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ORIGINAL ARTICLE

Survival prolongation after treatment failure of first-line chemotherapy in patients with advanced gastric cancer: combined analysis of the Japan Clinical Oncology Group Trials JCOG9205 and JCOG9912

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Abstract
Background Two randomized phase III trials of first-line chemotherapy for advanced gastric cancer (JCOG9205 and JCOG9912) conducted by the Japan Clinical Oncology Group used 5-fluorouracil continuous infusion (5-FUci) as the control arm. New active agents (e.g., S-1, irinotecan, and taxanes) were introduced as second-line chemotherapy in the late 1990s after JCOG9205. This combined analysis evaluated whether patients in the 5-FUci arm of JCOG9912 exhibited better survival after adjusting for baseline factors and also investigated the cause of survival prolongation.
Patients and methods The subjects were patients assigned to the 5-FUci arms who met the eligibility criteria of both JCOG9205 and JCOG9912. Overall survival (OS), time to treatment failure (TTF), and survival after treatment failure in the first-line chemotherapy (OS-TTF) were compared after adjusting baseline characteristics using the Cox proportional hazard model. Second-line chemotherapy details were also reviewed.
Results The combined analysis included 89 and 230 patients in JCOG9205 and JCOG9912, respectively. After adjusting baseline characteristics, TTF was similar between groups (HR 0.95; 95 % CI, 0.73–1.26). However, both OS (HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (HR, 0.76; 95 % CI, 0.57–1.01) were longer in JCOG9912. More patients in JCOG9912 received second-line chemotherapy (83 vs. 52 %) with new drugs (77 vs. 10 %) than in JCOG9205. OS-TTF was substantially prolonged in patients who received second-line chemotherapy (HR, 0.66; 95 % CI, 0.46–0.95).
Conclusion OS and OS-TTF were longer in JCOG9912 than JCOG9205. Second-line chemotherapy with new drugs is a potential reason for the observed prolongation of survival.

Keywords Gastric cancer · Post-treatment failure survival · Second-line chemotherapy

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Introduction

Although advanced gastric cancer (AGC) cannot be cured by systemic chemotherapy, some randomized controlled trials [1–3] and meta-analyses [4] demonstrate a survival benefit for first-line chemotherapy compared to best supportive care alone. The survival benefit attributable to second-line chemotherapy was unclear until recently [5]. However, two randomized trials comparing second-line chemotherapy and best supportive care have demonstrated the survival benefit of second-line chemotherapy [6, 7].

Two randomized phase III trials of first-line chemotherapy for AGC [i.e., Japan Clinical Oncology Group (JCOG) 9205 and JCOG9912] conducted by the JCOG involved 5-fluorouracil continuous infusion (5-FUci) as the control arm. In JCOG9205, a combination of 5-FU plus cisplatin did not confer a survival benefit over 5-FUci alone; 5-FUci was regarded as standard chemotherapy in the 1990s [8]. Thereafter, monotherapy with S-1 exhibited non-inferiority to 5-FUci in JCOG9912 in the 2000s [9]. When these two trials are compared directly, the survival of the 5-FUci arm in JCOG9912 is longer than that in JCOG9205 [median survival times: 7.1 months (95 % confidence interval (CI), 5.8–8.2) vs. 10.8 months (95 % CI, 8.9–12.0), respectively].

The periods of patient accrual for JCOG9205 and JCOG9912 were 1992–1997 and 2000–2006, respectively. In Japan, after some new active agents such as S-1, irinotecan, paclitaxel, and docetaxel were approved for AGC in the late 1990s [10–14], they have been used not only in first-line chemotherapy but in second-line chemotherapy as well. The proportions of patients in the 5-FUci arms in JCOG9205 and JCOG9912 who received second-line chemotherapy were 53 and 78 %, respectively. It is speculated that second-line chemotherapy might have contributed to the prolongation of overall survival (OS) in JCOG9912 compared to JCOG9205.

However, survival is possibly affected by other factors including baseline factors. Furthermore, the details of regimens employed as second-line chemotherapy have not been reviewed in either trial. Therefore, it is necessary to adjust the patient backgrounds of JCOG9205 and JCOG9912 to assess the influence of second-line chemotherapy on survival.

This combined analysis evaluated whether patients in the 5-FUci arm of JCOG9912 exhibited better survival even after adjusting the baseline factors of patients who met the common eligibility criteria. If survival prolongation was evident, we aimed to investigate the underlying causes of survival prolongation.

Patients and methods

Patient population

The subjects in this combined analysis were the patients assigned to the 5-FUci arms in JCOG9205 ($N = 105$) and JCOG9912 ($N = 234$). The subjects were selected according to the following eligibility criteria of common to both trials: histologically confirmed unresectable or recurrent gastric adenocarcinoma; adequate self-supported nutrition intake; age 20–75 years; ECOG performance status 0, 1, or 2; no history of chemotherapy or radiotherapy; preserved organ functions; and written informed consent. Patients with intestinal stenosis, who were eligible in JCOG9205 but not JCOG9912, and those with a history of adjuvant chemotherapy, who were eligible in JCOG9912 but not JCOG9205, were excluded from this study.

In both trials, the protocol treatment was continuous infusion of 5-FU (800 mg m^{-2} day^{-1}) from day 1 to 5 repeated every 4 weeks until progressive disease or unacceptable toxicity was observed. The tumor response was evaluated by computed tomography and endoscopy every 4 and 8 weeks in JCOG9205 and JCOG9912, respectively.

The study protocol of this ad hoc combined analysis was approved by the Protocol Review Committee of the JCOG as well as the institutional review boards at the institutions of the study chair and study coordinator in compliance with the Japanese Ethical Guidelines for Clinical Studies.

Statistical analysis

The study endpoints were OS, time to treatment failure (TTF), survival after treatment failure (OS-TTF), the proportions of patients who received second-line chemotherapy, and the type of treatment regimens of second-line chemotherapy.

OS was counted from the date of randomization to the date of death from any cause or was censored at the date of the last follow-up for surviving patients. TTF was defined as the period from the date of randomization to the date of off-treatment from any cause (e.g., death, documentation of disease progression, adverse event, or patient refusal) or was censored at the date of last follow-up for surviving patients on treatment. OS-TTF was calculated by subtracting TTF from OS in each patient or censored in case of survival. OS-TTF was counted as 0 if the protocol treatment (i.e., first-line chemotherapy) was terminated because of death. OS, TTF, and OS-TTF were compared between JCOG9205 and JCOG9912 using the Cox proportional hazard model after adjusting the following baseline factors: age (<65 vs. ≥65 years), sex (male vs. female), performance status (PS, 0–2), macroscopic type (0–5) [15], histological type (intestinal vs. diffuse) [16], prior gastrectomy (+ vs. −), target lesion (+ vs. −), peritoneal metastasis (+ vs. −), and number of metastatic sites (0–2). Prognostic factors for OS-TTF were also analyzed using the Cox proportional hazard model. For Cox regression analysis, all variables were treated as categorical variables.

OS, TTF, and OS-TTF were estimated using the Kaplan–Meier method. All analyses were carried out with SAS release 9.1 (SAS Institute, Cary, NC, USA).

Results

Patients

The study schema is shown in Fig. 1. There were 105 and 234 patients assigned to the 5-FUci arms in JCOG9205 and JCOG9912, respectively. Sixteen and 4 patients in JCOG9205 and JCOG9912 were excluded from this combined analysis because they did not meet the eligibility criteria or had missing data. Finally, 319 patients, 89 from JCOG9205 and 230 from JCOG9912, were included in the combined analysis.

The patients' baseline characteristics are shown in Table 1. JCOG9912 contained more patients ≥65 years old, with better PS, and fewer metastatic sites and fewer patients with peritoneal metastasis compared to JCOG9205. Thus, there appear to be substantial differences in patient background between JCOG9205 and JCOG9912.

Reasons for treatment failure and second-line chemotherapy

The reasons for treatment failure in both trials were similar: disease progression or death in 84 % (disease progression, 68; death, 7/89) and 86 % (disease progression, 197; death, 1/230) in JCOG9205 and JCOG9912, respectively.

Second-line chemotherapy is summarized in Table 2. A greater proportion of patients received second-line chemotherapy in JCOG9912 than JCOG9205 [83 % (190/230) vs. 52 % (46/89), respectively]. The drugs used in second-line chemotherapy largely differed between JCOG9205 and JCOG9912. In JCOG9912, regimens containing new-generation drugs (e.g., irinotecan, paclitaxel, docetaxel, and S-1) were used as second-line chemotherapy in 178/190 patients (94 %). On the other hand, only 9/46 (20 %) patients received new-generation drugs in JCOG9205.

OS and OS-TTF

TTF adjusted by the Cox model did not differ significantly between trials [adjusted hazard ratio (HR), 0.95; 95 % CI, 0.73–1.26]. However, both OS (adjusted HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (adjusted HR, 0.76; 95 % CI, 0.57–1.01) were longer in JCOG9912 (Fig. 2a–c).

Subgroup analyses by second-line chemotherapy are shown in Fig. 3. Among the patients with second-line chemotherapy, OS-TTF was remarkably longer in JCOG9912 than JCOG9205 (adjusted HR, 0.66; 95 % CI, 0.46–0.95). On the other hand, among the patients who did not receive second-line chemotherapy, OS-TTF was longer in JCOG9205 than JCOG9912 (adjusted HR, 1.37; 95 % CI, 0.74–2.53).

Multivariate analysis was performed to determine the prognostic factors for OS-TTF. PS ($p < 0.001$), gastrectomy ($p = 0.031$), peritoneal metastasis ($p = 0.015$), and number of metastatic sites ($p = 0.011$) were selected as the prognostic factors for OS-TTF (Table 3).

Discussion

Even after selecting patients on the basis of common eligibility criteria and adjusting baseline factors, the OS (adjusted HR, 0.74; 95 % CI, 0.56–0.99) and OS-TTF (adjusted HR, 0.76; 95 % CI, 0.57–1.01) of the 5-FUci arm was longer in JCOG9912 than JCOG9205.

We tried to align the two groups as much as possible to maximize comparability. Only the patients from the 5-FUci

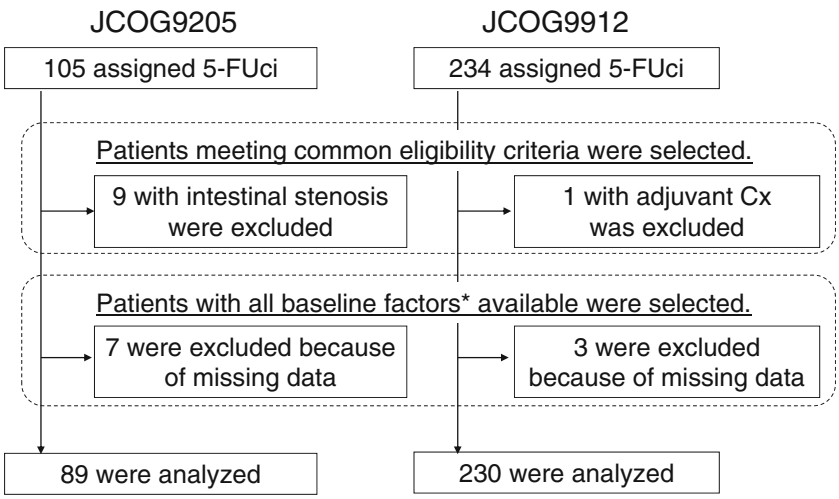


Fig. 1 Study profile. The baseline factors used in this study were age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and number of metastatic sites. *Cx* chemotherapy

Table 1 Patient characteristics

	JCOG9205		JCOG9912		*p* value[a]
No. of patients	89	%	230	%	
Age (years)					
Median (range)	63 (27–75)		63 (24–75)		0.4
<65	52	58	119	52	0.06
≥65	37	42	111	48	
Sex					
Male	63	71	172	75	0.48
Female	26	29	58	25	
PS[b]					
0	41	46	149	65	<.0001
1	33	37	78	34	
2	15	17	3	1	
Macroscopic type[c]					
0	0	0	5	2	0.75
1	5	6	8	4	
2	20	22	53	23	
3	45	51	120	52	
4	17	19	40	17	
5	2	2	4	2	
Histological type					
Intestinal	45	51	110	48	0.71
Diffuse	44	49	120	52	
Gastrectomy					
−	69	78	161	70	0.21
+	20	22	69	30	
Target lesions					
−	20	22	59	26	0.66
+	69	78	171	74	
Peritoneal metastasis					
−	76	85	143	62	<.0001
+	13	15	87	38	
Number of metastatic sites					
0	0	0	2	1	0.06
1	51	57	100	43	
≥2	38	43	128	56	

[a] All *p* values are two sided. The Wilcoxon rank-sum test was used to analyze continuous variables, and Fisher's exact test was used to analyze categorical data

[b] PS was evaluated at treatment initiation in JCOG9205 and at registration in JCOG9912

[c] Japanese Classification of Gastric Carcinoma

arms meeting the common eligibility criteria of both trials were analyzed, and baseline characteristics were adjusted in multivariate analysis. In addition, both trials were conducted by the same study group. The results show that TTF (adjusted HR, 0.95; 95 % CI, 0.73–1.26) and the reasons for treatment discontinuation did not differ between trials. This finding indicates that the impact of the first-line chemotherapy with 5-FUci on OS might be comparable between the two trials.

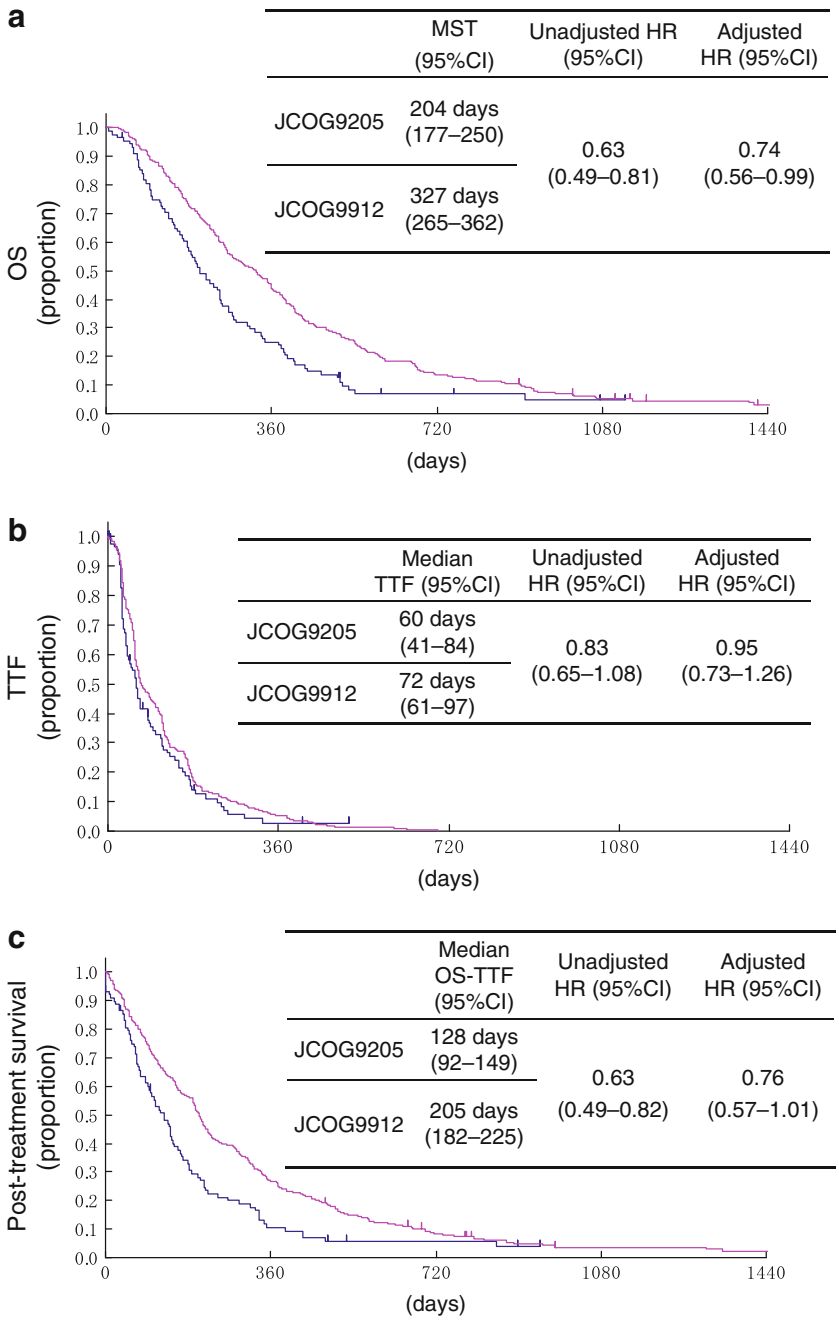
Table 2 Second-line chemotherapy

Second-line chemotherapy	JCOG9205		JCOG9912	
+	46	51.7 %	190	82.6 %
PTX, DTX, irinotecan, or S-1-containing regimen	9	10.1 %	178	77.4 %
PTX/DTX containing	2		60	
Irinotecan containing	6		100	
S-1 containing	1		29	
Other	37	41.6 %	12	5.2 %
5-FU/MTX	25		7	
5-FU/CDDP	6		0	
Other	6		5	
−	39	43.8 %	35	15.2 %
Unknown	4	4.5 %	5	2.2 %

PTX paclitaxel, *DTX* docetaxel, *CDDP* cisplatin, *MTX* methotrexate

To evaluate the effect of second-line chemotherapy, it would be ideal to estimate the time from the start of second-line chemotherapy to death. However, because we did not collect the start date of second-line chemotherapy in the case report form, we adopted OS-TTF as the endpoint. Survival post progression is another endpoint sometimes used to evaluate the effect of second-line chemotherapy. However, protocol treatment is sometimes terminated for reasons other than progression. Moreover, second-line chemotherapy is started before progression. Therefore, we considered OS-TTF to be a more suitable surrogate of the time from the start of second-line chemotherapy than survival post progression.

The present comparison between the two trials performed in different decades is considered to contain some bias. There have been many changes in patient management during this time, leading to better survival in the recent trial. Considering OS was longer in JCOG9912 than JCOG9205, even though TTF did not differ between trials, it can be speculated that patient management after treatment failure might have changed in the era of JCOG9912 compared to that of JCOG9205. One of the major changes that occurred was the availability of antitumor drugs in second-line chemotherapy. A greater proportion of patients received second-line chemotherapy in JCOG9912 than JCOG9205 (83 vs. 52 %, respectively) (Table 2). In particular, new-generation drugs (e.g., irinotecan, paclitaxel, docetaxel, and S-1) were used more frequently in JCOG9912 than JCOG9205 (77 vs. 10 %, respectively). Moreover, the improvements in OS and OS-TTF from JCOG9205 to JCOG9912 were only observed in the subset of patients who received second-line chemotherapy (HR, 0.66; 95 %



	MST (95%CI)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
JCOG9205	204 days (177–250)	0.63 (0.49–0.81)	0.74 (0.56–0.99)
JCOG9912	327 days (265–362)		

	Median TTF (95%CI)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
JCOG9205	60 days (41–84)	0.83 (0.65–1.08)	0.95 (0.73–1.26)
JCOG9912	72 days (61–97)		

	Median OS-TTF (95%CI)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
JCOG9205	128 days (92–149)	0.63 (0.49–0.82)	0.76 (0.57–1.01)
JCOG9912	205 days (182–225)		

Fig. 2 Overall survival (OS) (**a**), time to treatment failure (TTF) (**b**), and OS-TTF (**c**). Seven patients and one patient in JCOG9205 and JCOG9912, respectively, who died during first-line chemotherapy, were considered to have events on day 0. Adjustment factors included patient age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and number of metastatic sites. *MST* median survival time, *OS* overall survival, *TTF* time to treatment failure

CI, 0.46–0.95) (Fig. 3). These results suggest second-line chemotherapy with new-generation drugs might have contributed to survival prolongation. Kawakami et al. [17] reported the post-progression survival (PPS) of AGC is significantly longer in trials published in 2006 or later than in those published before 2005 published trials (5.34 vs. 3.74 months, $p = 0.001$). The present results corroborate these previous results, further indicating the increasing availability of active drugs in subsequent therapies is a potential reason for the observed survival prolongation.

As mentioned in the Introduction, the survival benefit attributable to second-line chemotherapy was unclear until recently [5]. However, two randomized trials compared second-line chemotherapy and best supportive care in AGC (6, 7). The first trial compared best supportive care with irinotecan monotherapy [6]. Irinotecan-treated patients had significantly longer survival (median survival time, 4.0 vs. 2.4 months for patients receiving best supportive care alone; HR, 0.48; 95 % CI, 0.25–0.92). These results suggest second-line chemotherapy with irinotecan confers a survival benefit.

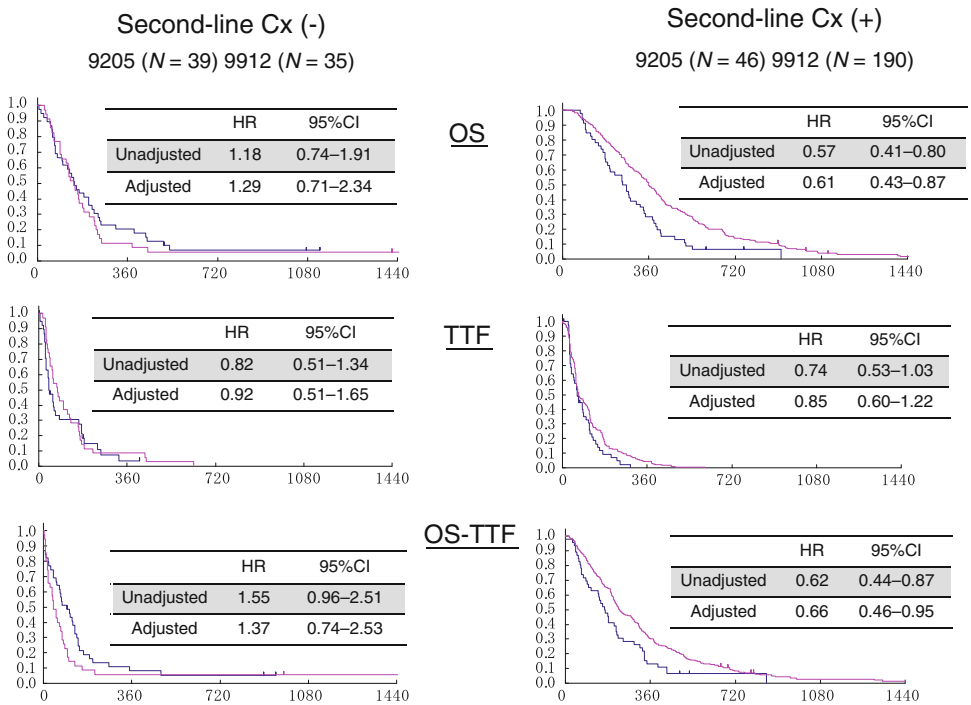


Fig. 3 Subgroup analyses according to the presence of second-line chemotherapy. Adjustment factors included age, sex, PS, macroscopic type, histological type, gastrectomy, target lesion, peritoneal metastasis, and the number of metastatic sites. *Cx* chemotherapy, *MST* median survival time

Table 3 Mutivariate analysis of survival after treatment failure

	HR	95 % CI	*p* value
Trial			
JCOG9912 (vs. JCOG9205)	0.76	0.57–1.01	0.06
Age (years)			
≥65 (vs. ≤64)	1.04	0.82–1.31	0.77
Sex			
Male (vs. female)	0.84	0.63–1.10	0.20
Performance status (PS)			
PS1 (vs. 0)	1.51	1.17–1.95	<0.0001
PS2 (vs. 0)	3.67	2.11–6.37	
Macroscopic type			
1 (vs. 0)	0.61	0.20–1.85	0.63
2 (vs. 0)	0.53	0.21–1.37	
3 (vs. 0)	0.67	0.27–1.69	
4 (vs. 0)	0.61	0.23–1.64	
5 (vs. 0)	0.54	0.15–1.95	
Histological type			
Intestinal (vs. diffuse)	0.97	0.76–1.24	0.78
Gastrectomy			
+ (vs. −)	0.73	0.55–0.97	0.03
Target lesions			
+ (vs. −)	1.08	0.80–1.47	0.61
Peritoneal metastasis			
+ (vs. −)	0.70	0.52–0.93	0.01
Number of metastatic sites			
1 (vs. 0)	2.24	0.30–16.8	0.01
≥2 (vs. 0)	3.26	0.43–24.9	

However, the study was terminated early because of poor accrual. The second study, which compared treatment with irinotecan or docetaxel to best supportive care, also showed a survival benefit of second-line chemotherapy compared to best supportive care (median survival time, 5.3 vs. 3.8 months for patients receiving best supportive care alone; HR, 0.66; 95 % CI, 0.49–0.89) [7]. This result is currently the only evidence from a completed randomized trial justifying the use of second-line chemotherapy for AGC. Besides these two studies, the present results provide additional evidence supporting a survival benefit of second-line chemotherapy in AGC.

The present combined analysis has some limitations. There may be some other reasons for the prolongation of post-treatment failure survival in this analysis, including better general condition at treatment failure in JCOG9912, recent advances in supportive care, lead-time bias of diagnosis of metastasis, and unidentified baseline factors in first-line chemotherapy; however, these factors could not be adjusted in the analysis. In particular, prognostic factors at the failure of first-line chemotherapy that could strongly influence survival after treatment failure, such as PS, were not collected in either trial.

At present, regional differences in clinical outcomes between Asian and Western countries are major obstacles for conducting global trials for AGC [18]. Although better survival in Asian countries is considered to be mainly the result of a higher proportion of patients who receive second-line chemotherapy than in Western countries, the true reason for this difference remains unknown [19]. The

present study suggests "PS," "gastrectomy," "peritoneal metastasis," and "number of metastatic sites" are strongly associated with OS-TTF. These factors are well-known prognostic factors for OS in advanced gastric cancer patients undergoing first-line chemotherapy. Patient condition before both first- and second-line chemotherapy is speculated to substantially impact OS-TTF as well as OS. Therefore, when comparing OS and OS-TF among various regions, the aforementioned patient background characteristics should be considered in addition to second-line chemotherapy. Moreover, collecting the data of prognostic factors at the time of treatment failure is recommended in future trials to clarify the effect of survival after treatment failure.

In conclusion, the longer OS and OS-TTF in JCOG9912 than in JCOG9205, even after adjusting for baseline characteristics, suggest the increasing availability of active drugs (e.g., irinotecan, taxanes, etc.) in subsequent therapies is a potential reason for the observed survival prolongation.

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Conflict of interest The authors have declared no conflicts of interest.

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