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ORIGINAL ARTICLE

A phase II study of neoadjuvant chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy for type 4 or large type 3 gastric cancer (OGSG 1402)

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Abstract

Background A multi-institutional phase II study (OGSG 1402) evaluated the efficacy and safety of neoadjuvant docetaxel, cisplatin, and S-1 (DCS) therapy for type 4 or large type 3 gastric cancers.

Methods Patients with macroscopic type 4 or large type 3 gastric cancer received two or three cycles of neoadjuvant DCS therapy (docetaxel 40 mg/m^2 and cisplatin 60 mg/m^2 intravenously on day 1, and S-1 80–120 mg/body orally for 14 days, every 4 weeks), followed by gastrectomy with D2 lymphadenectomy. After R0 resection, adjuvant S-1 chemotherapy was administered for 1 year. The primary endpoint was the R0 resection rate.

Results Between March 2015 and June 2018, 48 patients were enrolled, 47 of whom were eligible. The R0 resection rate was 68.1% (32/47, 95% confidence interval [CI] 52.9–80.9). Forty-two patients (89.4%) completed neoadjuvant chemotherapy (NAC). The most common grade 3 or 4 adverse event during NAC was neutropenia (23/47, 48.9%). Surgical morbidity of Clavien–Dindo grade IIIa or higher occurred in 8.5% (4/47) of patients. The pathological response rate, defined as grades 1b to 3, was 42.6% (20/47, 95% CI 28.3–57.8). The 5-year overall survival rate was 38.3% (95% CI 24.6–51.8) and the 5-year progression-free survival rate was 29.8% (95% CI 17.6–43.0).

Conclusions In patients with type 4 or large type 3 gastric cancer, neoadjuvant DCS therapy did not meet the predefined threshold for the R0 resection rate. Despite its acceptable feasibility and manageable toxicity, the addition of docetaxel to the S-1 plus cisplatin regimen is unlikely to provide a survival benefit for this high-risk population.

Trial registration The study was registered with UMIN-CTR (number UMIN 000015631).

Keywords Stomach neoplasms · Adenocarcinoma, scirrhous · Neoadjuvant therapy · Docetaxel

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1]. Among its subtypes, type 4 GC, including linitis plastica and scirrhous-type cancer, exhibits several unique characteristics such as diffuse invasion inside the gastric wall, easy spread to the peritoneum, and poor prognosis even after radical gastrectomy. Large ulcero-invasive type (type 3) GC with a tumor diameter > 8 cm shares aggressive biological characteristics with type 4 GC in terms of easily developing peritoneal dissemination and poor prognosis [2, 3].

Neoadjuvant chemotherapy (NAC) followed by surgery with curative intent has been proposed as a promising strategy to improve the prognosis of patients with aggressive types of GC. This approach may offer several advantages, including the eradication of micrometastases in the peritoneal cavity, improved local control, better compliance with intensive chemotherapy than postoperative adjuvant

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therapy, and the potential to avoid futile surgery by identifying occult metastases during NAC.

Among NAC regimens, S-1 plus cisplatin (SP), the standard first-line chemotherapy for advanced and metastatic GC in Japan, is considered the most promising candidate. The Japan Clinical Oncology Group (JCOG) conducted a phase II study of neoadjuvant SP (JCOG 0210) [4] for type 4 or large type 3 GC and reported good feasibility and a 3-year overall survival (OS) rate of 24.5%. Based on these results, a subsequent phase III trial (JCOG0501) was conducted to verify the survival benefit of neoadjuvant SP therapy compared with standard therapy (upfront surgery followed by adjuvant S-1) for type 4 or large type 3 GC. Although an R0 resection rate of 74.2% was favorable, the trial failed to demonstrate a survival benefit of neoadjuvant SP; that is, the 3-year OS was 60.9% versus 62.4% for standard treatment, and the hazard ratio was 0.916 (95% confidence interval [CI] 0.679–1.236) [5].

Subsequently, the addition of docetaxel to cisplatin plus fluorouracil has demonstrated efficacy as a first-line therapy for advanced GC [6]. In Japan, a modified regimen combining docetaxel, cisplatin, and S-1 (DCS) was developed by substituting the continuous intravenous infusion of 5-fluorouracil with the oral formulation S-1, with the aim to improve the convenience and antitumor activity of the treatment. However, to date, the clinical benefit of DCS therapy has not been clearly established in the preoperative setting for GC with extensive lymph node metastasis [7] or advanced GC [8].

Herein, we report the results of the OGSG 1402 trial, the first phase II trial to evaluate the efficacy and safety of neoadjuvant DCS therapy for type 4 or large type 3 GC.

Methods

Patients

Eligible patients had histologically confirmed gastric adenocarcinoma of type 4 or large type 3 ($\geq$ 8 cm), were 20–75 years of age, had an Eastern Cooperative Oncology Group performance status of 0–1, and adequate organ function. Importantly, no evidence of distant metastasis was found, except for localized peritoneal metastasis adjacent to the stomach or positive peritoneal lavage cytology, which was confirmed by exploratory laparoscopy and computed tomography (CT). The eligibility criteria are listed in Supplementary Table 1. The key exclusion criteria were prior treatment for GC, uncontrolled comorbidities, active infection, and known drug hypersensitivity. The detailed exclusion criteria are listed in Supplementary Table 2.

Study design

This multicenter, open-label, single-arm phase II study was conducted by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) (UMIN000015631). This study evaluated the efficacy and safety of DCS therapy consisting of NAC followed by gastrectomy with D2 lymphadenectomy and adjuvant S-1 therapy.

The primary endpoint was the R0 resection rate, defined as the percentage of patients who achieved R0 resection with D2 or greater lymphadenectomy among all eligible patients who received at least one dose of S-1, docetaxel, or cisplatin (the full analysis set). The secondary endpoints included the NAC completion rate, which was defined as the percentage of patients who completed two or three planned cycles of NAC; adverse events (AEs) associated with NAC or surgery; and OS, progression-free survival (PFS), and clinical and pathological responses to NAC.

AEs related to either chemotherapy or gastrectomy were evaluated using the Common Toxicity Criteria for Adverse Events version 4.0 and Clavien–Dindo classification [9], respectively. The clinical response to NAC in measurable lesions was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 [10]. Tumors were staged according to the Japanese classification of gastric carcinoma [11]. The pathological response of the primary tumor was graded by institutional pathologists according to the Japanese classification of gastric carcinoma as follows: grade 0, none of the tumors affected; grade 1a, viable tumor cells occupying two-thirds or more of the tumorous area; grade 1b, viable tumor cells occupying one-third or more, but less than two-thirds of the tumorous area; grade 2, viable tumor cells occupying less than one-third of the tumorous area; and grade 3, no viable tumor cells. A significant pathological response was defined as grades 1b through 3.

Follow-up included laboratory tests, physical examinations, and CT every 6 months and annually thereafter for 5 years. All patients were followed up for at least 5 years from the date of registration until death. None of the patients were lost to follow-up.

OS and PFS were estimated for up to 5 years from the date of registration for all eligible patients, and censoring was performed at the last follow-up for surviving patients. OS was defined as the time from registration until death from any cause. PFS was defined as the time from registration to the first occurrence of disease progression, including progression before surgery, inability to undergo R0 or R1 resection, or death from any cause, whichever occurred first. Positive peritoneal cytology (CY1) or peritoneal metastasis (P1) incidentally detected during surgery was not considered an event if R0 or R1 resection could be performed.

Treatment

Patients received two cycles of docetaxel (40 mg/m^2) and cisplatin (60 mg/m^2) intravenously on day 1 and oral S-1 twice daily on days 1–14, followed by a 2-week rest period; a third cycle was allowed when an R0 resection was not considered feasible after reassessment. This schedule was determined with reference to the protocol framework of the JCOG0210 and JCOG0501 trials, in which two preoperative courses of S-1 plus cisplatin were administered before surgery. The resectability was reassessed after two cycles. The dose of S-1 was determined based on body surface area (BSA): 40 mg for BSA < 1.25 m^2, 50 mg for BSA 1.25–1.5 m^2, and 60 mg for BSA > 1.5 m^2. The patients were monitored every 2 weeks during NAC through verbal interviews, physical examinations, and laboratory tests. Subsequent cycles required recovery of hematologic and organ function. Dose reduction or discontinuation was performed for patients with severe toxicity (Supplementary Table 3).

After the first cycle of DCS therapy, the therapeutic response was evaluated using contrast-enhanced CT. A second cycle was administered unless disease progression was observed. Within 42 days of completing the second DCS cycle, patients proceeded to surgery if R0 resection was deemed radiologically possible and organ function was adequate. The patients underwent total or distal gastrectomy with D2 or greater lymphadenectomy, depending on the tumor location. If R0 resection was considered impossible even after the third cycle of DCS therapy or if R1/2 resection was unavoidable intraoperatively because of the peritoneal lavage cytology results, peritoneal dissemination, or obvious distant metastases, the treatment protocol was discontinued.

Adjuvant chemotherapy comprising eight cycles of S-1 was initiated within 42 days after surgery in patients who underwent R0 resection. S-1 was administered orally at the same dose as NAC on days 1–28 of each 6-week cycle. Treatment was discontinued upon clinically or radiographically confirmed disease progression, serious AEs resulting in a treatment delay of > 4 weeks, need for a third dose reduction, patient refusal, or physician discretion for any other reason. After 1 year of adjuvant S-1 therapy, no further treatment was administered unless tumor recurrence occurred.

Statistical analysis

In the JCOG0501 trial, the R0 resection rate after two courses of SP therapy was 74.2% [5]. Based on this percentage, the present study set the expected R0 resection rate to 80% and the threshold rate to 65%. Assuming a one-sided alpha level of 10% and statistical power of 80%, the required sample size was calculated as 40 patients. To account for an estimated 10% dropout rate, the planned enrollment was set at 45 patients.

Quantitative values are expressed as medians and ranges, and categorical values as absolute counts. Survival curves were estimated using the Kaplan–Meier method, and 95% CIs for survival rates were estimated using Greenwood's formula. All statistical analyses were performed by the OGSG Data Center using R software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between March 2015 and June 2018, 48 patients from 12 Japanese institutions were enrolled in the study. One patient who did not undergo exploratory laparoscopy before registration was ineligible, and 47 patients received neoadjuvant DCS therapy. A flow diagram of patient enrollment is provided in Fig. 1.

The characteristics of the 47 eligible patients are summarized in Table 1. The median age was 65 years, and 26 patients were men. Twenty and 27 patients had types 3 and 4 GC, respectively. Positive peritoneal cytology was found in 14 patients, and limited peritoneal metastasis was found in six patients.

Neoadjuvant chemotherapy

Five patients discontinued treatment because of AEs (1), consent withdrawal (1), progression (2), or other reasons (1). The remaining 42 patients received two or three cycles of preoperative DCS: 34 received two cycles and eight received three cycles. The NAC completion rate was 89.4% (42/47; 95% CI 76.9–96.5). In the neoadjuvant setting, the mean (standard deviation) relative dose intensities of S-1, cisplatin, and docetaxel were 95.7% (5.7), 97.0% (4.0), and 97.8% (3.1), respectively. Dose reductions or treatment delays were mainly due to AEs.

Among the 14 patients with measurable lesions, the clinical responses to NAC included a partial response in six, stable disease in six, and progressive disease in two. The objective response rate, defined as the proportion of patients who achieved a complete or partial response, was 42.9% (95% CI 17.7–71.1). The disease control rate, defined as the proportion of patients with a complete response, partial response, or stable disease, was 85.7% (12/14).

The chemotherapy-related AEs among the 47 patients who received at least one dose of DCS are presented in Table 2. The most common toxicity of any grade was anorexia (38

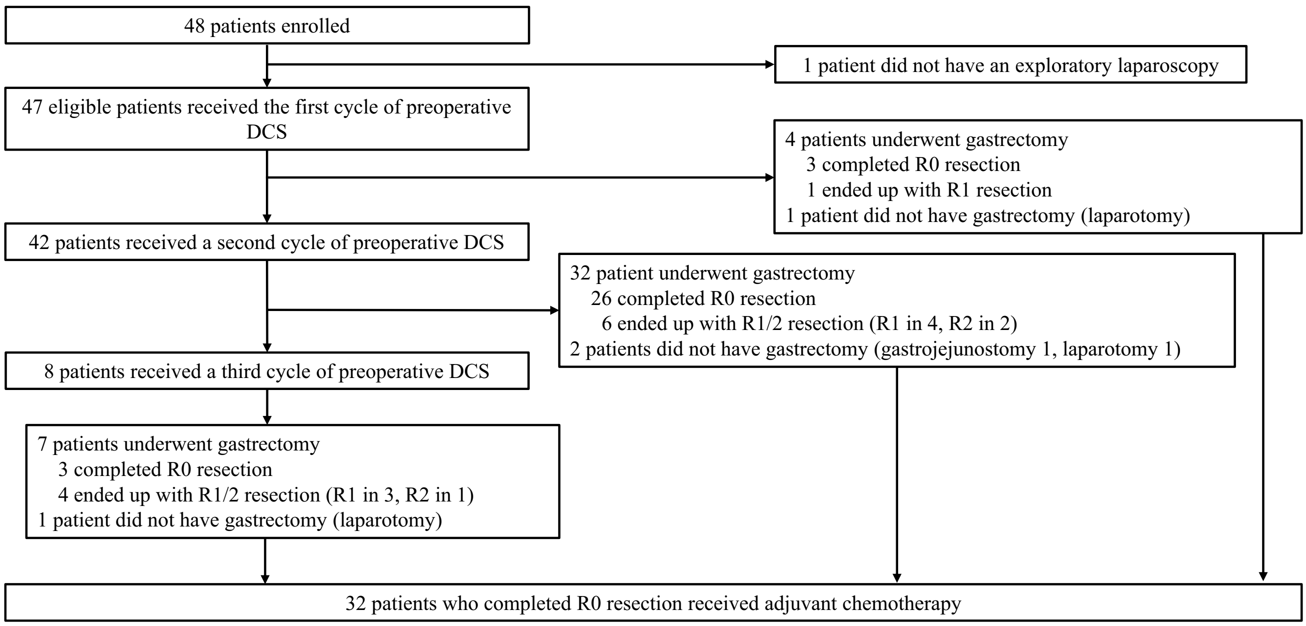


Fig. 1 Patient flow diagram

patients, 81%), followed by anemia (36 patients, 77%), and leukopenia (35 patients, 75%). Grade 3 or 4 hematological toxicities included neutropenia in 23 patients (49%) and leukopenia in 11 patients (23%). No serious AEs required hospitalization, and there were no chemotherapy-related deaths.

Surgical procedures and postoperative complications

In our cohort, the median time from registration to surgery was 79 days (interquartile range: 74–89 days). The surgical procedures are summarized in Table 3. Total gastrectomy was performed in 35 patients, distal gastrectomy in eight, and palliative surgery in four. R0 and R1 resections were achieved in 32 and eight patients, respectively. Among the 43 patients who underwent gastrectomy, a positive surgical margin was obtained in two patients, and positive peritoneal cytology was observed in six patients. Regarding the six patients with limited peritoneal metastasis at baseline, R0 resection was achieved in four patients, whereas one patient underwent R2 resection and one patient did not undergo resection. Among the patients with P0 and CY0 status at registration, three patients were found to have unexpected intraoperative peritoneal involvement (CY1 in two and P1 in one), and all of them underwent R1 resection. The R0 resection rate was 68.1% (95% CI 52.9–80.9), which did not significantly exceed the predefined threshold of 65% required for statistical significance ($p = 0.391$). To explore the impact of neoadjuvant dose modification on outcomes, we divided patients into a full-dose group (all three neoadjuvant agents administered at the planned dose without reduction; $n = 24$) and a reduction-dose group (any dose reduction or omission of S-1, cisplatin, or docetaxel; $n = 23$). When patients were stratified according to the relative dose intensity of neoadjuvant chemotherapy, the R0 resection rates among those who underwent gastrectomy were 78.3% (18/23) in the full-dose group and 70.0% (14/20) in the reduction-dose group (odds ratio: 1.527 [95% CI 0.314–7.793]; $p = 0.727$).

Postoperative complications were identified in 10 patients (21.3%, 95% CI 10.7–35.7) (Table 4). Clavien–Dindo grade IIIa or higher complications occurred in four patients (8.5%), including pancreatic fistula in two (4.3%) and ascites and anastomotic leakage in one (2.1%) patient each. None of the patients required reoperation, and there were no in-hospital or 30-day postoperative deaths.

Pathological findings

The pathological findings are presented in Table 5. Following neoadjuvant DCS therapy, the number of patients with positive peritoneal cytology decreased from 14 to ten, while the number with macroscopic peritoneal metastases decreased from six to five. The pathological response of the primary tumor graded 1b or greater was 42.6% (20/47, 95% CI 28.3–57.8) and included two patients (4.3%) with a complete response. When stratified by the presence or absence of a signet-ring cell component, the pathological response rates were 18.2% (2/11, 95% CI 2.3–51.8) in patients with signet-ring cell carcinoma and 50.0% (18/36, 95% CI 32.9–67.1) in those without. Furthermore, when stratified by the relative dose intensity of neoadjuvant chemotherapy, the

Table 1 Patient characteristics of the 47 eligible patients

Variable	n (%)
Age (years), median (range)	65 (29–75)
Sex	
Male	26 (55.3)
Female	21 (44.7)
ECOG PS	
0	33 (70.2)
1	14 (29.8)
Location	
Upper third	17 (36.2)
Middle third	19 (40.4)
Lower third	11 (23.4)
Macroscopic type	
Type 3	20 (42.6)
Type 4	27 (57.4)
cT	
T3	3 (6.4)
T4a	41 (87.2)
T4b	3 (6.4)
cN	
N0	12 (25.5)
N1	17 (36.2)
N2	12 (25.5)
N3	6 (12.8)
Histological type	
Differentiated	14 (29.8)
Undifferentiated	33 (70.2)
Peritoneal metastasis	
P0	41 (87.2)
P1	6 (12.8)
Peritoneal cytology	
CY0	33 (70.2)
CY1	14 (29.8)
cStage	
IIB	4 (8.5)
IIIA	11 (23.4)
IIIB	10 (21.3)
IIIC	5 (10.6)
IV	17 (36.2)

ECOG PS, Eastern Cooperative Oncology Group performance status; cT, clinical tumor status; cN, clinical nodal status; cStage, clinical stage

Table 2 Adverse events of neoadjuvant chemotherapy in the 47 eligible patients

Toxicity	Any grade*	Grade 3–4
	n (%)	n (%)
Laboratory findings		
Leucopenia	35 (74.5)	11 (23.4)
Neutropenia	37 (78.7)	23 (48.9)
Anemia	36 (76.6)	2 (4.3)
Thrombocytopenia	15 (31.9)	0
Hypoalbuminemia	32 (68.1)	2 (4.3)
T-Bil increased	4 (8.5)	0
Increased AST	14 (29.8)	1 (2.1)
Increased ALT	11 (23.4)	1 (2.1)
Increased Cr	10 (21.3)	0
Hyponatremia	18 (38.3)	6 (12.8)
Hypokalemia	13 (27.7)	4 (8.5)
Hyperkalemia	7 (14.9)	0
Febrile neutropenia	2 (4.3)	2 (4.3)
Objective findings		
Anorexia	38 (80.9)	6 (12.8)
Nausea	32 (68.1)	4 (8.5)
Fatigue	25 (53.2)	4 (8.5)
Diarrhea	19 (40.4)	2 (4.3)
Malaise	22 (46.8)	0
Alopecia	12 (25.5)	0
Vomiting	9 (19.1)	0
Stomatitis	6 (12.8)	0
Constipation	6 (12.8)	0
Dysgeusia	5 (10.6)	0

*Common Toxicity Criteria for Adverse Events (version 4.0) T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cr, creatinine

pathological response rate (grade ≥ 1b) was 45.8% (11/24) in the full-dose group and 39.1% (9/23) in the reduction-dose group (odds ratio: 1.306 [95% CI 0.356–4.916]; p = 0.770).

Survival

Adjuvant S-1 chemotherapy was administered to 32 patients who underwent R0 resection, and 21 patients completed the planned 1-year course. Among the remaining 11 patients, treatment was discontinued because of disease recurrence (n = 5), AEs (n = 5), or patient preference (n = 1). In the adjuvant setting, the mean (standard deviation) relative dose intensity of S-1 was 90.9% (9.4), and dose reductions or treatment interruptions were likewise primarily attributable to AEs.

Survival analyses were performed in all 47 eligible patients, nine of whom died from disease recurrence, 12 from disease progression after R1/2 resection or palliative surgery, and four from causes other than GC. Among the 32 patients who underwent R0 resection, first recurrence occurred in the peritoneum in 15 patients, liver in one patient, and para-aortic lymph nodes in three patients. In total, 17 patients experienced recurrence, and some patients had multiple sites of first recurrence. All surviving patients were followed up for at least 5 years. The 5-year OS rate was 38.3% (95% CI 24.6–51.8), and the median OS was 46.0 months (95% CI 28.9–61.5) (Fig. 2a). The 5-year PFS rate was 29.8% (95% CI 17.6–43.0), and the median PFS was 25.4 months (95% CI 18.9–35.2) (Fig. 2b).

Among patients who underwent surgery, Kaplan–Meier analyses using a landmark at the time of surgery showed that the 3-year/5-year OS rates were 84.4/53.1% in the R0 resection group and 18.2/9.1% in the R1/2 resection group

Table 3 Surgical procedures in the 47 eligible patients

Variable	n
Operation time (min)	
median (range)	283 (42–735)
Blood loss (mL)	
median (range)	250 (0–1915)
Type of surgery	
Total gastrectomy	35
Distal gastrectomy	8
Palliative surgery	4
Gastrojejunostomy	1
Exploratory laparoscopy	2
Exploratory laparotomy	1
Combined resection	
None	13
Gallbladder	27
Spleen	21
Pancreatic tail	1
Liver	1
Colon	1
Lymph nodes dissection	
D1	3
D2	36
D2+	4
Reconstruction	
Roux-en-Y	40
Billroth I	2
Billroth II+Braun	1
Residual tumor	
R0	32
R1	8
R2	3

Table 4 Postoperative complications in the 47 eligible patients

Variable n (%)	Grade*				Grade ≧ IIIa n (%)
	I	II	IIIa	> IIIa	
Pancreatic fistula	1	1	2	0	4.3
Anastomotic leakage	0	0	1	0	2.1
Ascites	0	0	1	0	2.1
Intra-abdominal abscess	0	2	0	0	0
Hypertension	0	1	0	0	0
Urinary tract infection	0	1	0	0	0
Incisional infection	2	0	0	0	0

*Clavien–Dindo classification

Table 5 Pathological findings in the 47 eligible patients

Variable	n (%)
ypT	
T1a	3 (6.4)
T1b	1 (2.1)
T2	2 (4.3)
T3	16 (34.0)
T4a	20 (42.6)
T4b	5 (10.6)
ypN	
N0	18 (38.3)
N1	12 (25.5)
N2	7 (14.9)
N3	10 (21.3)
ypM	
M0	34 (72.3)
M1	13 (27.7)
Peritoneal metastasis	5 (10.6)
Peritoneal cytology positive	10 (21.3)
Para-aortic lymph node	1 (2.1)
Hepatic metastasis	1 (2.1)
ypStage	
IA	2 (4.3)
IB	2 (4.3)
IIA	7 (14.9)
IIB	3 (6.4)
IIIA	9 (19.1)
IIIB	6 (12.8)
IIIC	5 (10.6)
IV	13 (27.7)
Pathological response	
Grade 0	1 (2.1)
Grade 1a	22 (46.8)
Grade 1b	11 (23.4)
Grade 2	7 (14.9)
Grade 3	2 (4.3)
No resection	4

ypT, pathological tumor status after neoadjuvant therapy; ypN, pathological nodal status after neoadjuvant therapy; ypM, pathological metastatic status after neoadjuvant therapy; ypStage, pathological stage after neoadjuvant therapy

(hazard ratio: 0.191 [95% CI 0.084–0.434]; $p < 0.001$) (Fig. 3a), and the 3-year PFS rates were 50.0% in the R0 resection group and 9.1% in the R1/2 resection group (hazard ratio: 0.269 [95% CI 0.122–0.590]; $p < 0.001$) (Fig. 3b).

An exploratory analysis according to the relative dose intensity of neoadjuvant chemotherapy showed no significant differences in survival between the full-dose and reduction-dose groups. In this analysis, 24 patients were allocated to the full-dose group and 23 to the reduction-dose group. The median OS was 49.9 months in the full-dose group and 39.6 months in the reduction-dose group, and the 3-year OS rates were 66.7% and 56.5%, respectively (hazard ratio: 0.881 [95% CI 0.444–1.747]; $p = 0.717$). The median PFS was 25.1 and 27.4 months, and the 3-year PFS rates were 33.3% and 39.1% in the full-dose and reduction-dose groups, respectively (hazard ratio: 1.144 [95% CI 0.583–2.246]; $p = 0.699$).

An exploratory analysis was conducted to evaluate the prognostic impact of the presence of signet-ring cell carcinoma components identified in biopsy or resected specimens. The 5-year OS rate was 29.2% in 24 patients with signet-ring cell carcinoma and 47.8% in 23 patients without signet-ring cell carcinoma; these rates did not differ

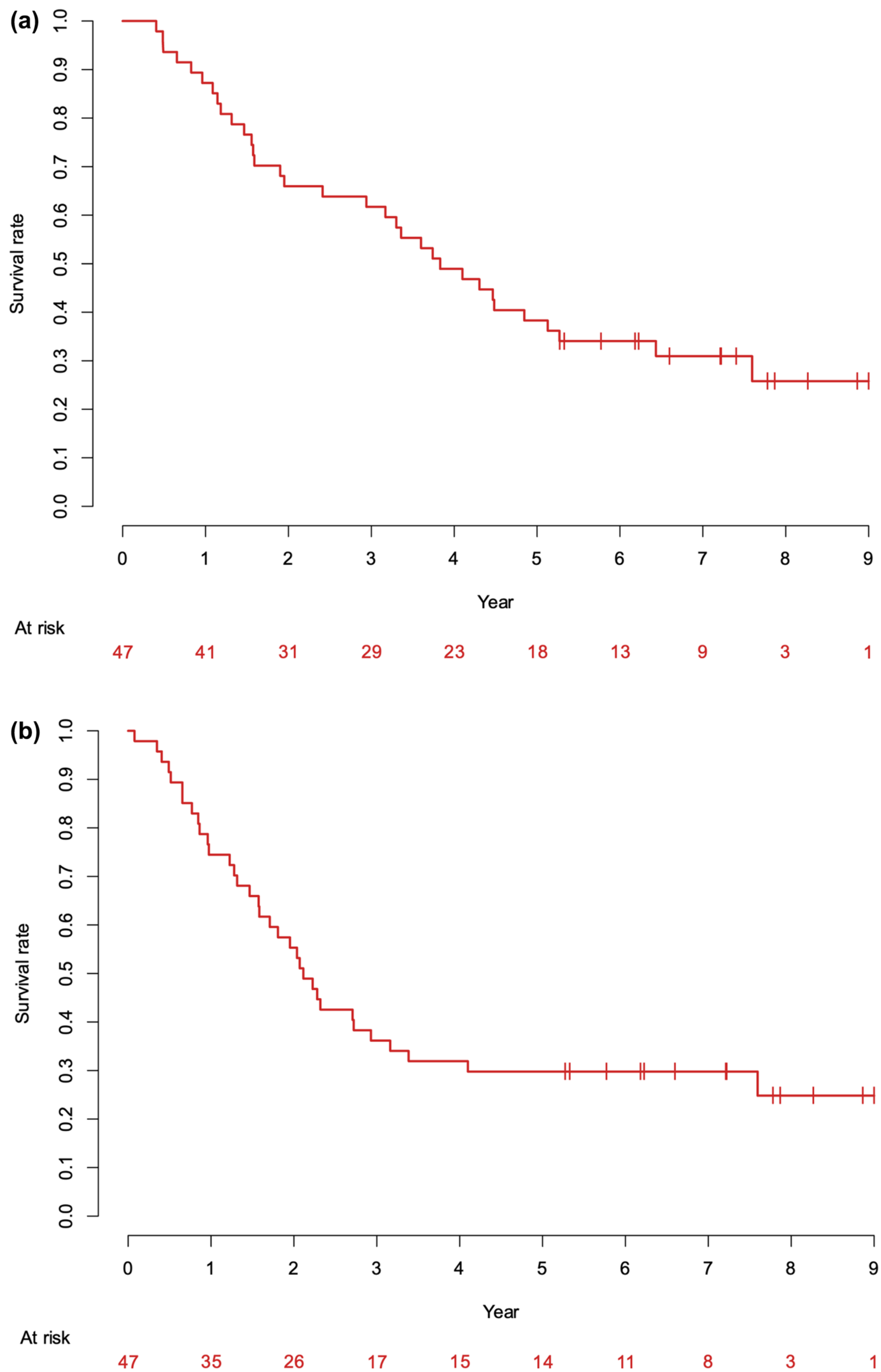


Fig. 2 Kaplan–Meier estimates of overall survival **a** and progression-free survival **b** for all 47 eligible patients

significantly between the groups (harzard ratio, 1.669 [95% CI, 0.831–3.351]; p = 0.146, Fig. 4a). Similarly, the 5-year PFS rate was 16.7% in patients with signet-ring cell carcinoma and 43.5% in those without signet-ring cell carcinoma, with no significant difference (harzard ratio, 1.762 [95% CI, 0.879–3.530]; p = 0.106, Fig. 4b).

In multivariable Cox proportional-hazards analyses with backward stepwise selection using the Akaike information criterion, pretreatment peritoneal cytology (CY1 vs. CY0) remained significantly associated with OS (hazard ratio: 3.686 [95% CI 1.762–7.711]; p < 0.001), together with the presence of a signet-ring cell component (hazard ratio: 0.380

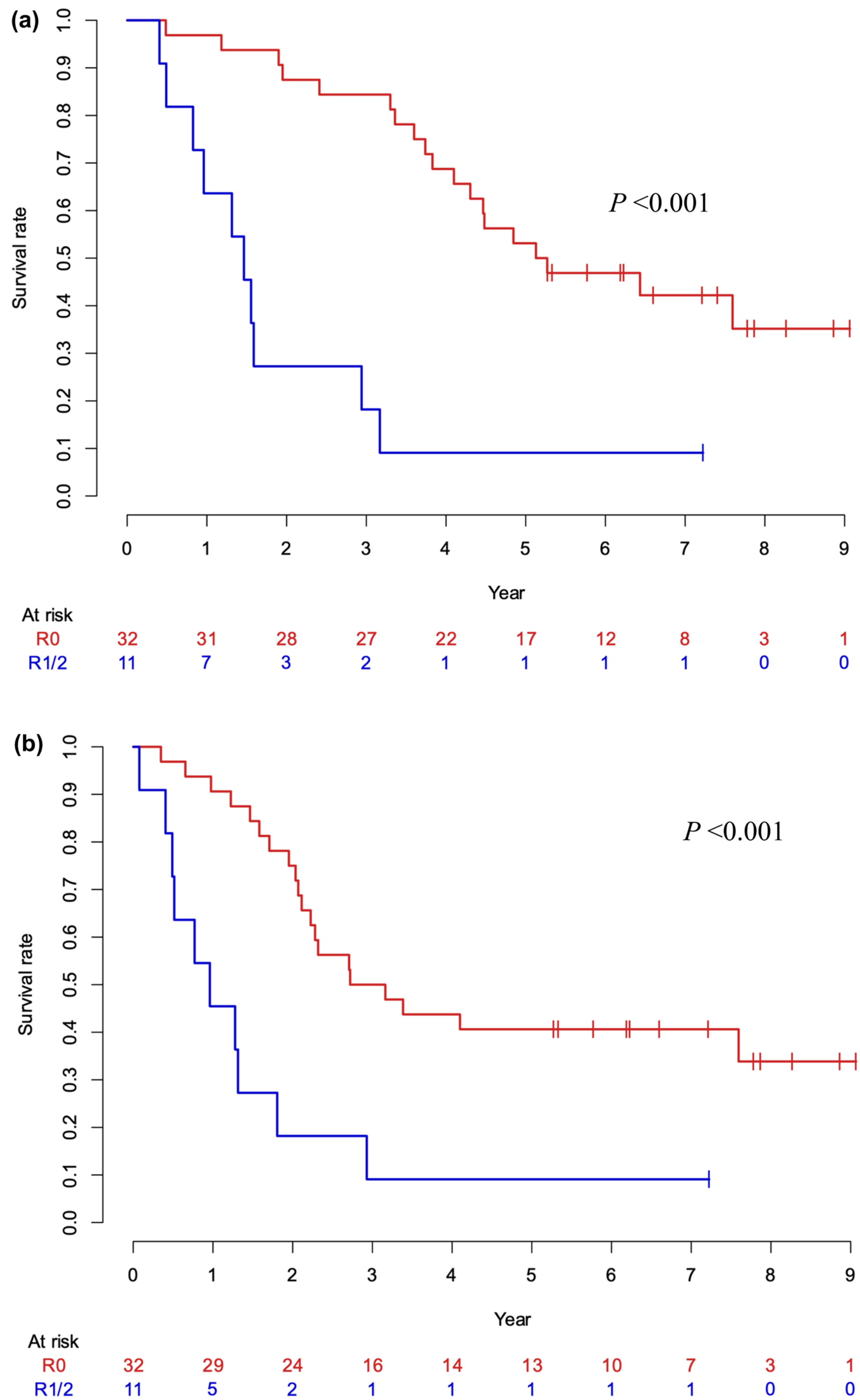
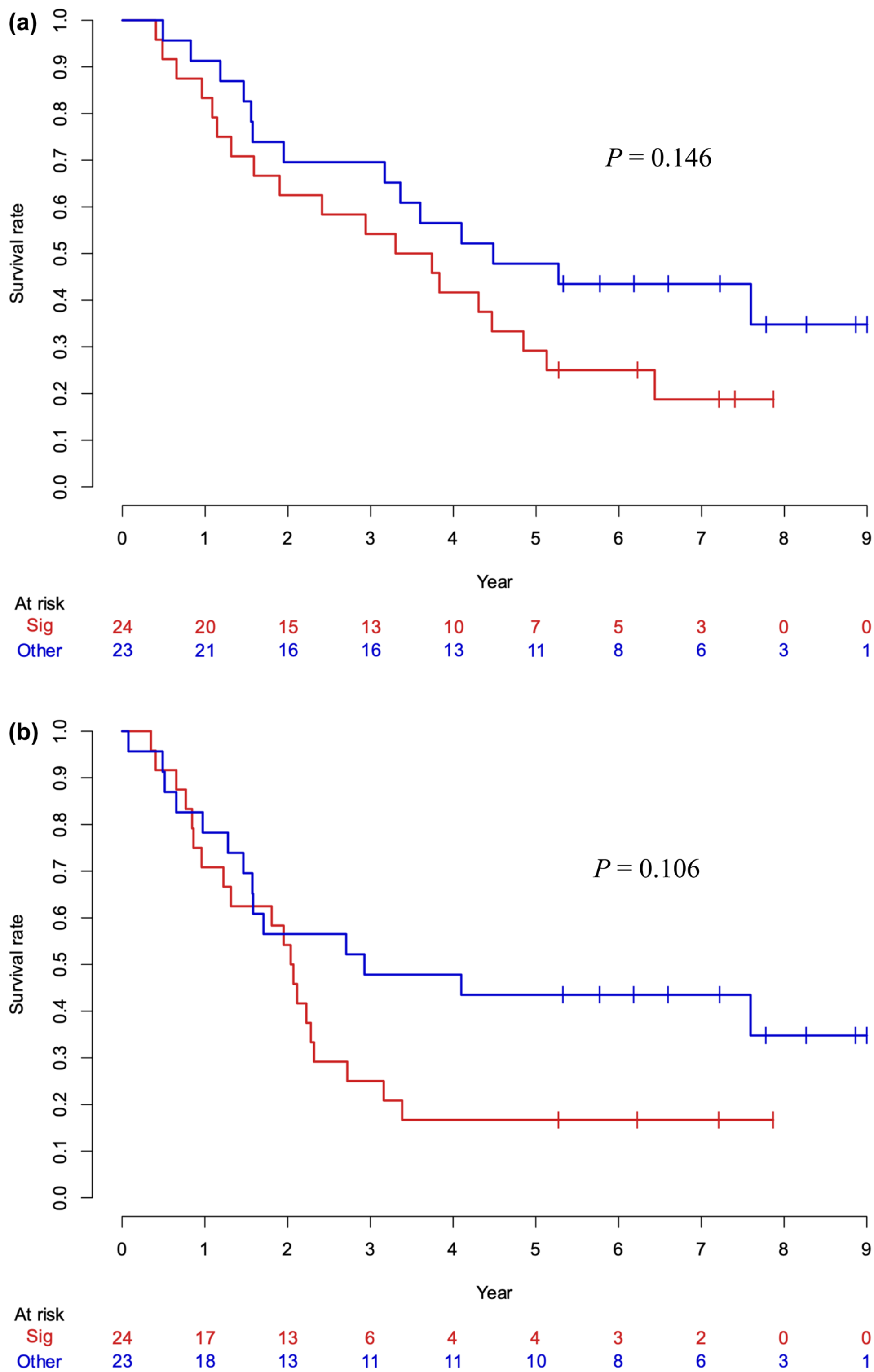


Fig. 3 Kaplan–Meier estimates of overall survival **a** and progression-free survival **b** stratified by R0 resection (red line) or R1/2 resection (blue line). Progression-free survival rates are reported up to 3 years because of the limited number of patients at risk beyond 3 years, particularly in the R1/2 group

Fig. 4 Kaplan–Meier estimates of overall survival **a** and progression-free survival **b** stratified by the presence (red line) or absence (blue line) of signet-ring cell carcinoma components



[95% CI 0.154–0.936]; p = 0.035). For PFS, pretreatment CY1 status (hazard ratio: 6.914 [95% CI 3.025–15.803]; $p < 0.001$) and a signet-ring cell component (hazard ratio: 0.280 [95% CI 0.111–0.707]; p = 0.007) were retained in the final model, while age ≥ 65 years showed a borderline association (hazard ratio: 0.527 [95% CI 0.253–1.098]; p = 0.087) (Supplementary Table 4).

Discussion

This phase II trial (OGSG 1402) was designed to assess the efficacy and safety of NAC with DCS in patients with type 4 or large type 3 GC for whom standard treatment outcomes remain suboptimal. Although neoadjuvant DCS therapy was feasible, the primary endpoint of the R0 resection rate was 68.1% among the 47 eligible patients, which was not significantly higher than the prespecified threshold of 65% (p = 0.391). These results suggest that DCS with this regimen has limited effectiveness in achieving curative resection in high-risk populations.

A possible explanation for the R0 resection rate being not significantly higher than the prespecified threshold in this study may reflect the high percentage of patients with CY1 or P1 status at baseline: 29.8% of patients were classed as CY1 and 12.8% as P1 before treatment. This relatively high proportion may be attributed to the study design, which mandated exploratory laparoscopy and allowed the inclusion of patients with CY1 or localized peritoneal metastasis. In comparison, the JCOG0501 trial reported an R0 resection rate of 74.2% in the NAC group; only 21.2% of the patients had CY1 disease and 3.3% had P1 disease at baseline [5]. Similarly, the KDOG1001 study reported a higher R0 resection rate [12], likely reflecting differences in the eligibility criteria and number of chemotherapy cycles administered. Although 36.2% of the present cohort had Stage IV (CY1 and/or limited P1 disease) disease at baseline, the observed R0 resection rate of 68.1% may still be regarded as unsatisfactory in this clinical context. In addition, conversion to CY0/P0 status following chemotherapy was lower than anticipated, suggesting limited efficacy in downstaging peritoneal disease. Specifically, peritoneal cytology remained positive in eight of the 14 patients, and macroscopic peritoneal metastases persisted in four of the six patients after treatment.

The pathological response rate observed in this study (42.6%) was lower than that in previous trials: 47% in JCOG0210, 51% in JCOG0501, and 51% in JCOG0405 [13]. One possible explanation is the relatively low planned doses used in our regimen. DCS regimens with varying doses have been studied for unresectable GC, and higher-dose regimens have been shown to have greater efficacy at the expense of increased toxicity [14, 15]. Phase II studies in Japan aimed to identify the optimal preoperative DCS dosing [12, 16, 17]. The doses used in the current study were lower (docetaxel 10 mg/m^2/week, cisplatin 15 mg/m^2/week, and S-1 280 mg/m^2/week) than those used in previous high-dose protocols [16]. Our findings support the notion of a dose–response relationship, which warrants further investigation.

In terms of long-term outcomes, the 3- and 5-year OS rates were 61.7% and 38.3%, respectively. These results compare favorably with those of the JCOG0501 trial (3-year OS.

60.9%) and the JCOG0210 trial (3-year OS, 24.5%). Despite the use of a triplet-agent chemotherapy regimen, the survival benefit of neoadjuvant DCS therapy appeared to be limited in this cohort, which included a high proportion of patients with Stage IV disease. Given that there are no previous reports on 5-year survival outcomes in prospective studies targeting type 4 or large type 3 GC, the results of this study may serve as a valuable benchmark for the future development of chemotherapy in this high-risk population.

Considering that GCs with a signet-ring cell component are generally associated with more aggressive biological behaviors and resistance to chemotherapy, we conducted an exploratory analysis to assess whether the presence of signet-ring cell carcinoma affects long-term outcomes. Although the 5-year OS and PFS rates were numerically higher in patients without signet-ring cell carcinoma than in those with it, the differences were not statistically significant, likely because of the limited sample size. Consistent with our observations, Voron et al. conducted a retrospective cohort study involving 1799 patients and demonstrated that signet-ring cell carcinoma was an independent predictor of poor prognosis and exhibited lower responsiveness to chemotherapy [18]. In our cohort, the pathological response rate was 50.0% in patients without a signet-ring cell component, whereas it was markedly lower (18.2%) in patients with signet-ring cell carcinoma. This substantial disparity underscores the need for more effective and targeted therapeutic strategies for signet-ring cell GC, which appears to be less responsive to current NAC regimens.

Given the limitations of adjuvant therapy for GC, NAC has gained traction as a feasible alternative and has become the cornerstone of perioperative treatment strategies. Triplet regimens comprising docetaxel, a platinum-based compound, and fluorouracil have become the mainstay of neoadjuvant chemotherapy. In recent years, oxaliplatin, which is less nephrotoxic than cisplatin, has been increasingly favored as the platinum component. In Western countries, the perioperative fluorouracil/leucovorin, oxaliplatin, and docetaxel (FLOT) regimen has been shown to improve OS compared with epirubicin, cisplatin, and fluorouracil/

capecitabine (ECF) and has become the standard of care [19]. More recently, the phase III MATTERHORN trial demonstrated improved outcomes with the addition of durvalumab to perioperative FLOT [20]. In Asia, the PRODIGY study, a phase III trial conducted in Korea, demonstrated that neoadjuvant DOS (docetaxel, oxaliplatin, and S-1) significantly improved the OS compared with upfront surgery, which suggests the promise of this regimen [21]. The OGSG 1902 trial was conducted in Japan and involved administration of neoadjuvant DOS therapy every 3 weeks for three cycles in patients with type 4 or large type 3 GC [22, 23]. Despite the presence of CY1 disease in 20.8% of the patients (and no cases of P1 disease), the R0 resection rate reached 89.6%. These findings are consistent with a broader shift from cisplatin- to oxaliplatin-based triplet regimens in perioperative treatment strategies for this high-risk patient population. Notably, our study focused exclusively on macroscopic type 4 or large type 3 GC and allowed the inclusion of patients with peritoneal involvement (CY1 and/or limited P1 disease), a subgroup that is underrepresented in many international perioperative trials. To facilitate the interpretation of our findings in the context of these contemporary regimens, Supplementary Table 5 summarizes the key eligibility criteria, treatment delivery, pathological outcomes, perioperative morbidity, and available 3 and 5-year survival results from major neoadjuvant/perioperative trials (JCOG0210, JCOG0501, PRODIGY, OGSG 1902, FLOT4, and MATTERHORN), alongside the present study. Because eligibility criteria, staging procedures (including assessment of peritoneal involvement), and pathological response criteria were not uniform across studies, these cross-trial comparisons are descriptive and should be interpreted with caution.

This study has several limitations. First, this was a single-arm phase II trial with a relatively small sample size. Second, a selection bias may have occurred because the enrollment may have favored patients deemed fit for triplet chemotherapy and surgery, which limits the generalizability of the findings to broader clinical populations, including frail or elderly patients. Third, intraoperative detection of positive peritoneal cytology or peritoneal metastasis (CY1 or P1) was not classified as a progression event when R0 or R1 resection was achieved according to the study protocol, which may have led to underestimation of the true risk of disease progression. Fourth, most patients received only two cycles of neoadjuvant DCS, which may have limited the extent to which the theoretical advantages of neoadjuvant therapy (e.g., eradication of micrometastatic peritoneal disease and improved local control) could be fully realized.

In conclusion, this study did not meet its primary endpoint (R0 resection rate) and neoadjuvant DCS therapy failed to demonstrate sufficient efficacy in patients with type 4 or large type 3 GC. Further investigation of intensified or novel neoadjuvant regimens, as well as multimodal approaches, is warranted to improve the prognosis of this high-risk population.

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Author contributions Study concept: KF; Study design: KF, JK, TT, YK, TSh, and TSa; Acquisition of data: RT, SWL, TY, YA, KT, NW, OT, HF, MM, KS, YO, IK, SU, TK, JM, and TM; Statistical analysis of the data: TSh; Analysis and/or interpretation of data: RT, SWL, KF, JK, TT, YK, TSh, and TSa; Drafting the manuscript: RT, SWL, SE, and KF; and Revising the manuscript critically for important intellectual content: All authors. All of the authors approved the final version of the manuscript.

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Declarations

Conflict of interest The authors declare their conflict of interest/personal relationships, which may be considered as potential conflict of interests, in Supplementary Text 3.

Informed consent All procedures were performed in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and its later versions. Written informed consent for inclusion in this study was obtained from all patients.

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