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ORIGINAL ARTICLE

Three-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 plus docetaxel versus S-1 alone in stage III gastric cancer: JACCRO GC-07

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Abstract

Purpose The second planned interim analysis (median follow-up 12.5 months) in a phase III trial of postoperative adjuvant chemotherapy for stage III gastric cancer revealed significant improvement in relapse-free survival (RFS) for S-1 plus docetaxel over S-1 alone. Although enrollment was terminated on the recommendation of the independent data and safety monitoring committee, we continued follow-up and herein report on 3-year RFS, the primary endpoint.

Patients and methods Patients with histologically confirmed stage III gastric cancer who underwent gastrectomy with D2 lymphadenectomy were randomly assigned to receive adjuvant chemotherapy with either S-1 plus docetaxel or S-1 alone. In the S-1 plus docetaxel group, S-1 was given orally for 2 weeks followed by 1 week of rest for seven courses, and docetaxel was given intravenously on day 1 of the second to seventh courses. The combination therapy was followed by S-1 monotherapy for up to 1 year.

Results The 3-year RFS rate of the S-1 plus docetaxel group was 67.7%. This was significantly superior to that of 57.4% in the S-1 group (hazard ratio [HR] 0.715, 95% CI 0.587–0.871, $P=0.0008$). This translated into a significant benefit in the 3-year overall survival (OS) rate in the S-1 plus docetaxel group (77.7% versus 71.2%, HR 0.742, 95% CI 0.596–0.925, $P=0.0076$).

Conclusion On 3-year follow-up data, postoperative adjuvant therapy with S-1 plus docetaxel was confirmed to improve both RFS and OS and can be recommended as a standard of care for patients with stage III gastric cancer treated by D2 dissection.

Keywords S-1 · Docetaxel · Gastric cancer · Adjuvant chemotherapy

Introduction

Although the incidence of gastric cancer (GC) has declined worldwide in recent decades, GC remains the fifth commonest cancer with over one million new cases annually, and is the fourth most common cause of cancer mortality with about 760,000 deaths [1]. Whereas surgical resection remains a mainstay, multimodality treatment is the standard of care for advanced resectable GC. Perioperative chemotherapy with the FLOT regimen (5-fluorouracil, folinic acid, oxaliplatin, and docetaxel) is the standard treatment in Europe [2]. In Asian countries, local control by D2 dissection had been the norm. However, a surgery-first approach followed by postoperative adjuvant chemotherapy using oral fluoropyrimidine, with or without platinum, has become the standard of care [3–8]. S-1 monotherapy, one of the most common regimens in Asia for stage II/III GC based on a pivotal phase III trial [4, 5], has recently been questioned due to a lack of efficacy as cancer develops into more advanced stages and its inability to reduce the incidence of hematogenous recurrence [4, 5].

JACCRO GC-07 was a randomized phase III study designed to explore the superiority of S-1 plus docetaxel over S-1 alone in a postoperative adjuvant setting for patients with pathologic stage III GC who had undergone D2 gastrectomy [8]. Early study termination had been planned on the basis of the efficacy or futility at interim analyses, and a

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preplanned second interim analysis was conducted when the number of events reached 216 among 915 enrolled patients (median follow-up 12.5 months). Analysis demonstrated the significant superiority of S-1 plus docetaxel (66%) over S-1 (50%) in terms of 3-year relapse-free survival (hazard ratio [HR] 0.632; 99.99% confidence interval [CI] 0.400–0.998; stratified log-rank test, $P < 0.001$) [8], and the enrollment was terminated on the recommendation of the independent data and safety monitoring committee in September 2017, although the follow-up for 5 years after surgery was to be completed to allow the primary and secondary endpoints to be evaluated.

As 3 years have passed since enrollment termination, preplanned analysis to evaluate relapse-free survival (RFS) at 3 years, the primary endpoint, was performed using the updated information of the patients.

Patients and methods

Study design and patients

The study was conducted in accordance with the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects. This study was designed by the steering committee members and the sponsor (Japan Clinical Cancer Research Organization [JACCRO]). The protocol was approved by the institutional review board of each participating hospital. The steering committee and an independent data and safety monitoring committee oversaw the study conduct. Written informed consent was obtained from all patients. Data were maintained by the independent JACCRO GC-07 data center and analyzed by the JACCRO Statistical Analysis Department. The protocol, amendments, and statistical analysis plan are available in the Data Supplement.

This study involved patients aged 20–80 years who underwent R0 resection by D2 or more extensive gastrectomy and were determined by pathologic examination to belong to one of the following subsets of patients with stage III GC defined by the 3rd English edition of the Japanese Classification of Gastric Carcinoma where the staging is identical to that for stomach cancer in the 7th edition of the TNM classification: stage IIIA (T2N3, T3N2, T4aN1), stage IIIB (T3N3, T4aN2, T4bN0, T4bN1), or stage IIIC (T4aN3, T4bN2, T4bN3) [9, 10].

Procedures

Treatment was to be started within 42 days postoperatively. The daily S-1 dose was determined by body surface area (< 1.25 m^2, 80 mg; ≥ 1.25 to < 1.5 m^2, 100 mg; ≥ 1.5 m^2, 120 mg) and administered orally twice a day. Patients who were assigned to the S-1 plus docetaxel group were treated with S-1 on days 1 to 14 of a 3-week cycle during the first course. During the second to seventh courses, patients received intravenous infusion of docetaxel (40 mg/m^2 body surface area) on day 1 of each cycle and S-1 on days 1 to 14 of a 3-week cycle. After the eighth course, treatment with S-1 continued on days 1 to 28 of 6-week cycles for up to 1 year. In the S-1 group, patients were treated with S-1 on days 1 to 28 of 6-week cycles for up to 1 year. The criteria for dose reduction and toxicity have been described previously [8]. Patients were observed for 5 years following surgery.

Outcomes

The primary endpoint was 3-year RFS. Secondary endpoints were 3-year OS, 5-year OS, 5-year RFS, and adverse events. We assessed disease stage, extent of lymph node dissection, and histologic type in accordance with the standards defined by the Japanese Gastric Cancer Association [9]. Relapse was determined by diagnostic imaging and/or clinical evidence

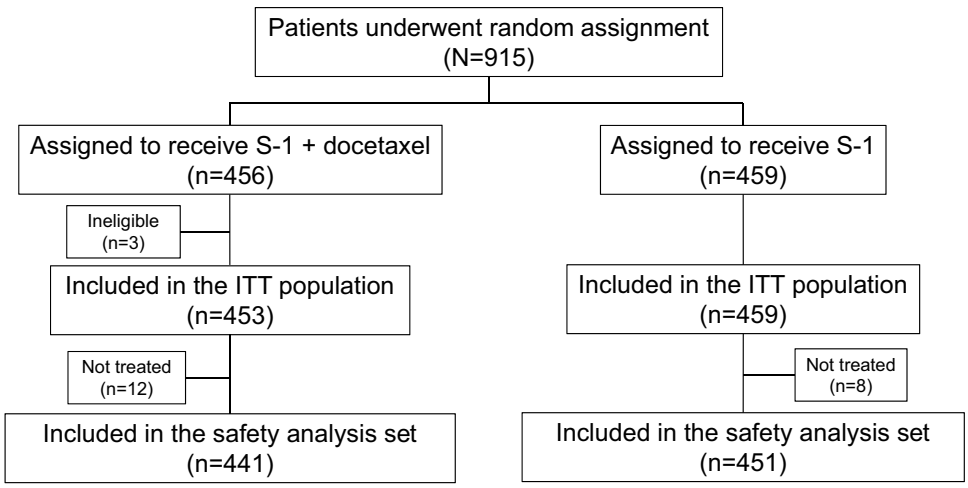


Fig. 1 CONSORT diagram. *ITT* intention-to-treat

Table 1 Patient baseline characteristics

Characteristic	S-1 + docetaxel ($n=453$)	S-1 ($n=459$)
Sex		
Male	310 (68)	332 (72)
Female	143 (32)	127 (28)
Age, years (range)	66 (29–80)	66 (29–80)
pStage		
IIIA	147 (32)	149 (32)
IIIB	157 (35)	160 (35)
IIIC	149 (33)	150 (33)
pT-categories		
T2	18 (4)	26 (6)
T3	168 (37)	174 (38)
T4	267 (59)	259 (56)
pN-categories		
N0	6 (1)	3 (1)
N1	55 (12)	42 (9)
N2	143 (32)	153 (33)
N3	249 (55)	261 (57)
Histologic type		
Differentiated	182 (40)	186 (41)
Undifferentiated	271 (60)	273 (59)
ECOG performance status		
0	388 (86)	401 (87)
1	65 (14)	58 (13)
Extent of gastrectomy		
Total gastrectomy	174 (38)	194 (42)
Distal gastrectomy	274 (61)	260 (57)
Others	5 (1)	5 (1)
Tumor location		
Upper	100 (22)	114 (25)
Middle	179 (39)	157 (34)
Lower	162 (36)	174 (38)
Others	12 (3)	14 (3)

Data are presented as No. (%), unless otherwise indicated

ECOG Eastern Cooperative Oncology Group

of progression of the disease. Ultrasonography or computed tomography was performed every 6 months, and endoscopy was performed every 12 months until the end of the follow-up period or recurrence/metastasis. We carried out hematologic tests and clinical symptom assessments during adjuvant chemotherapy at 3-week intervals for the S-1 plus docetaxel group and at 2-week intervals for the S-1 group. Adverse events were monitored throughout treatment courses until the end of treatment and were graded according to the Common Terminology Criteria for Adverse Events (version 4.0), Japanese edition, Japan Clinical Oncology Group version. The planned dose was defined as the total dose if the whole treatment cycles had been completed without dose reduction. As an exploratory analysis, we also assessed the relative dose intensity, which was defined as the ratio of delivered dose to the planned dose.

Statistical analysis

The sample size was planned on the basis of the results of the ACTS-GC study [5] in which 3-year RFS in the S-1 group was estimated to be 68% for stage IIIA disease, 50% for stage IIIB disease, and 62% for stage III disease (stage IIIA plus stage IIIB) as defined by the 2nd English edition of the Japanese Classification of Gastric Carcinoma [11]. Accordingly, 3-year RFS in the present S-1 group was estimated to be 62%. As no previous study was available for use as a basis to estimate 3-year RFS in the S-1 plus docetaxel group, it was determined that S-1 plus docetaxel could be regarded as a standard therapy if 3-year RFS was 7% higher than that in the S-1 group, with acceptable safety. The sample size for each treatment group was estimated at 530 assuming a 3-year follow-up period, two-sided $\alpha=0.05$, and $\beta=0.2$. After taking patient withdrawals into account, we estimated that 1100 patients (550 per group) needed to be recruited. The cumulative number of primary outcome events after 3 years of follow-up was estimated to be 507.

Enrolled patients were stratified by disease stage (IIIA, IIIB, or IIIC), histologic type (differentiated or undifferentiated), and trial site and were randomly assigned to the S-1 plus docetaxel group or the S-1 group at a 1:1 ratio by the minimization method using a centralized patient registration system at the JACCRO GC-07 data center.

Efficacy endpoints were evaluated in the intention-to-treat (ITT) analysis set, which consisted of all patients who met the eligibility criteria and did not fall under the exclusion criteria. The safety endpoint was evaluated in the safety analysis set, which consisted of all patients who received at least one study drug treatment.

RFS was analyzed by a stratified log-rank test with allocation adjustment factors in the ITT analysis set. We estimated cumulative survival curves and annual survival rates using Kaplan–Meier curves. Between-group analyses were performed with a stratified log-rank test with allocation adjustment factors, except for study sites. For between-group efficacy comparisons, the HR and two-sided 95% CI were estimated using the Cox proportional hazards regression model. The same analyses were applied to OS. In all cases, the significance level was set at a two-sided α of 0.05.

Results

Of 915 randomly assigned patients, three patients in the S-1 plus docetaxel group were excluded (stage IV, double registration, and special type histology); therefore, 912 patients

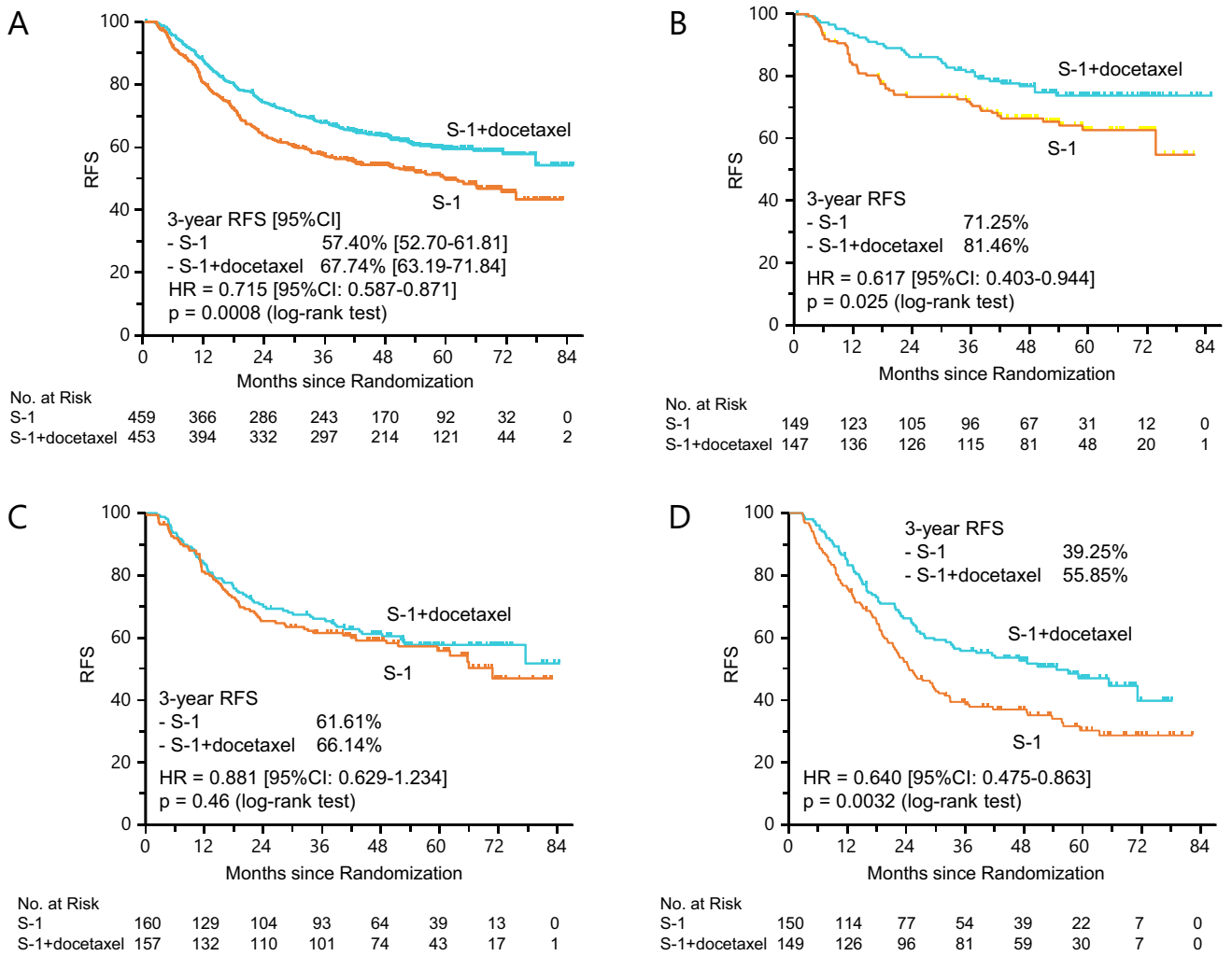


Fig. 2 Relapse-free survival (RFS). Kaplan–Meier estimates of RFS in all patients (**A**) and in those with stage IIIA (**B**), IIIB (**C**), and IIIC disease (**D**)

($n=453$ in S-1 plus docetaxel group; $n=459$ in S-1 group) were included in the ITT analysis set. Twelve and eight untreated patients in the S-1 plus docetaxel group and S-1 group, respectively, were excluded from the safety analysis set. Therefore, a total of 892 patients (441 patients in the S-1 plus docetaxel group and 451 patients in the S-1 group) were included in the treatment compliance and adverse event analyses, which had been conducted in 689 patients at the interim analysis and reported previously [8] (Fig. 1). Overall, patient baseline characteristics were well balanced between the two groups (Table 1).

Among the 912 patients in the S-1 plus docetaxel and S-1 alone groups, during the median follow-up period of 42.5 months (0.3–85.16), 144 and 180 died, 33 and 43 patients are alive with recurrence, 276 and 236 are alive without recurrence, respectively. Data on 34 patients lost to follow-up within 3 years from the date of random assignment were censored. The 3-year RFS of 67.7% in the S-1 plus docetaxel group was significantly superior to 57.4% in the S-1 group (HR 0.715, 95% CI 0.587–0.871, $P=0.0008$) (Fig. 2). The 3-year RFS rates of those with stage IIIA were 81.5% in the S-1 plus docetaxel group and 71.3% in the S-1 group (HR 0.617, 95% CI 0.403–0.944, $P=0.025$). Those with stage IIIB were 66.1% in the S-1 plus docetaxel group and 61.6% in the S-1 group (HR 0.881, 95% CI 0.629–1.234, $P=0.46$). For stage IIIC, the percentage was 55.9% in the S-1 plus docetaxel group and 39.3% in the S-1 group (HR 0.640, 95% CI 0.475–0.863, $P=0.0032$). The 3-year OS was 77.7% in the S-1 plus docetaxel group and 71.2% in the S-1 group (HR 0.742, 95% CI 0.596–0.925, $P=0.0076$) (Fig. 3), confirming that patient survival was significantly better in the S-1 plus docetaxel group.

Supplement Table 1 summarizes treatment compliance with the two drugs. Of the 441 patients in the S-1 plus docetaxel group, 28 (6%) did not receive docetaxel. Of the 413 patients who received docetaxel, 297 (67%) received all six

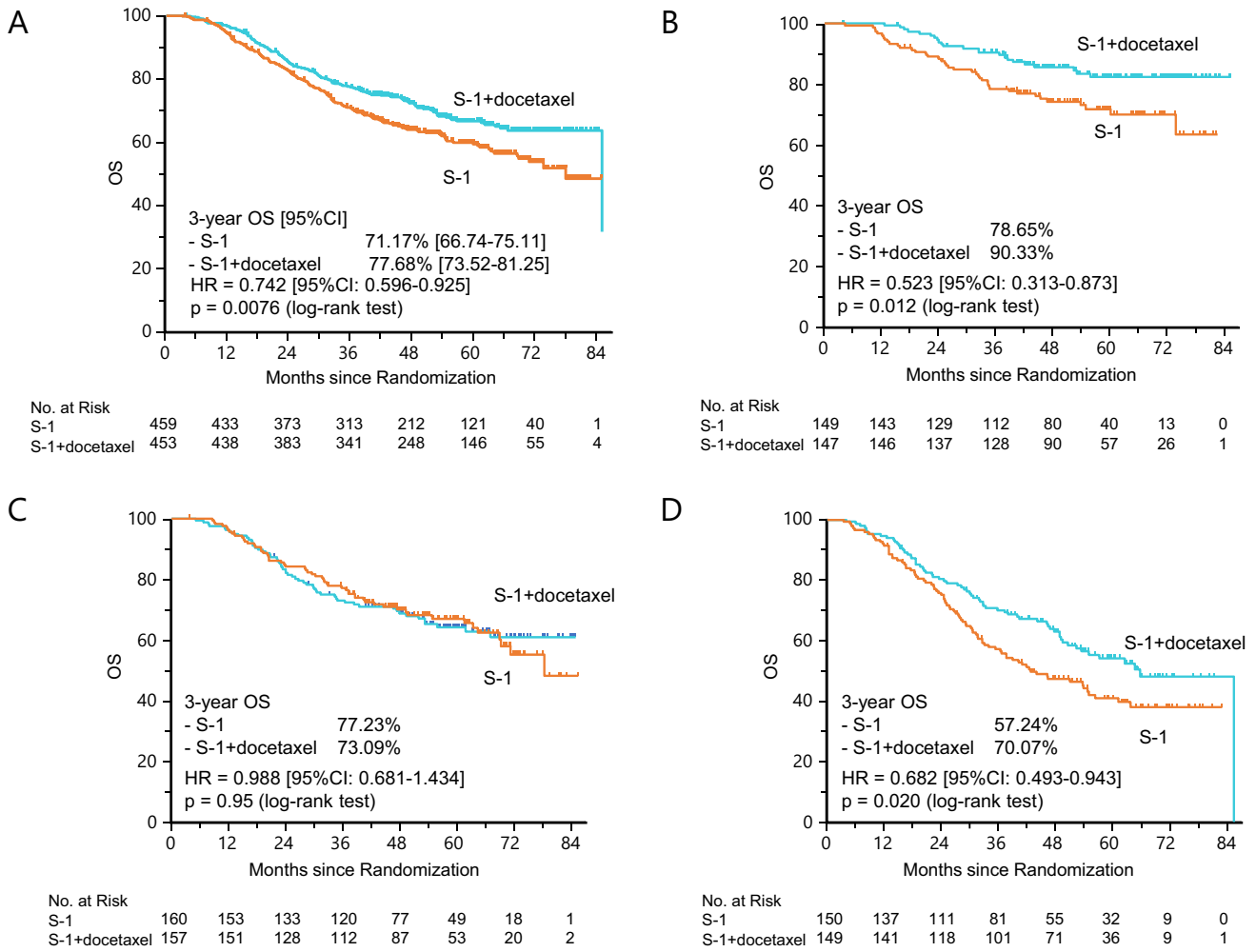


Fig. 3 Overall survival (OS). Kaplan–Meier estimates of OS in all patients (**A**) and in those with stage IIIA (**B**), IIIB (**C**), and IIIC disease (**D**)

doses, and dose reduction was applied in 123 patients (28%). S-1 dose reduction was necessary in 177 patients (40%) in the S-1 plus docetaxel group and 134 patients (30%) in the S-1 alone group. Dose intensities of S-1 and docetaxel were 61.6% and 77.5% in the S-1 plus docetaxel group, respectively. The dose intensity of S-1 was 71.4% in the S-1 alone group. Common reasons for treatment discontinuation with an incidence exceeding 5% were the same in both groups—patient request, adverse event that lasted for more than 28 days, physicians' decision, and recurrence.

Common adverse events are summarized in Table 2 and were similar to findings in the previous report [8]. One patient in the S-1 group died of respiratory failure, which was considered to be an adverse drug reaction. Hospitalization as a result of severe adverse events occurred in 76 patients (17%; 95% CI 13% to 20%) in the S-1 plus docetaxel group and 67 patients (15%; 95% CI 11% to 18%) in the S-1 group.

Common sites of first relapse were the peritoneum, hematogenous sites, and lymph nodes (Table 3). The S-1 plus docetaxel group had significantly lower relapse rates than the S-1 group for hematogenous sites (9.7% [95% CI 7.0%–12.4%] v 15.5% [95% CI 12.2%–18.8%]; $P = 0.009$) and lymph nodes (6.4% [95% CI 4.1%–8.7%] v 15.0% [95% CI 11.8%–18.3%]; $P < 0.001$). In contrast, we observed no difference in the incidence of local recurrence (2.9% [95% CI 1.3%–4.4%] v 4.4% [95% CI 2.5%–6.2%]; $P = 0.287$) and recurrence on the peritoneal surface (18.8% [95% CI 15.2%–22.4%] v 21.4% [95% CI 17.6%–25.1%]; $P = 0.363$).

We analyzed the RFS and OS of eligible patients according to sex, age, cancer stage, tumor stage, nodal stage, histologic type, performance status, operative method, and primary lesion (Fig. 4A, B). There were no significant interactions between treatment groups and these variables.

Table 2 Adverse events by grade and treatment group

	S-1 + docetaxel ($n=441$)		S-1 ($n=451$)	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Leukopenia	56.2	22.4	45.0	2.7
Neutropenia	58.0	39.2	47.7	16.4
Thrombocytopenia	21.5	1.4	24.4	0.2
Anemia	46.5	4.3	42.8	2.7
AST increased	20.4	1.6	22.8	2.0
ALT increased	14.1	1.4	16.2	1.3
Bilirubin increased	21.3	0.5	31.9	1.8
Creatinine increased	2.9	0.0	7.1	0.0
Anorexia	63.3	13.6	52.3	12.0
Nausea	36.5	3.6	31.9	1.8
Vomiting	11.6	1.1	12.2	1.6
Diarrhea	49.2	3.4	46.1	8.9
Mucositis oral	39.2	4.1	23.1	1.6
Fatigue	32.9	2.0	25.5	1.3
Malaise	49.9	–	37.0	–
Alopecia	56.7	–	3.8	–
Febrile neutropenia	5.7	5.7	0.4	0.4

Adverse event grades were determined using the Common Terminology Criteria for Adverse Events, version 4.0

Table 3 Site of first relapse

Site	Stage IIIA ($n=147$)	Stage IIIB ($n=157$)	Stage IIIC ($n=149$)	All ($n=453$)
S-1 plus docetaxel group				
Local	3 (2.0)	5 (3.2)	5 (3.4)	13 (2.9)
Lymph nodes	4 (2.7)	14 (8.9)	11 (7.4)	29 (6.4)
Peritoneum	13 (8.8)	28 (17.8)	44 (29.5)	85 (18.8)
Hematogenous	14 (9.5)	15 (9.6)	15 (10.1)	44 (9.7)
Others	2 (1.4)	3 (1.9)	5 (3.4)	11 (2.4)
Total	33 (22.4)	58 (36.9)	70 (47.0)	161 (35.5)
Site	Stage IIIA ($n=149$)	Stage IIIB ($n=160$)	Stage IIIC ($n=150$)	All ($n=459$)
S-1 alone group				
Local	6 (4.0)	2 (1.3)	12 (8.0)	20 (4.4)
Lymph nodes	17 (11.4)	25 (15.6)	27 (18.0)	69 (15.0)
Peritoneum	15 (10.1)	30 (18.8)	53 (35.3)	98 (21.4)
Hematogenous	16 (10.7)	26 (16.3)	29 (19.3)	71 (15.5)
Others	2 (1.3)	5 (3.1)	6 (4.0)	13 (2.8)
Total	48 (32.2)	67 (41.9)	97 (64.7)	212 (46.2)

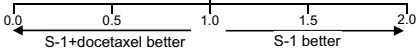
Data are presented as No. (%), unless otherwise indicated. Others include pleural dissemination, retroperitoneal relapse, and relapse in the gastric remnant. Some patients had their first relapse at more than one site

Discussion

The superiority of S-1 plus docetaxel over S-1 alone in a postoperative adjuvant setting for patients with pathologic stage III GC was found to be robust in terms of 3-year RFS, the primary endpoint, and this applied even for the Stage IIIC subset (HR 0.640). We could also demonstrate 6.5% improvement in 3-year OS with a HR of 0.742 ($P=0.0076$). In the previous trial, S-1 monotherapy significantly decreased the rates of recurrence in the lymph nodes and peritoneal surface when compared with surgery alone [5]. In contrast, while retaining the capacity to suppress recurrences to the peritoneum and having even greater suppressive effects on nodal recurrences, S-1 plus docetaxel resulted in a significant

A

Baseline Characteristic	No. of events / total no. of patients		Hazard Ratio for RFS (95% CI)	P value for interaction
	S-1+docetaxel	S-1		
Total	177/453	223/459	0.715 (0.587-0.871)	
Sex				
Male	121/310	163/332	0.705 (0.557-0.893)	0.8251
Female	56/143	60/127	0.743 (0.516-1.069)	
Age				
≤70 yr	123/328	155/328	0.696 (0.549-0.881)	0.6694
>70 yr	54/125	68/131	0.761 (0.532-1.089)	
Stage				
IIIA	36/147	52/149	0.617 (0.403-0.944)	0.2975
IIIB	65/157	71/160	0.881 (0.629-1.234)	
IIIC	76/149	100/150	0.64 (0.475-0.863)	
Tumor stage				
T2	1/18	11/26	0.104 (0.013-0.806)	0.1352
T3	63/168	75/174	0.801 (0.573-1.12)	
T4	113/267	137/259	0.707 (0.551-0.908)	
Nodal stage				
N0	3/6	1/3	1.291 (0.134-12.485)	0.6007
N1	14/55	9/42	1.154 (0.499-2.669)	
N2	45/143	61/153	0.695 (0.472-1.022)	
N3	115/249	152/261	0.689 (0.541-0.878)	
Histologic type				
Differentiated	56/182	75/186	0.679 (0.48-0.961)	0.7042
Undifferentiated	121/271	148/273	0.73 (0.574-0.928)	
Performance status				
0	143/388	193/401	0.675 (0.543-0.838)	0.2453
1	34/65	30/58	0.941 (0.576-1.538)	
Extent of gastrectomy				
Total gastrectomy	77/174	110/194	0.69 (0.516-0.924)	0.4583
Distal gastrectomy	96/274	110/259	0.741 (0.563-0.974)	
Other	4/5	3/6	1.964 (0.429-9.001)	
Primary lesion				
Upper	41/100	66/114	0.587 (0.397-0.868)	0.1475
Middle	70/179	74/157	0.766 (0.552-1.063)	
Lower	62/162	73/174	0.846 (0.603-1.187)	
Other	4/12	10/14	0.239 (0.072-0.792)	



B

Baseline Characteristic	No. of events / total no. of patients		Hazard Ratio for OS (95% CI)	P value for interaction
	S-1+docetaxel	S-1		
Total	144/453	180/459	0.742 (0.596-0.925)	
Sex				
Male	97/310	132/332	0.735 (0.565-0.955)	0.8455
Female	47/143	48/127	0.766 (0.511-1.149)	
Age				
≤70 yr	97/328	120/328	0.73 (0.558-0.954)	0.7711
>70 yr	47/125	60/131	0.778 (0.531-1.14)	
Stage				
IIIA	23/147	40/149	0.523 (0.313-0.873)	0.1107
IIIB	55/157	56/160	0.988 (0.681-1.434)	
IIIC	66/149	84/150	0.682 (0.493-0.943)	
Tumor stage				
T2	1/18	8/26	0.148 (0.018-1.188)	0.2788
T3	46/168	59/174	0.759 (0.516-1.116)	
T4	97/267	113/259	0.766 (0.583-1.005)	
Nodal stage				
N0	3/6	0/3	—	0.7121
N1	12/55	8/42	1.141 (0.466-2.794)	
N2	30/143	47/153	0.632 (0.4-1)	
N3	99/249	125/261	0.74 (0.568-0.964)	
Histologic type				
Differentiated	36/182	55/186	0.615 (0.404-0.936)	0.3263
Undifferentiated	108/271	125/273	0.791 (0.611-1.024)	
Performance status				
0	119/388	153/401	0.734 (0.577-0.933)	0.9216
1	25/65	27/58	0.768 (0.446-1.324)	
Extent of gastrectomy				
Total gastrectomy	68/174	92/194	0.726 (0.529-0.995)	0.4736
Distal gastrectomy	74/274	87/259	0.752 (0.551-1.025)	
Other	2/5	1/6	3.311 (0.299-36.696)	
Primary lesion				
Upper	35/100	53/114	0.677 (0.442-1.039)	0.0962
Middle	54/179	56/157	0.812 (0.558-1.18)	
Lower	52/162	61/174	0.844 (0.582-1.225)	
Other	3/12	10/14	0.165 (0.043-0.625)	

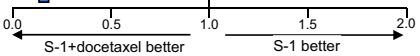


Fig. 4 **A** Forest plot of relapse-free survival (RFS). Subgroup analyses of RFS were performed using patient baseline characteristics. **B** Forest plot of overall survival (OS). Subgroup analyses of OS were performed using patient baseline characteristics

decrease in hematogenous recurrence, an effect which had not been observed with S-1 alone (Table 3). These preventive effects of S-1 plus docetaxel in relation to relapse sites were evident in patients with each stage of the disease, IIIA, IIIB, and IIIC. Interestingly, improvements in RFS and OS curves were not as spectacular in the Stage IIIB subset. We could

not find any specific subgroup included in Stage IIIB (suppl. Table 2). In suppl. Table 3, survival improvement by S-1 plus docetaxel was clearly observed in T3N3b and T4aN2 (these groups comprised 51% of the all Stage IIIB cases). However, the very slight difference of RFS in T3N3a (43%) and the inverted RFS in T4bN0 and T4bN1 (6%) might offset the clear improvement of the survival in stage IIIB.

The survival benefit was accompanied by a favorable safety profile and treatment compliance. More than two thirds of patients in the S-1 plus docetaxel group received docetaxel six times as planned, despite its well-documented toxicities [8]. All adverse events were manageable and well tolerated by patients with no treatment-related deaths. We may keep in mind the S-1 dose intensity, 61.6% in the S-1 plus docetaxel group and 71.4% in the S-1 alone group. The patients might tolerate additional docetaxel burden with about 10% decrease of S-1 dose intensity. Compliance rates for S-1 and S-1 plus docetaxel were almost identical to those reported in previous studies [4, 5, 12, 13]. Details of the adverse events were similar to those previously reported, [8] and hematologic adverse events, such as leukopenia and neutropenia, were more common in the S-1 plus docetaxel group. Nevertheless, capecitabine plus oxaliplatin (CAPOX) could still be selected for those who wish to shorten the duration of treatment to 6 months and those who wish to avoid adverse events specific to docetaxel, such as alopecia.

In recent large clinical trials of adjuvant chemotherapy after curative D2 gastrectomy, 3-year RFS or DFS has been evaluated as a surrogate measure of 5-year OS [4, 6, 8], since strong concordance has been observed between 3-year RFS or DFS and 5-year OS [5, 7, 14]. Since 5-year RFS and OS are the secondary endpoints of this study, additional follow-up will be conducted to confirm if the survival difference between the two arms is robust. However, a significant difference in OS with a HR of 0.742 ($P=0.0076$) has already been observed at the median follow-up period of 42.5 months following surgery. This is encouraging, given that the superiority in 3-year RFS did not translate into improvement in OS until 5 years after surgery in another phase III trial that evaluated the CAPOX regimen [7]. Moreover, the control arm of that trial had been treatment by surgery alone.

This study has several limitations. Due to the inherent difference in the standard of care, the results of this study are only applicable to countries and regions where perioperative chemotherapy is not the standard of care. No efforts were made in this study to shorten the duration of adjuvant treatments, although it has been shortened to 6 months or less for most types of cancer. One of the reasons for this is that we hold in high regard the data from a Japanese phase III trial [15] where the non-inferiority of 6 months of S-1 monotherapy compared with 12 months was not shown, despite the fact that there were several randomized trials conducted in Asia in which durations of postoperative adjuvant therapy using doublets were confined to 6 months. While combinations of oral fluoropyrimidines with platinum are still the favored options in these Asian trials, the current study provides no signpost as to whether these or the S-1/docetaxel combination should be chosen.

In conclusion, the 3-year outcomes of the study confirmed that adjuvant chemotherapy with S-1 plus docetaxel improved RFS and OS with risk reduction of 29% and 26%, respectively, compared with S-1 alone. This combination can be recommended as a standard of care for patients with stage III GC treated by D2 dissection.

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Declarations

Conflict of interest Yoshihiro Kakeji reports grants and personal fees from Taiho Pharma, Tsumura, Abbott, Chugai Pharma, Sanofi, Nippon Kayaku, Kaken Pharma, Lilly Japan, Takeda Pharma, Terumo Corp., Astellas Pharma, Otsuka Pharma Factory, Ono Pharma, personal fees from Bayer, MSD, Daiichi Sankyo, Miyarisan Pharma, Merck, Bristol-Myers squibb, Olympus, Covidien, Yakult Honsha, Johnson & Johnson, EA Pharma, Fluidigm, outside the submitted work. Kazuhiro Yoshida reports grants and personal fees from Sanofi, Taiho Pharm., during the conduct of the study; grants and personal fees from Asahi Kasei Pharma, Chugai Pharma, Covidien Japan, Daiichi Sankyo, Eli Lilly Japan, Johnson & Johnson, Merk Serono, MSD, Nippon Kayaku, Novartis Pharma, Ono Pharm., Otsuka Pharm., Takeda Pharm., TERUMO, Tsumura & Co., Yakult Honsha, Abbott, grants from Abbvie, Astellas, Biogen Japan, Celgene, Eisai, EP-CRSU, EPS Corporation, FUJIFILM, GlaxoSmithKline K.K., Kaken Pharm., Kyowa Kirin, Meiji Seika Pharma, Philips, Toray Medical, personal fees from AstraZeneka, Bristol-Myers Squibb Japan, Denka Co., Ltd, EA Pharma, Olympus, Pfizer, Sanwa Kagaku Kenkyusho, SBI Pharma, Teijin Phamra, outside the submitted work. Yasuhiro Kodera reports grants from Kaken Pharma, Covidien, EA Pharma, Novartis, KCI, Maruho, Otsuka, Sawai, Sanofi, Shionogi, Nihon Kayaku, grants and personal fees from Daiichi Sankyo, Tsumura, Taiho Pharma, Chugai Pharma, Lilly Japan, Johnson & Johnson, Takeda, Yakult, Otsuka, Ono Pharma, Covidien, MSD, personal fees from Bristol, outside the submitted work. Wataru Ichikawa reports grants and personal fees from Chugai Pharma, Taiho Pharma, Takeda Pharma, Daiichi Sankyo, Merck Pharma, Ono Pharma, grants from Eli Lilly Japan, personal fees from Yakult Honsha, Bayer Yakuhin, Eizai, Shionogi, AstraZeneca, Bristol Myers Squibb, Nippon Kayaku, AstraZeneca K.K, outside the submitted work. The other authors declare that they have no conflicts of interest.

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