Gastric Cancer (2023) 26:788–797
https://doi.org/10.1007/s10120-023-01408-y

ORIGINAL ARTICLE

Effect of the number of cycles of docetaxel + S-1 therapy on long-term survival in adjuvant chemotherapy for stage III gastric cancer. A pooled analysis of the OGSG0604 and OGSG1002 trials

Yutaka Kimura[1] · Hisato Kawakami[2] · Shigeyuki Tamura[3] · Kazumasa Fujitani[4] · Jin Matsuyama[5] · Hiroshi Imamura[6] · Shohei Iijima[7] · Daisuke Sakai[8] · Yukinori Kurokawa[9] · Toshio Shimokawa[10] · Toshimasa Tsujinaka[11] · Hiroshi Furukawa[12] · Taroh Satoh[8]

Received: 15 March 2023 / Accepted: 4 June 2023 / Published online: 19 June 2023

Abstract

Background S-1 plus docetaxel (DS) therapy followed by S-1 is the standard of care in Japan in postoperative adjuvant chemotherapy for stage III gastric cancer, but long-term survival and the number of DS cycles required are unclear. The purpose of this study was to investigate the impact of the number of cycles of DS therapy on the 5-year survival in stage III gastric cancer in a pooled analysis of two phase II trials (OGSG0604 and OGSG1002).

Patients and methods Patients with histologically confirmed stage III gastric cancer who underwent gastrectomy with D2 lymphadenectomy were enrolled in this pooled analysis. They received DS therapy for four or eight cycles, followed by S-1 until 1 year postgastrectomy. The 5-year overall survival (OS) and the 5-year disease free survival (DFS) by the landmark analysis was evaluated.

Results In total, 113 patients from the OGSG0604 and OGSG1002 trials were enrolled in this study. The landmark analysis showed a 5-year OS that was better with four to eight cycles of DS therapy than with one to three cycles of DS therapy, with the best 5-year OS of 77.4% (95% confidence interval, 66.5–90.1%) for eight cycles. The 5-year DFS was approximately 66% when four or eight cycles of DS therapy were given.

Conclusion Although eight cycles of DS therapy may prolong prognosis, the present study did not provide a clear conclusion as to how many DS therapy cycles are needed to improve prognosis after D2 gastrectomy for stage III gastric cancer.

Trial registration Registration number: UMIN00000714 and UMIN000004440.

Keywords Stage III gastric cancer · Adjuvant chemotherapy · S-1 · Docetaxel

✉ Yutaka Kimura
you_kimura@aol.com

[1] Department of Surgery, Kindai University Nara Hospital, 1248-1 Otoda-Cho, Ikoma, Nara 630-0293, Japan

[2] Department of Medical Oncology, Kindai University, Faculty of Medicine, Osaka-Sayama, Japan

[3] Department of Surgery, Yao Municipal Hospital, Yao, Japan

[4] Department of Gastroenterological Surgery, Osaka General Medical Center, Osaka, Japan

[5] Department of Gastroenterological Surgery, Higashiosaka City Medical Center, Higashiosaka, Japan

[6] Department of Surgery, Toyonaka Municipal Hospital, Toyonaka, Japan

[7] Department of Nutritional Oncology, Osaka International Cancer Institute, Osaka, Japan

[8] Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan

[9] Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Japan

[10] Clinical Study Support Center, Wakayama Medical University, Wakayama, Japan

[11] Department of Surgery, Izumi City General Hospital, Izumi, Japan

[12] Department of Surgery, Faculty of Medicine, Kindai University, Osaka-Sayama, Japan

Introduction

Gastric cancer is one of the leading causes of cancer-related mortality because of its poor prognosis [1]. Preoperative and/or postoperative chemotherapy is the global standard of care for advanced gastric cancer, because surgery alone is insufficient to achieve a satisfactory outcome [2, 3]. In Japan, postoperative adjuvant chemotherapy with 1 year of S-1 or 6 months of capecitabine plus oxaliplatin therapy was the standard treatment for stage II and III gastric cancer, respectively [4–7]. In the JACCRO GC-07 trial of postoperative adjuvant chemotherapy in stage III gastric cancer, the 3-year recurrence-free survival (RFS) rate of docetaxel (DTX) plus S-1 (DS) therapy was 67.7%, better than that of S-1 therapy (hazard ratio (HR): 0.715, 95% confidence interval (CI), 0.587–0.871, P = 0.0008), thus DS therapy became the standard treatment for adjuvant chemotherapy in stage III gastric cancer [8, 9]. DS therapy in the JACCRO GC-07 trial was a protocol of six cycles of DS therapy for 5 months followed by S-1 monotherapy for up to 1 year. However, the follow-up period was still short and the 5-year long-term results have, to date, not been determined.

By contrast, we, the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG), have conducted two long-term phase II trials of adjuvant DS therapy for stage III gastric cancer: OGSG0604 with DS for 3 months (four cycles) and S-1 until the end of the first year, and OGSG1002 with DS for 6 months (eight cycles) and S-1 until the end of the first year [10, 11]. In the OGSG0604 trial, the 3-year overall survival (OS) was 78.3% (95% CI, 67.8–90.5%) and the 3-year disease-free survival (DFS) for the four cycles of DS was 70.8% (95% CI, 57.1–87.8%), which was favorable compared with the JACCRO GC-07 trial, but the 5-year long-term results were not reported. In the OGSG1002 trial, the 5-year OS was 72.4% (95% CI, 62.1–84.5%) and the 5-year DFS for the eight cycles of DS was 60.0% (95% CI, 48.4–73.9%).

Therefore, adjuvant DS therapy consistently improved prognosis in stage III gastric cancer in various trials, but there were variations in the number of cycles of DS of four, six, and eight cycles. However, it is unclear how many cycles of DS therapy are needed to improve long-term survival in stage III advanced gastric cancer. To address this clinical question, we reported here on the long-term results of the OGSG0604 trial of four cycles of DS. In addition, we performed a pooled analysis of the OGSG0604 trial and the OGSG1002 trial with eight cycles of DS to investigate the long-term prognostic impact of the number of DS cycles in postoperative adjuvant chemotherapy for stage III gastric cancer.

Patients and methods

Study design and patients

The OGSG 0604 trial is a single-arm, prospective, multicenter phase II trial [10, 12]. It was conducted in accordance with the international ethical recommendations stated in the Declaration of Helsinki. The protocol was approved by the institutional review and ethics board of each participating hospital and was registered in the University Hospital Medical Information Network (UMIN) database (UMIN00000714). Written informed consent was obtained from all patients before enrollment. Patients were enrolled within 6 weeks after surgery. The study design of OGSG1002 was described elsewhere (UMIN000004440). [11]

For the pooled analysis, a total of 51 patients from the OGSG0604 trial and 62 patients from the OGSG1002 trial were analyzed together.

Eligibility

The eligibility criteria of the two studies were described previously. [10–12] The summary of the eligibility criteria was as follows: (i) histologically proven gastric cancer of stage IIIA or IIIB after residual tumor (R) 0 surgery with D2 lymph node dissection; (ii) age 20–80 years; (iii) Eastern Cooperative Oncology Group performance status of 0–1; (iv) duration of the period from surgery < 6 weeks; (v) adequate organ function; (vi) no previous treatment for cancer except for an initial resection of the primary gastric lesion; and (vii) absence of other severe medical conditions. Tumor stage and D classifications were in accordance with the Japanese Classification of Gastric Carcinoma, second English edition and the seventh edition of the International Union Against Cancer TNM staging system [13, 14].

Treatment

Treatment methods of the two studies were described previously. [10–12] Patients who met the eligibility criteria described above were given 40 mg/m^2 of S-1 orally twice daily for 2 weeks with intravenous DTX (40 mg/m^2) on day 1, repeated every 3 weeks (one cycle). The treatment was initiated within 45 days after surgery and repeated for four or eight cycles. Following four and eight cycles of this treatment in OGSG0604 and OGSG1002, respectively, S-1 was administered as a daily monotherapy (4 weeks on, 2 weeks off) until 1 year after surgery.

Follow-up

Adverse events were assessed according to the Common Toxicity Criteria for Adverse Events, version 3.0. All patients were followed up for a minimum of 5 years from the start of treatment. Computed tomography scans were performed every 6 months until the third postoperative year and every year until the fifth postoperative year. Relapse was confirmed by imaging studies, including ultrasonography, computed tomography, and gastrointestinal endoscopy.

The DS treatment completion rate, which was defined as the percentage of patients who completed four and eight cycles of this treatment in OGSG0604 and OGSG1002, respectively, and the S-1 treatment completion rate at 3, 6, 9, and 12 months postoperatively were calculated. The relative dose intensity (RDI), which was defined as the ratio of delivered dose intensity to the planned dose intensity of S-1 or DTX, was also calculated.

Statistical analysis

For OGSG0604, the primary end point was the treatment completion rate of four cycles of DS therapy, with secondary end points including safety, DFS, OS, and feasibility of S-1 administration until 1 year after surgery.

For the pooled analysis, the primary endpoints were the 5-year DFS and 5-year OS. The DFS was defined as the time from the date of treatment initiation to the date when recurrence or a second malignancy was confirmed, mortality from any cause occurred, or the final follow-up, whichever came first. OS was defined as the time from the date of treatment initiation to the date of mortality from any cause or the final follow-up. Surviving patients were censored at the last confirmation date of survival. The survival curve was estimated using the Kaplan–Meier method. For the comparison of two survival curves, stratified log-rank test was applied.

Landmark analyses of OS and DFS were performed using cycles of treatment as time points. The Kaplan–Meier method was used to estimate the 3-year survival rates and 95% CIs. Multivariate Cox proportional hazards regression models were adopted to determine the HR for OS and DFS. Multivariate analysis was performed with adjustment for age, sex ECOG performance status, T factor, N factor, stage, and regimen. A backward stepwise method was used as the algorithm for estimating regression models using Akaike's Information Criteria as the evaluation criterion.

Statistical analysis was performed using R version 4.2.1 (R Core team, Vienna, Austria). A P value of < 0.05 was considered to be statistically significant.

Results

OGSG0604

For the OGSG0604 trial, 53 patients from 13 institutions from the OGSG were enrolled in this study between May 2007 and August 2008, but analysis was performed of the 51 cases that met the eligibility criteria. The detailed results of OGSG0604 are shown in the Supplementary materials. Table 1 shows patients' characteristics of OGSG0604.

OS and DFS curves from the OGSG0604 trial are shown in Supplementary Fig. 1 and Supplementary Fig. 2, together

Table 1 Patient characteristics

	Total (n = 113)	OGSG0604 (n = 51)	OGSG1002 (n = 62)
Age, years			
Median (range)	(30–79)	65 (43–78)	63.5 (30–79)
Gender			
Male	81	40	41
Female	32	11	21
ECOG PS			
0	75	31	44
1	38	20	18
Pathological type			
Intestinal	48	23	25
Diffuse	65	28	37
Surgical procedure			
Total gastrectomy	–	–	24
Proxymal gastrectomy	–	–	3
Distal gastrectomy	–	–	35
Stage[a]			
IIIA	67	35	32
IIIB	46	16	30
pT[b]			
T2a	11	8	3
T2b	30	12	18
T3	66	29	37
T4	6	2	4
pN[b]			
N0	3	1	2
N1	51	26	25
N2	41	17	24
N3	18	7	11
pM[b]			
M0	113	51	62
M1	0	0	0

ECOG PS Eastern Cooperative Oncology Group performance status

[a]Japanese classification, 13th edition

[b]TNM classification, 7th edition

with data from the OGSG1002 trial, for reference. The 3-year and 5-year OS in OGSG0604 were 78.3% and 68.3%, respectively, while the 3-year and 5-year OS in OGSG1002 were 83.9% and 72.4%, respectively (HR: 0.778 [95% CI, 0.397–1.524], P = 0.500) (Supplementary Fig. 1a). The 5-year OS of stage IIIA and stage IIIB in OGSG0604 was 73.7% and 56.2%, respectively, while 74.5% and 70.0% in OGSG1002, respectively (HR: 0.826 [95% CI, 0.396–2.094], p = 0.700 and HR: 0.620 [95% CI, 0.230–1.667], P = 0.340) (Supplementary Fig. 1b and c).

The 3-year and 5-year DFS in OGSG0604 were 68.5% and 62.4%, respectively, while those in OGSG1002 were 70.5% and 60.0%, respectively (HR: 1.121 [95% CI, 0.608–2.066], P = 0.710) (Supplementary Fig. 2a). The 5-year DFS of stage IIIA and stage IIIB in OGSG0604 was 68.1% and 56.2%, respectively, while 62.2% and 60.0% in OGSG1002, respectively (HR: 1.238 [95% CI, 0.546–2.808], P = 0.610 and HR: 0.882 [95% CI, 0.347–2.241], p = 0.790) (Supplementary Fig. 2b and 2c).

Pooled analysis of OGSG0604 and OGSG1002

In total, 113 patients from the OGSG0604 and OGSG1002 trials were enrolled for this pooled analysis between May 2007 and December 2012. Table 1 shows the patients' characteristics for the pooled analysis. The most frequent grades 3–4 hematological toxicity was neutropenia, observed in 58 of 113 patients (51%) (Supplementary Table 1). Grade 3 febrile neutropenia was observed in 6 patients (5%).

Treatment completion rates of DS for four cycles in OGSG0604 and DS for eight cycles in OGSG1002 were 80.4% (95% CI, 66.9–90.2%) and 77.4% (95% CI, 65.0–87.1%), respectively. In OGSG0604, the reason for DS therapy discontinuation was adverse events in all ten patients. There were one, two, three and four treatment cycles in 2, 2, 6 and 41 patients, respectively. In OGSG1002, the reasons for DS therapy discontinuation were relapse in 2 patients and adverse events in 12 patients. There were seven cycles in the two relapsed patients. The number of treatment cycles was one cycle in 2 patients, two in 2, three in 1, four in 3, six in 1, seven in 5 and eight in 48. The S-1 treatment completion rate at 1 year for both trials was nearly equivalent, and the rates were 69% for all cases, 67% for OGSG0604, and 71% for OGSG1002 (Table 2a). The RDI of DTX in OGSG0604 and OGSG1002 was 89.1% and 82.5%, respectively. The RDI of S-1 for all cases, OGSG0604, and OGSG1002 was 80.9%, 80.8%, and 80.9%, respectively (Table 2b).

Recurrence was observed in 35 cases (31.0%), and the sites of recurrence are shown in Table 3. The 3-year and 5-year OS were 81.4% (95% CI, 74.5–88.9%) and 70.6% (95% CI, 62.6–79.5%), respectively (Fig. 1a). The 5-year OS of stage IIIA and stage IIIB was 74.1% (95% CI, 64.2–85.5%) and 65.2% (95% CI, 52.8–80.5%), respectively (Fig. 1b). The 3-year and 5-year DFS were 68.7% (95%CI, 60.6–77.9%) and 62.1% (95%CI, 53.7–71.9%), respectively (Fig. 2a). The 5-year DFS of stage IIIA and stage IIIB was 64.3% (95%CI, 53.5–77.2%) and 58.7% (95% CI, 46.1–74.8%), respectively (Fig. 2b).

Landmark analysis

Figure 3 shows the results of a landmark analysis examining DS therapy by the number of cycles actually performed.

Table 2 Feasibility (a) and relative dose intensity (b) of S-1 plus docetaxel and S-1 monotherapy following S-1 plus docetaxel

	Patients	Completed	Not completed	Treatment completing rate [95%CI]	OR [95%CI] P value (Fisher's exact test)
(a) Feasibility					
OGSG0604 S-1 plus docetaxel for 4 cycles	51	41	10	80.4% [66.9–90.2]	1.194 [0.439–3.353] p = 0.818
OGSG1002 S-1 plus docetaxel for 8 cycles	62	48	14	77.4% [65.0–87.1]	
All cases	113	78	37	69.0% [59.6–77.4]	
OGSG0604 S-1 for 1 year	51	34	17	66.7% [52.1–79.2]	0.910 [0.386–2.159] p = 0.910
OGSG1002 S-1 for 1 year	62	44	18	71.0% [58.1–81.8]	

	S-1	docetaxel
(b) Relative dose intensity		
All cases	80.9%	–
OGSG0604 S-1 plus docetaxel for 4 cycles and S-1 for 1 year	80.8%	89.1%
OGSG1002 S-1 plus docetaxel for 8 cycles and S-1 for 1 year	80.9%	82.5%

CI confidence interval, *OR* odds ratio

Table 3 Recurrent site

	Total (n = 113)	OGSG0604 (n = 51)	OGSG1002 (n = 62)
Recurrence (–)	78	36	42
Recurrence (+)	35	15	20
Local	3	1	2
Lymph node	16	9	7
Peritonium	14	5	9
Metastatic	14	6	8
Liver	7	4	3
Lung	2	0	2
Others	5	2	3
Unkown	2	0	2

For the 3-year and 5-year OS, survival was better with four to eight cycles of DS therapy than with one to three cycles, with the best 3-year OS of 89.8% (95% CI, 81.7–98.7%) and 5-year OS of 77.4% (95% CI, 66.5–90.1%) for eight cycles (Supplementary Fig. 3a and Fig. 3a). The 3-year DFSs were 72% and 75% for four and eight cycles of DS therapy, respectively, whereas there was little difference at 69–71% when one to three or five to seven cycles were given (Supplementary Fig. 3b). The 5-year DFS was approximately 66% when four or eight cycles of DS therapy were given, whereas there was little difference at 62–63% when one to three or five to seven cycles were given (Fig. 3b).

Multivariate analysis

In the multivariate analysis of OS, N2–3 was extracted as a significant variable, but the difference by trials was not significant (Table 4a). No variables were found to significantly affect the DFS in the multivariate analysis of the DFS (Table 4b).

Discussion

This 5-year follow-up study of the OGSG0604 trial suggested that postoperative adjuvant chemotherapy with four cycles of DS followed by S-1 monotherapy for up to 1 year after D2 gastrectomy was efficacious in patients with stage III gastric cancer, as were the results for eight cycles (OGSG1002 trial) and six cycles of DS therapy (JACCRO GC-07 trial). Moreover, in this pooled analysis of the OGSG0604 and OGSG1002 trials with a follow-up of a minimum of 5 years, landmark analysis showed that four or more cycles, preferably eight, are recommended as postoperative adjuvant chemotherapy for stage III gastric cancer, because DS therapy tended to show a better 5-year OS with four or more cycles compared with three or less cycles, with eight cycles being the most favorable. By contrast, while the 5-year DFS was somewhat better with four and eight cycles of DS therapy, however, there was little difference between the numbers of DS cycles. Although eight cycles of DS therapy may prolong prognosis, the present study did not provide a clear conclusion as to how many cycles of DS therapy are needed.

The present study showed that a good 5-year OS can be achieved with four or more cycles of DS therapy for stage III gastric cancer. In the 5-year DFS, the survival of four or eight cycles of DS was better than that of one to three cycles. However, two patients with seven cycles of DS developed relapses, which may have contributed to the poor survival of five to seven cycles of DS. In the multivariate analysis, the number of scheduled cycles of DS therapy was not a significant variable as a factor associated with the OS or DFS. In the landmark analysis, both the 5-year OS and 5-year DFS or RFS were more favorable than the results of stage III gastric cancer in the ACTS-GC trial, and both the 3-year OS and 3-year DFS or RFS were not inferior to the JACCCRO GC-07 trial results, even if only one cycle of DS therapy had been given. [5, 9] However, the stage classification in the inclusion criteria and the different years of follow-up of these trials differ somewhat, thus caution is required in interpreting the results. Data disclosure showing the actual number of DS therapy cycles in the JACCRO GC-07 trial and its association with survival would also be desirable. One possible reason for the better survival outcome with four or more cycles of DS therapy may be that the 1-year continuation rate of S-1 in both OGSG trials was similar to that in the ACTS-GS trial, in addition to the relatively high DS therapy continuation rate. DS therapy followed by S-1 monotherapy not only had a good continuation rate of S-1, but also good compliance with DS therapy, whether four, six, or eight cycles in the OGSG0604, JACCRO GC-07, or OGSG1002 trials. In the two OGSG trials, as in the JACCRO GC-07 trial, there were no treatment-related mortalities and adverse events were shown to be manageable and well tolerated, leading to a favorable survival benefit. [8, 10, 11] Because there was no difference in the treatment completion rates between four and eight cycles of DS therapy (80.4% and 77.4%, respectively), serious adverse events were unlikely to occur after four cycles. The 1-year treatment completion rate for S-1 in the ACTS-GC and JACCRO GC-07 trials was 65.8% and 49.3%, respectively, while it was 69.0% for all cases in both OGSG trials. [4, 8] Because the results of the OPAS trial showed that S-1 should be continued for

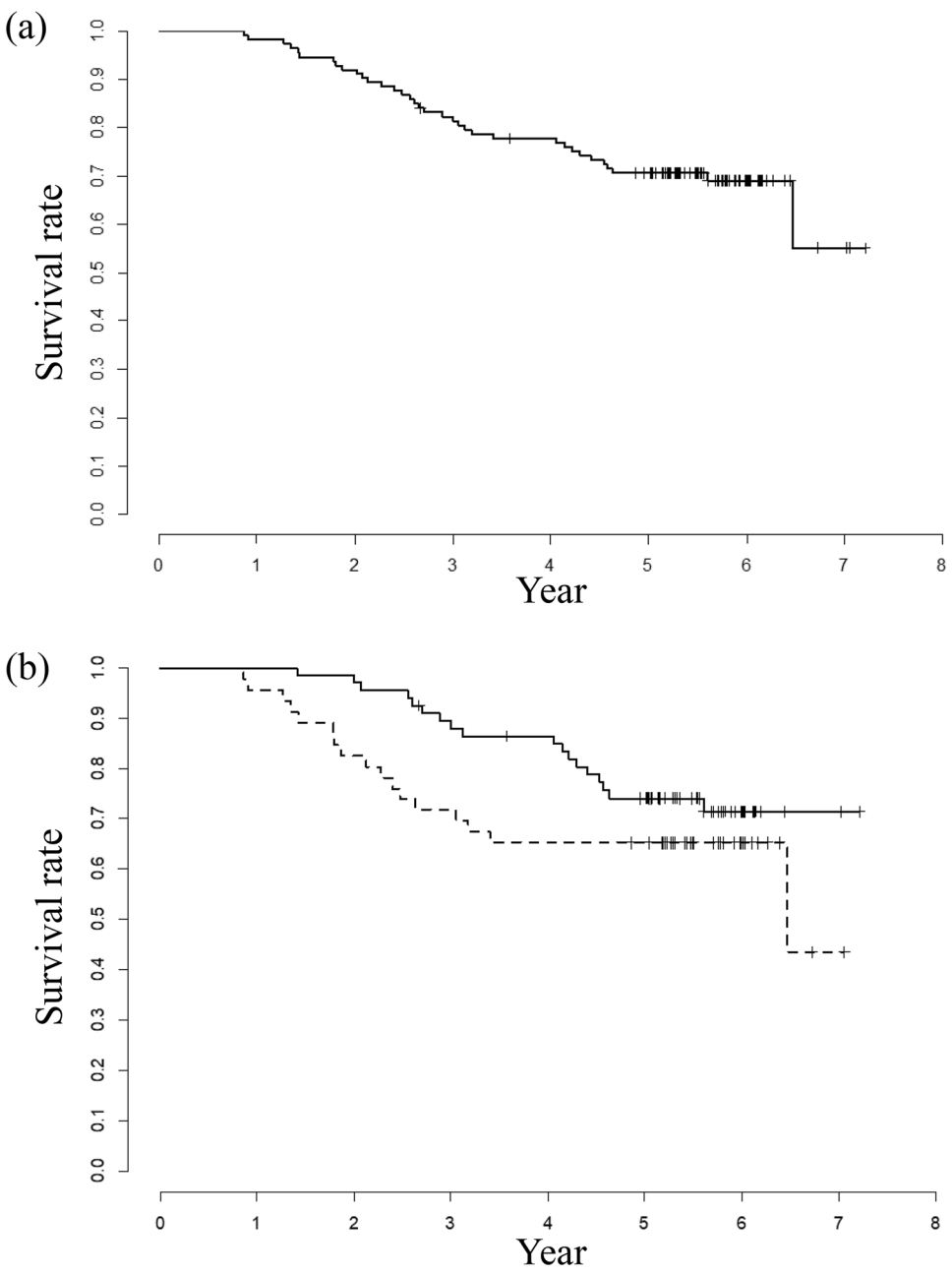


Fig. 1 Kaplan–Meier estimates of the 5-year overall survival for all patients (**a**) and for patients with stage IIIA (solid line) or IIIB (dotted line) gastric cancer (**b**)

1 year instead of 6 months in stage II gastric cancer [15], it appeared important to continue S-1 monotherapy after DS therapy until the first postoperative year in stage III gastric cancer. One year of postoperative adjuvant chemotherapy, including doublet therapy such as DS, is the standard of care in Japan, however, capecitabine plus oxaliplatin, which is administered for 6 months, is a regimen that should be considered as an adjuvant chemotherapy option for stage III gastric cancer with fewer adverse events such as alopecia.

In clinical trials of adjuvant chemotherapy, the 3-year DFS is considered a surrogate marker for the 5-year OS. It is interesting to note that the results of the landmark analysis in the present study also showed that the 3-year DFS was generally consistent with the 5-year OS for any number of DS therapy cycles, which is in agreement with previous reports. [5, 6]

There are some limitations to this study. The first is that this study was a pooled analysis of two single-arm phase II trials with a small number of cases. Second, it is necessary to take into account that the enrollment period for both trials was somewhat old, from 2007 to 2012, when ramucirumab and immune checkpoint inhibitors were not available for chemotherapy at relapse. Although there are some limitations, it can be said that this is a valuable study showing the long-term results of the 5-year OS in more than 110 cases

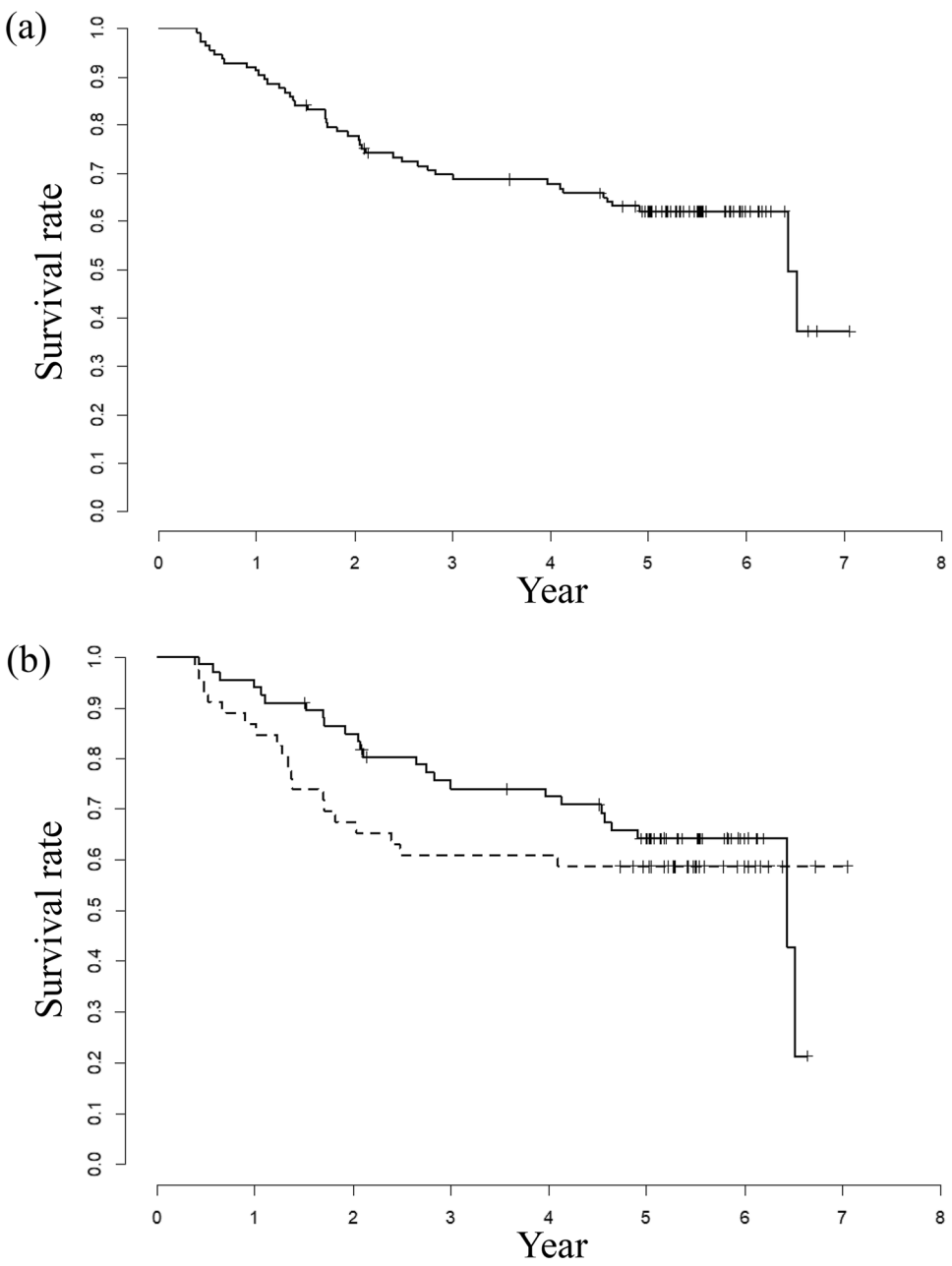
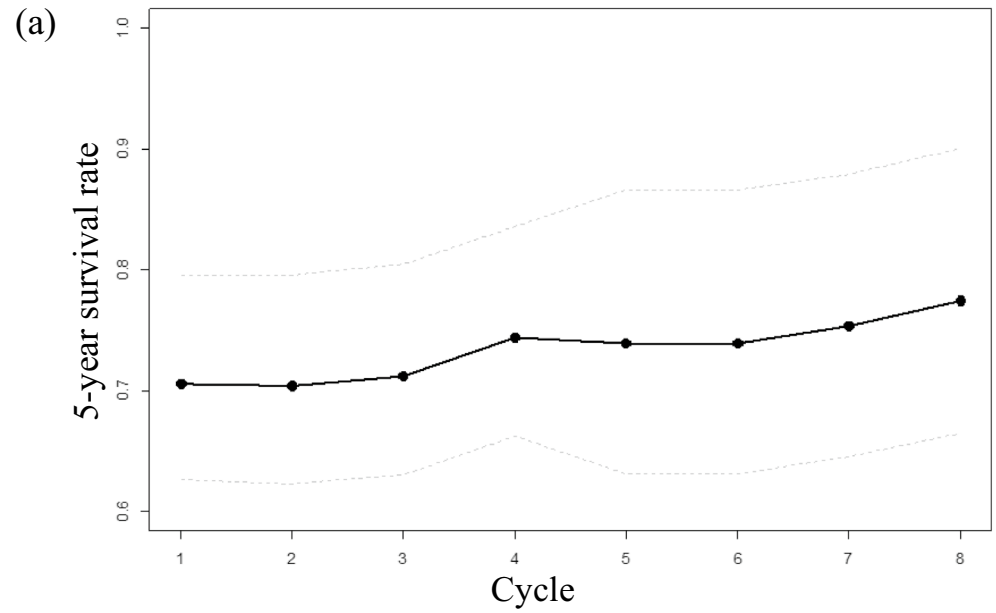


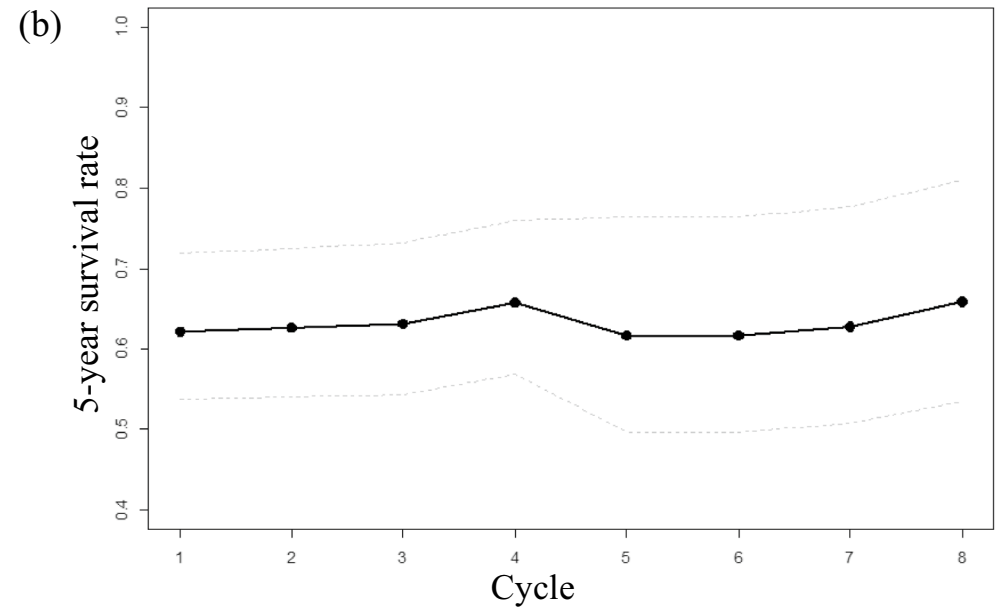
Fig. 2 Kaplan–Meier estimates of the 5-year disease-free survival for all patients (**a**) and for patients with stage IIIA (solid line) or IIIB (dotted line) gastric cancer (**b**)

of postoperative adjuvant chemotherapy with DS therapy for stage III gastric cancer.

In conclusion, it is possible that eight cycles of DS therapy followed by S-1 monotherapy for up to 1 year after D2 gastrectomy for stage III gastric cancer may prolong the prognosis, but the present study did not provide a clear conclusion as to how many DS therapy cycles are needed to improve the prognosis. Further analysis of the 5-year OS results and their relationship with the number of cycles of DS therapy is awaited in the JACCRO GC-07 trial.



Cycle	1	2	3	4	5	6	7	8
Survival rate	0.706	0.704	0.712	0.744	0.739	0.739	0.753	0.774
[95%CI]	[0.626, 0.795]	[0.623, 0.796]	[0.630, 0.805]	[0.662, 0.836]	[0.631, 0.867]	[0.631, 0.867]	[0.645, 0.879]	[0.665, 0.901]



Cycle	1	2	3	4	5	6	7	8
Survival rate	0.621	0.626	0.631	0.658	0.617	0.617	0.628	0.659
[95%CI]	[0.537, 0.719]	[0.541, 0.725]	[0.544, 0.732]	[0.569, 0.760]	[0.497, 0.765]	[0.497, 0.765]	[0.508, 0.777]	[0.535, 0.810]

Fig. 3 The 5-year overall survival (**a**) and 5-year disease-free survival (**b**) by landmark analysis. CI, confidence interval

Table 4 Multivariate analysis of 5-year overall survival (a) and 5-year disease-free survival (b)

Factor	N (%)		Multivariate analysis		Variable selection	
			HR [95%CI]	p-value	HR [95%CI]	P-value
(a) 5-year overall survival						
Age (< 65/ > = 65)	59 (52.2)	54 (47.8)	0.625 [0.302, 1.295]	0.207	–	–
Sex (male/female)	81 (71.7)	32 (28.3)	0.815 [0.385, 1.723]	0.591	–	–
ECOG PS (0/1)	75 (66.4)	38 (33.6)	1.187 [0.567, 2.487]	0.649	–	–
Histological type (intentinal/diffuse)	47 (41.6)	66 (58.4)	0.822 [0.379, 1.783]	0.619	–	–
T (T2/T3-4)	41 (36.3)	72 (63.7)	1.273 [0.432, 3.748]	0.661	–	–
N (N0-1/N2-3)	54 (47.8)	59 (52.2)	0.558 [0.244, 1.274]	0.166	0.433 [0.211, 0.869]	0.022
Stage (IIIA/IIIB)	67 (59.3)	46 (40.7)	0.577 [0.195, 1.707]	0.321	–	–
Regimen (OGSG0604/OGSG1002)	51 (45.1)	62 (54.9)	1.438 [0.718, 2.877]	0.305	–	–
Factor	N (%)		Multivariate analysis		Variable selection	
			HR [95%CI]	p-value	HR [95%CI]	P-value
(b) 5-year disease-free survival						
Age (< 65/ > = 65)	59 (52.2)	54 (47.8)	0.675 [0.348, 1.309]	0.245	–	–
Sex (male/female)	81 (71.7)	32 (28.3)	0.747 [0.383, 1.460]	0.394	–	–
PS (0/1)	75 (66.4)	38 (33.6)	1.158 [0.591, 2.269]	0.67	–	–
Histological type (intentinal/diffuse)	47 (41.6)	66 (58.4)	0.712 [0.351, 1.442]	0.345	–	–
T (T2/T3-4)	41 (36.3)	72 (63.7)	1.212 [0.501, 2.930]	0.67	–	–
N (N0-1/N2-3)	54 (47.8)	59 (52.2)	0.809 [0.396, 1.653]	0.561	0.620 [0.337, 1.139]	0.123
Stage (IIIA/IIIB)	67 (59.3)	46 (40.7)	0.734 [0.296, 1.824]	0.506	–	–
Regimen (OGSG0604/OGSG1002)	51 (45.1)	62 (54.9)	0.892 [0.473, 1.684]	0.725	–	–

ECOG PS Eastern Cooperative Oncology Group performance status, *HR* hazard ratio, *CI* confidence interval

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10120-023-01408-y.

Acknowledgements We thank Dr. Yoshihiro Matsubara from the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) for data management. We thank all the patients, investigators, and medical staff who participated in this study as well as the OGSG data center for their contribution. We thank Robert Blakytny, DPhil, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Author contributions Study concept: YK, HK, ST, and KF; study design: YK, HK, ST, and KF; acquisition of data: YK, ST, KF, JM, HI, and SI; statistical analysis of data: TS; analysis and/or interpretation of data: YK, HK, ST, KF, and TS; drafting the manuscript: YK; revising the manuscript critically for important intellectual content: YK, HK, ST, KF, DS, YK, TT, HF, and TS. All authors approved the final version of the manuscript.

Data availability Data is available upon reasonable request.

Declarations

Conflict of interest The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Y. Ki. was supported by grants and personal fees from Daiichi Sankyo Co. Ltd., outside the submitted work. H. K. has received fees and research funding from Bristol-Myers Squibb Co. Ltd., Taiho pharmaceutical Co. Ltd., Eisai Co. Ltd., and Kobayashi Pharmaceutical. Co., Ltd. as well as honoraria and lecture fees from Bristol-Myers Squibb Co. Ltd., Bayer Yakuhin Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Merck Biopharma Co., Ltd., Teijin Pharma Ltd., Taiho Pharmaceutical Co. Ltd., Otsuka Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co. Ltd. K. F. has received honoraria and lecture fees from Taiho Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Bristol-Myers Squibb Co. Ltd., Ono Pharmaceutical Co. Ltd., and Yakult Honsha Co. Ltd., outside the submitted work. H. I. has received honoraria and lecture fees from Taiho Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co. Ltd. outside the submitted work. Y. Ku has received research funding from Yakult Honsha Co. Ltd. and Taiho Pharmaceutical Co. Ltd. and lecture fees from Yakult Honsha Co. Ltd., Taiho Pharmaceutical Co. Ltd., and Nippon Kayaku Co. Ltd. outside of the submitted work. T. Sa. has received fees and research funding from Bristol-Myers Squibb Co. Ltd., T Ono Pharmaceutical Co. Ltd., Eisai Co. Ltd., Eli Lilly Japan K.K., Daiichi-Sankyo Co. Ltd., Chugai Pharmaceutical Co. Ltd., Yakult Honsha Co. Ltd., and HUTCHMED Ltd., as well as honoraria and lecture fees from Bristol-Myers Squibb Co. Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd., and Daiichi-Sankyo Co. Ltd.. All remaining authors have declared no conflicts of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. All patients provided written informed consent.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
3. Al-Batran S-E, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomized, phase 2/3 trial. Lancet. 2019;393:1948–57.
4. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357:1810–20.
5. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29:4387–93.
6. Noh SH, Park SR, Yang H-K, Chung HC, Chung I-J, Kim S-W, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomized phase 3 trial. Lancet Oncol. 2014;15:1389–96.
7. Nakamura Y, Yamanaka T, Chin K, Cho H, Katai H, Terashima M, et al. Survival outcomes of two phase 2 studies of adjuvant chemotherapy with S-1 plus oxaliplatin or capecitabine plus oxaliplatin for patients with gastric cancer after D2 gastrectomy. Ann Surg Oncol. 2019;26:465–72.
8. Yoshida K, Kodera Y, Kochi M, et al. Addition of docetaxel to oral fluoropyrimidine improves efficacy in patients with stage III gastric cancer: interim analysis of JACCRO GC-07, a randomized controlled trial. J Clin Oncol. 2019;37:1296–304.
9. Kakeji Y, Yoshida K, Kodera Y, et al. 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. Gastric Cancer. 2022;25:188–96.
10. Fujitani K, Tamura S, Kimura Y, Tsuji T, Matsuyama J, Iijima S, et al. Three-year outcomes of a phase II study of adjuvant chemotherapy with S-1 plus docetaxel for stage III gastric cancer after curative D2 gastrectomy. Gastric Cancer. 2014;17:348–53.
11. Fujitani K, Tamura S, Kimura Y, Matsuyama J, Imamura H, Yamamoto K, et al. Five-year outcome of a phase II study of adjuvant chemotherapy with S-1 plus docetaxel for stage III gastric cancer after curative D2 gastrectomy (OGSG1002). Gastric Cancer. 2020;23:520–30.
12. Tamura S, Fujitani K, Kimura Y, Tsuji T, Matsuyama J, Iijima S, et al. Phase II feasibility study of adjuvant S-1 plus docetaxel for stage III gastric cancer patients after curative D2 gastrectomy. Oncology. 2011;80:296–300.
13. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma-2nd English edition. Gastric Cancer. 1998;1:10–24.
14. Sobin LH, Gospodarowicz MK, Wittekind CH. International union against cancer (UICC) TNM classification of malignant tumours. 7th ed. New York: Wiley-Blackwell; 2011.
15. Yoshikawa T, Terashima M, Mizusawa J, Nunobe S, Nishida Y, Yamada T, et al. Four courses versus eight courses of adjuvant S-1 for patients with stage II gastric cancer (JCOG1104[OPAS-1]): an open-label, phase 3, non-inferiority, randomized trial. Lancet Gastroenterol Hepatol. 2019;4:208–16.