cm, with no involvement of the duodenum; (7) lymph node metastasis limited to the regional lymph nodes; (8) no evidence of distant metastases, no peritoneal metastasis, and negative lavage cytology confirmed by staging laparoscopy; (9) no prior abdominal surgery; (10) no previous chemotherapy or radiotherapy; (11) no other previous or concurrent malignancies; (12) no bleeding from the main lesion or intestinal stenosis; and (13) adequate bone marrow function (white blood cell count ≥ 3000/mm^3, neutrophil count ≥ 1500/mm^3, hemoglobin ≥ 8.0 g/dL, platelet count ≥ 100 × 10^3/mm^3), adequate liver function (total serum bilirubin level ≤ 2.0 mg/dL, serum alanine transaminase and aspartate transaminase ≤ 100 U/L), and adequate renal function (creatinine clearance ≥ 40 mL/min). Written informed consent was obtained from all patients prior to their participation in the study.

The exclusion criteria were as follows: (1) other major medical disease or malignancy other than GC; (2) history of severe drug hypersensitivity; (3) treatment with a major tranquilizer, steroids, flucytosine, phenytoin, or warfarin; (4) lung fibrosis, intestinal pneumonitis, bowel obstruction, or ischemic heart disease; and (5) patients determined to be inappropriate for inclusion in this study.

The present trial was performed in accordance with the World Medical Association Declaration of Helsinki and the Japanese Good Clinical Practice guidelines. This study was approved by the ethics committee in each institution or hospital and registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN000013821).

Study design

The primary objective of this phase I study was to determine the RD of S-1 combined with neoadjuvant radiation therapy in elderly patients with type 4 and large type 3 GC using a conventional dose-escalation design. The secondary objectives were to evaluate the pathological response rate and the treatment safety profile.

Treatment schedule

The treatment schedule is summarized in Fig. 1. Combined CRT consisted of S-1 and radiotherapy. S-1 was administrated orally from Days 1 to 14 followed by rest for 14 days at levels 0 and 1. At level 2, S-1 was administered from Days 1 to 14 and Days 22 to 35. The dose of S-1 administered at level 0 was 60 mg/m^2/day. At levels 1 and 2, the dose of S-1 was 80 mg/m^2/day.

Radiotherapy was delivered using megavoltage (6–15 MV) X-rays and a multi-field technique. Patients

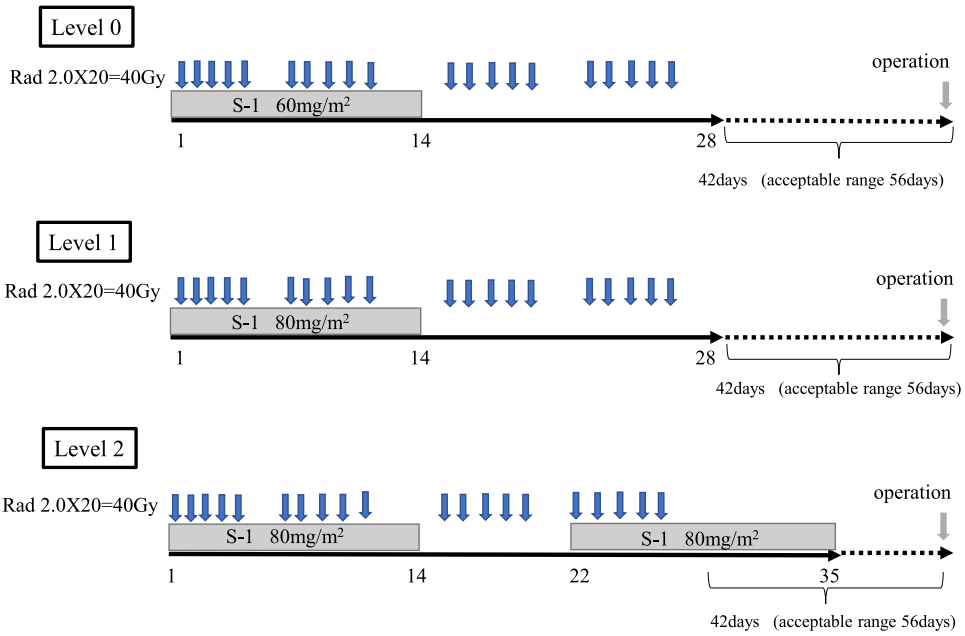

Fig. 1 The schema of dose escalation

received 2 Gy/day of radiation 5 days per week from the initiation of chemotherapy, with a total radiation dose of 40 Gy. Three-dimensional computed tomography (CT) simulation was required. CT simulation and daily radiation therapy were performed with the patient's stomach empty, 3 h after dietary intake. The gross volumes of the primary tumor (GTV primary) and the metastatic lymph nodes (GTV node) were defined by CT and positron emission tomography, with reference to an upper gastrointestinal series. The clinical target volume was calculated as the GTV primary and GTV node plus a 1-cm margin to account for subclinical extension. The planned target volume was the CTV plus 1–2 cm longitudinally and 0.5–1 cm transversely and vertically to account for setup variation and visceral motion. All patients were evaluated by abdominal and pelvic CT 4 weeks after completion of CRT to evaluate the possibility of R0 resection.

The surgical criteria were as follows: (1) achievable R0 resection; (2) white blood cell count $\geq 2500/mm^2$; and (3) platelet count $\geq 100{,}000/mm^2$. Surgery was performed between 7 and 9 weeks after the end of radiotherapy.

Determination of DLT, maximum-tolerated dose, and RD

This study followed a standard 3 + 3 dose escalation protocol. Level 1 was the starting dose; if DLT developed, three additional patients were needed. Once DLT development was confirmed in 3/6 patients at level 1, the next step comprised level 0. In principle, the RD was one level down from the maximum-tolerated dose (MTD). However, if the MTD was not expressed at level 2 in this study, we would recommend level 2 as the RD.

Toxicity was graded in accordance with the Common Toxicity Criteria for Adverse Events version 4.0 [13]. DLT was defined as follows: (1) grade 4 neutropenia; (2) grade 4 thrombocytopenia; (3) grade 3 febrile neutropenia lasting 4 days; (4) grade 3 non-hematologic toxicity except for appetite loss and general fatigue; and (5) inability to receive S-1 for > 10 days at levels 0 and 1 and > 19 days at level 2.

Surgery and postoperative chemotherapy

Surgery consisted of total or distal gastrectomy, depending on the location of the primary tumor. D2 lymphadenectomy was routinely performed, while splenectomy was performed only for tumor involvement in the upper one-third of the greater curvature or with nodal metastases in the splenic hilum. If resectable M1 disease (hepatic, peritoneal, and/or lymphatic metastases) was found during surgery, the affected nodes were removed to achieve R0 resection. If R0 resection was impossible, the protocol treatment was terminated.

Following R0 resection, 1 year of adjuvant chemotherapy with S-1 monotherapy was administered within 6 weeks after gastrectomy.

Postoperative follow-up

After treatment, in accordance with the protocol, patients were followed-up every 3 months for the first 2 years, then every 6 months for the next 5 years.

A schematic flowchart of this study is shown in Supplementary Fig. S1.

Assessment and statistical analysis

The tumor-node-metastasis categories were in accordance with the Japanese Classification of Gastric Carcinoma (3rd English edition) [14]. The pathological response rate was evaluated and graded by pathologists in accordance with the Japanese Classification of Gastric Carcinoma (3rd English edition) as grade 0 (no evidence of effect), grade 1a (viable tumor cells remain in more than two-thirds of the tumorous area), grade 1b (viable tumor cells remain in more than one-third but less than two-thirds of the tumorous area), grade 2 (viable tumor cells remain in less than one-third of the tumorous area), or grade 3 (no viable tumor cells). A pathological response was defined as a response greater than grade 1b. Toxicity and adverse events were described in accordance with the National Cancer Institute Common Toxicity Criteria grading version 4.0 [13]. Intra-and postoperative complications were graded in accordance with the Clavien–Dindo classification [15]. OS and progression-free survival (PFS) were calculated from the date of the initial staging laparoscopy to death or the date of the most recent follow-up, respectively. OS and PFS were estimated using the Kaplan–Meier method, with 95% confidence intervals (CI) determined using Greenwood's formula. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Between July 2014 and August 2018, 10 patients were enrolled in this study and underwent neoadjuvant CRT. The patients' characteristics are summarized in Table 1. The median age was 78.5 years (range: 75–81 years). The numbers of patients with large type 3 and type 4 tumors were 4 and 6, respectively.

MTD and RD

All 10 patients started treatment and could be evaluated for toxicity. The details of toxicity in levels 1 and 2 are shown in Table 2. Six patients were registered at level 1. The main toxicity was hematological and comprised anemia (50.0%) and leukopenia (33.3%). Additionally, three patients (50.0%) developed hypoalbuminemia. No patients experienced higher than grade 3 hematological toxicity. Regarding nonhematologic toxicity, two patients developed grade 2 anorexia, and one patient (16.7%) developed DLT as gastric

Table 1 Patient characteristics (n = 10)

Characteristic	Number
Age, years	
Median (range)	78.5 (75–81)
Sex	
Male	5
Female	5
ECOG performance status	
0	10
1	0
Macroscopic findings (JGCA)	
Type 3	4
Type 4	6
Tumor location in the stomach	
Upper	1
Middle	8
Lower	1
Histological subtype	
Tubular adenocarcinoma	5
Poorly differentiated adenocarcinoma	2
Signet-ring cell carcinoma	3
Clinical T stage	
T3	4
T4a	5
T4b	1
Clinical N stage	
N0	7
N1	0
N2	3
N3	0
Peritoneal metastasis	
P0	10
P1	0
Peritoneal lavage cytology	
CY0	10
CY1	0
Clinical M stage	
M0	10
M1	0
Clinical TMN stage	
IA	0
IB	0
IIA	3
IIB	4
IIIA	1
IIIB	1
IIIC	1
IV	0

ECOG Eastern Cooperative Oncology Group, *JGCA* Japan Gastric Cancer Association, *P0* No peritoneal metastasis, *P1* Peritoneal metastasis, *CY0* Peritoneal cytology negative for carcinoma cells, *CY1* Peritoneal cytology positive for carcinoma cells, *M0* No distant metastasis, *M1* Distance metastasis, *T* Tumor, *N* Node

Table 2 Adverse events (n = 10)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3/4
Level 1 (n = 6)					
Hematologic					
Leukopenia	1	1	0	0	0
Neutropenia	0	0	0	0	0
Thrombocytopenia	1	0	0	0	0
Anemia	2	1	0	0	0
Hypoalbuminemia	2	1	0	0	0
AST elevated	0	0	0	0	0
ALT elevated	1	0	0	0	0
Hyperbilirubinemia	1	1	0	0	0
Hypercreatininemia	1	0	0	0	0
Hyperkalemia	0	0	0	0	0
Hypernatremia	1	0	0	0	0
Hyponatremia	1	0	0	0	0
Gastrointestinal					
Anorexia	0	2	0	0	0
Nausea	1	0	0	0	0
Vomiting	0	0	0	0	0
Diarrhea	1	0	0	0	0
Fatigue	1	0	0	0	0
Malaise	1	0	0	0	0
Rash	0	0	0	0	0
Gastric stenosis	0	0	1	0	16.7
Level 2 (n = 4)					
Hematologic					
Leukopenia	0	2	0	0	0
Neutropenia	0	2	0	0	0
Thrombocytopenia	1	0	0	0	0
Anemia	0	1	0	0	0
Hypoalbuminemia	1	2	0	0	0
AST elevation	1	1	0	0	0
ALT elevation	1	1	0	0	0
Hyperbilirubinemia	0	0	0	0	0
Hypercreatininemia	0	0	0	0	0
Hyperkalemia	1	0	0	0	0
Hypernatremia	0	0	0	0	0
Hyponatremia	1	0	0	0	0
Gastrointestinal					
Anorexia	0	1	1	0	16.7
Nausea	0	3	0	0	0
Vomiting	2	0	0	0	0
Diarrhea	0	0	0	0	0
Fatigue	0	0	0	0	0
Malaise	0	1	0	0	0
Rash	1	0	0	0	0
Gastric stenosis	0	0	0	0	0

Toxicities were graded in accordance with the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0

ALT alanine transaminase, *AST* aspartate transaminase

Table 3 Surgical findings and postoperative complications (n = 10)

Finding	Number
Peritoneal lavage cytology	
CY0	9
CY1	1
Peritoneal metastasis	
P0	10
P1	0
Type of resection	
Total gastrectomy	9
Distal gastrectomy	1
Combined resection	
Transverse colon	1
Pancreatic tail	1
Diaphragm	1
Lymph node dissection	
D2	10
Residual tumor	
R0	9
R1	1
R2	0
Postoperative complications	
Anastomotic leakage	0
Pancreatic fistula	0
Intra-abdominal abscess	0
Wound infection	0
Transverse colonic necrosis	1 (*Gr.* IIIb)
30/60-day mortality	0/0

CY0 Peritoneal cytology negative for carcinoma cells, *CY1* Peritoneal cytology positive for carcinoma cells, *P0* No peritoneal metastasis, *P1* Peritoneal metastasis, *Gr.* Toxicity grade in accordance with the Clavien–Dindo classification

Table 4 Pathological findings (n = 10)

Finding	Number
Depth of tumor (T) invasion	
T0	0
T1a	0
T1b	1
T2	1
T3	5
T4a	1
T4b	2
Lymph node (N) metastasis	
N0	5
N1	2
N2	3
JCGA stage	
IA	1
IB	1
IIA	2
IIB	2
IIIA	1
IIIB	1
IIIC	1
IV	1
JCGA histological response	
Grade 0	0
Grade 1a	2
Grade 1b	1
Grade 2	7
Grade 3	0

JCGA Japanese Classification of Gastric Carcinoma (3rd English edition)

stenosis (grade 3). During dose level 2, two of four patients (50.0%) developed grade 2 leukemia and neutropenia, and one patient (25.0%) developed grade 2 anemia. The leukemia and neutropenia failed to respond to therapy, and as a result, the two patients (50.0%) were unable to continue the specified amount of S-1 for ≥ 19 days Therefore, the RD was determined as level 1.

Surgery and postoperative complications

All patients underwent the protocol surgery. The operation transition rate was 100% (95% CI 69.2%–100%). Total gastrectomy was performed in nine patients, while distal gastrectomy was performed in one patient. Peritoneal cytology positive for carcinoma cells (CY1) was observed in one patient. Therefore, the rate of R0 resection was 90% (9/10) (95% CI 55.5%–96.7%). Other surgical findings are shown in Table 3.

Surgical complications were observed in one patient (10%) and comprised transverse colonic necrosis (Grade IIIb), which required reoperation. There were no surgery-related deaths.

Pathological findings

The pathological effects of neoadjuvant CRT were as follows: grade 0 in 0 (0%) patients, grade 1a in two (20%), grade 1b in one (10%), grade 2 in seven (70%), and grade 3 in 0 (0%) patients. The pathological response rate, the secondary endpoint, was 80% (Table 4).

Postoperative chemotherapy

S-1 postoperative adjuvant chemotherapy was initiated in 7 of the 10 patients who underwent surgery. The remaining three patients declined postoperative adjuvant chemotherapy.

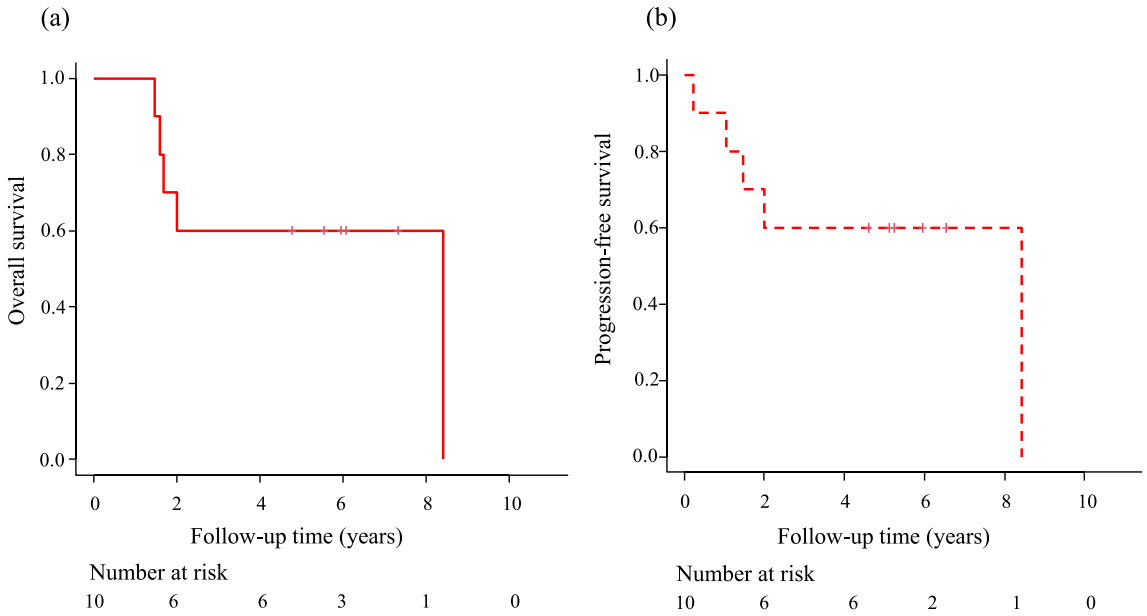

Fig. 2 Kaplan–Meier analyses of **a** overall survival and **b** progression-free survival for the 10 patients in this study

Survival

OS and PFS were evaluated in the 10 eligible patients. At the time of analysis (September 2023), six patients were alive without recurrence; three patients had died as a result of recurrence. Another patient died of other disease 16 months after surgery. The 3- and 5-year OS rates were both 60.0% (95% CI 25.3%–82.7%). The 3- and 5-year PFS rates were also both 60.0% (95% CI 25.3%–82.7%) (Fig. 2a and b).

Discussion

This phase I study was designed to evaluate neoadjuvant concurrent CRT in elderly patients with resectable type 4 or large type 3 GC and it determined the RD of S-1 as 80 mg/m^2/day on Days 1–14. The predominant adverse events in this study were anemia (40%), leukopenia (40%), and neutropenia (20%). No patients developed grade 3 or 4 hematologic toxicity at the two dose levels evaluated in this study. These adverse event results were consistent with those in several previous studies that examined the safety of S-1 in elderly patients with advanced GC [16, 17]. The chemotherapy completion rate was 80% (8/10), similar to that observed in the JCOG0002 trial (clinical trial for scirrhous GC) using S-1 for neoadjuvant chemotherapy (94%) [6].

In comparison, the radiotherapy completion rate was 100%, and eventually, 9 of the 10 (90%) patients underwent R0 resection. As a result, the lower limit of the 95% CI was 55.5%, suggesting that our neoadjuvant CRT regimen is feasible. However, CY1 was identified in one (10%) patient after neoadjuvant CRT. This may have resulted from the inadequate diagnostic accuracy of peritoneal lavage examination. The accuracy of conventional peritoneal lavage cytology for peritoneal metastasis diagnosis is still limited, with a sensitivity of < 60% [18, 19]. Therefore, in the affected patient in our study, CY1 might have been latent at the time of the initial staging laparoscopy. Recently, the usefulness of the cell block technique has been reported [20], and this technique is covered by insurance in Japan. Therefore, the cell block technique may increase the accuracy of peritoneal cytological diagnosis in the future.

Regarding surgical complications, the postoperative morbidity rate was low (10%) in our study compared with that of previous studies [21], and there were no surgery-related deaths in this study. However, colonic necrosis developed in one patient as a postoperative adverse event (Grade ≥ 3). Ischemic changes due to irradiation are considered to occur several years after irradiation when the total irradiation dose exceeds 55–60 Gy [22, 23]. There have been no reports of colonic necrosis following low doses of radiation, such as 40 Gy. The necrosis in the patient in our study occurred during the acute phase of radiation damage, and we believe it was caused by an additional complication, such as infection or an intraoperative procedure.

The low rate of surgical complications made it possible for 7 of the 10 patients (70%) to receive adjuvant chemotherapy as scheduled. Therefore, our neoadjuvant CRT regimen was considered safe.

Regarding therapeutic efficacy, our study achieved a pathological response rate of 80%, which was better than

that of the JCOG0002 trial (32%) [6]. It is assumed that the high pathological response rate in this study may be associated with the addition of concurrent radiation therapy. The prognostic outcome and pathological response rate are generally used as indicators to evaluate the effect of preoperative therapy [24]. The JCOG0002 trial indicated that the 3-year survival rate for type 4 GC was < 40% [6]. Although our sample size was small, the 5-year OS and PFS rates in our study were both 60.0%.

In a previous phase I neoadjuvant CRT study, Lee et al. reported a histological response rate of 50.0% and no postoperative complications (S-1 60 mg/m^2/day for 28 days + oxaliplatin 40 mg/m^2 on days 1,8,15 and 22 with concurrent radiotherapy at 41.4 Gy) for locally advanced GC patients aged 39–76 (median: 56 years) [25]. Additionally, Inoue et al. reported a histological response rate of 83.3% and a 3-year survival rate of 58.3% with neoadjuvant CRT (S-1 65 mg/m^2/day on days 1–14 and 22–35 with concurrent radiotherapy at 50 Gy) for locally advanced GC patients aged 51–81 (median: 69 years) [26]. Because our results showed a histological response rate of 80.0% and a 5-year survival rate of 60% in patients older than 75 (median: 78.5 years), our neoadjuvant CRT with S-1 may provide a favorable prognosis for elderly patients with type 4 or large type 3 GC.

In conclusion, the safety and efficacy of this regimen (S-1 80 mg/m^2/day from Days 1 to 14 with concurrent radiotherapy at 40 Gy) will be evaluated in a phase II study with larger numbers of patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12032-024-02583-3.

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Author contributions Study concept: MI and HF; study design: MI, MY, and HF; acquisition of data: MS, MI, JM, and YK; statistical analysis of the data: TS; analysis and/or interpretation of the data: MS, MI, and TS; drafting the manuscript: MS and MI; revising the manuscript critically for important intellectual content: HK, TS, TY, and HF. All authors approved the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval All procedures were performed in accordance with the ethical standards of the committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. This study was approved by the institutional review and ethics board of each participating hospital and registered in the University Hospital Medical Information Network (UMIN) database (UMIN000013821).

Consent to participate Informed consent or substitute consent was obtained from all patients included in the study.

Consent for publication The authors have approved publication.

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