

Inter-institutional heterogeneity in outcomes of chemotherapy for metastatic gastric cancer: correlative study in the JCOG9912 phase III trial

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ABSTRACT

Background: The standard chemotherapy regimen for gastric cancer has been established by several phase III trials. However, few studies have evaluated inter-institutional heterogeneity in randomised trials; such research may assure the generalisability of the results and also the reliability of the study group itself.

Patients and methods: The Japan Clinical Oncology Group (JCOG)9912 phase III trial compared irinotecan plus cisplatin and S-1 alone with fluorouracil alone for metastatic gastric cancer, and finally demonstrated the non-inferiority of S-1 alone with respect to overall survival (OS). Mixed effects models were used to evaluate outcomes of 658 patients from 22 hospitals. After adjustment for nine background factors, the heterogeneity in OS, progression-free survival (PFS), and incidences of grade 3–4 adverse events among hospitals was estimated. We also estimated the correlation between outcomes and either hospital volume or medical oncology clinical experience.

Results: A large degree of heterogeneity in median OS was observed for fluorouracil alone (range, 8.3–13.3 months), while the difference in median PFS between hospitals was small (range, 2.4–3.4 months). Although some heterogeneity in the treatment effect of irinotecan plus cisplatin or S-1 alone was observed in OS and PFS, the HRs did not exceed 1.00 in any hospital for either regimen. There was minimal heterogeneity in the incidences of grade 3–4 adverse events. There was a trend towards correlation between greater medical oncology clinical experience and both better OS after fluorouracil alone and a lower HR for OS after irinotecan plus cisplatin, but it was not statistically significant.

Conclusions: Large inter-institutional heterogeneity was observed in OS, but not in PFS, after the standard regimen, but there was little heterogeneity in the treatment effects of irinotecan plus cisplatin or S-1 alone, indicating that the final results of the JCOG9912 trial can be generalised to the target population.

Trial registration number: NCT00142350.

Key questions

What is already known about this subject?

A randomized phase III trial (JCOG9912) comparing irinotecan plus cisplatin and S-1 alone with fluorouracil alone for metastatic gastric cancer demonstrated the non-inferiority of S-1 alone in overall survival (OS).

What does this study add?

In the JCOG9912, large inter-institutional heterogeneity was observed in OS, but not in progression-free survival, after fluorouracil alone, but there was little heterogeneity in the treatment effects of irinotecan plus cisplatin or S-1 alone.

How might this impact on clinical practice?

The final results of the JCOG9912 can be generalised to the target population. The heterogeneity in OS was possibly caused by differences in the treatments subsequent to first-line chemotherapy.

INTRODUCTION

Gastric cancer is the third leading cause of cancer death worldwide.¹ The prognosis of unresectable or recurrent gastric cancer is poor. Until the late 1990s, continuous infusion of fluorouracil alone was recognised as the standard regimen of first-line chemotherapy in Japan because three phase III trials failed to confirm a survival benefit of fluorouracil plus cisplatin over fluorouracil alone.^{2–4} After the development of new anti-tumour agents in the late 1990s, a randomised phase III trial (Japan Clinical Oncology Group (JCOG)9912) comparing irinotecan plus cisplatin and S-1 alone with fluorouracil alone for metastatic gastric cancer was conducted by the JCOG, and finally demonstrated the non-inferiority of S-1 alone compared with fluorouracil alone with respect to overall survival (OS) (HR,

0.83; 95% CI 0.68 to 1.01; $p < 0.001$).⁵ The subsequent phase III trial (SPIRITS) proved a survival benefit of S-1 plus cisplatin over S-1 alone (HR, 0.77; 95% CI 0.61 to 0.98; $p = 0.04$),⁶ thus establishing the current standard regimen for advanced gastric cancer in eastern Asia.

The ICH-E9 international statistical guidelines recommend exploring the heterogeneity in treatment effects to evaluate the generalisability of conclusions of phase III trials.⁷ However, few reports have assessed the heterogeneity among participating institutions in randomised phase III trials. We therefore evaluated the inter-institutional heterogeneity of standard and experimental chemotherapies in the JCOG9912 phase III trial, after adjusting for various background factors that could affect outcomes. The goal was to assure the generalisability of the results and also the reliability of the JCOG study group itself.

PATIENTS AND METHODS

JCOG9912 phase III trial

JCOG9912 was a multicentre, prospective, randomised phase III trial investigating the superiority of irinotecan plus cisplatin and the non-inferiority of S-1 alone compared with fluorouracil alone, with respect to OS, in patients with metastatic gastric cancer (registered in ClinicalTrials.gov, number NCT00142350, and in UMIN-CTR, number C000000062).⁵ Eligibility criteria included histologically confirmed adenocarcinoma of the stomach, unresectable or recurrent disease, adequate self-supported nutritional intake, age 20–75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, no history of chemotherapy or radiation therapy, and preserved organ function. Between November 2000 and January 2006, 704 patients from 34 hospitals were randomised to either the standard regimen consisting of fluorouracil

Table 1 Characteristics of the patients in three regimen groups

	Fluorouracil alone (n=218)	Irinotecan plus cisplatin (n=221)	S-1 alone (n=219)
Age (years)			
Median (range)	64 (24–75)	63 (32–75)	64 (39–75)
Sex			
Male	163	169	164
Female	55	52	55
ECOG performance status			
0	139	142	140
1, 2	79	79	79
Mode of disease			
Unresectable	174	176	178
Recurrent	44	45	41
History of gastrectomy			
No	132	130	141
Yes	86	91	78
Borrmann macroscopic type			
0, 1, 2	63	74	70
3, 4, 5	155	147	149
Histological type			
Intestinal	103	98	104
Diffuse	115	123	115
Target lesions			
No	55	52	57
Yes	163	169	162
Number of metastatic sites			
0, 1	98	96	94
2 or more	120	125	125

Definition of target lesions was according to RECIST (V.1.0). ECOG, Eastern Cooperative Oncology Group.

alone (234 patients), an experimental regimen consisting of irinotecan plus cisplatin (236 patients), or another experimental regimen consisting of S-1 alone

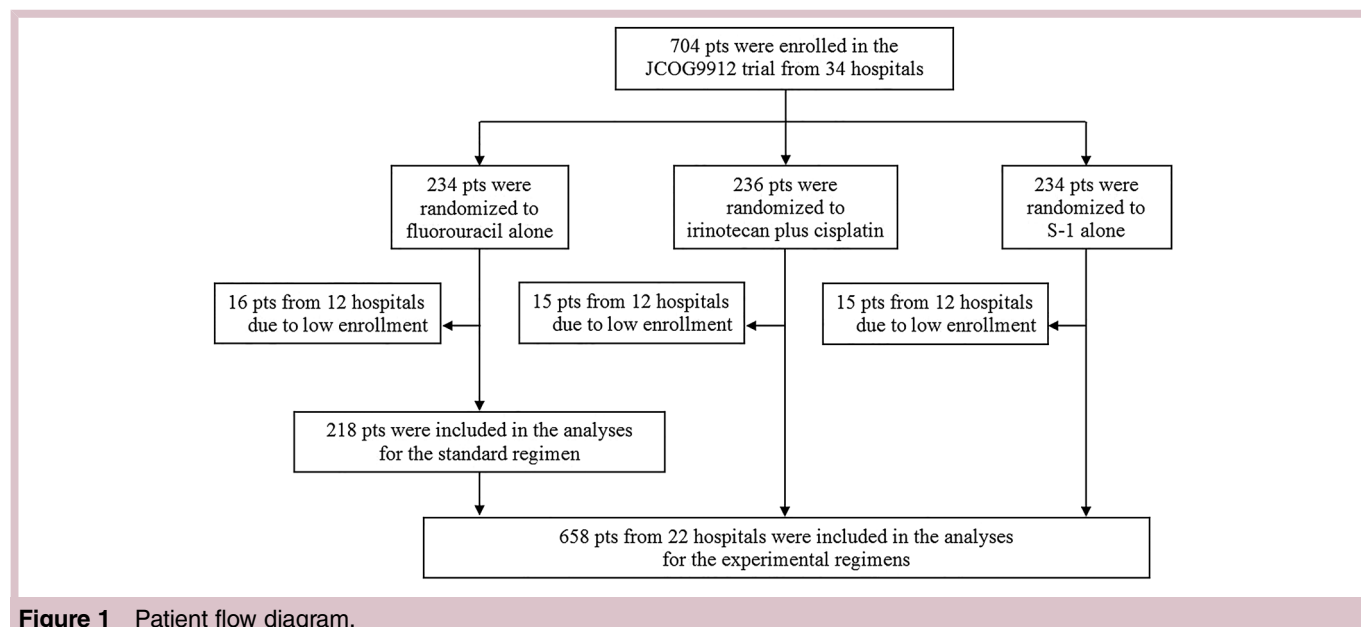


Figure 1 Patient flow diagram.

(234 patients). In the fluorouracil-alone group, patients received fluorouracil 800 mg/m² daily as continuous infusion for 5 days, repeated every 4 weeks. In the irinotecan plus cisplatin group, patients received infusions of 70 mg/m² irinotecan on days 1 and 15 and 80 mg/m² cisplatin on day 1, repeated every 4 weeks. In the S-1 alone group, patients received S-1 40 mg/m² twice a day orally for 4 weeks, followed by a 2-week rest. In each group, we continued the assigned treatment until disease progression. Subsequent treatment was not prespecified.

Outcomes in this study

Among the 34 participating hospitals in the JCOG9912 trial, those that enrolled fewer than two patients in either group were excluded from the analysis. The patients who were randomised into the fluorouracil-alone group were included in the evaluation of inter-institutional heterogeneity in the outcomes of the standard regimen. Outcomes included OS, progression-free survival (PFS) and incidences of grade 3–4 adverse events as defined by the National Cancer Institute's common toxicity criteria (V.2.0). We also examined the correlation between heterogeneity in each outcome and either hospital volume (number of all patients with gastric cancer who received systemic chemotherapy during the accrual period,

including patients not enrolled in JCOG9912) or median years of medical oncology clinical experience among participating physicians.

Statistical analysis

We used mixed effects proportional hazards models, under the assumptions that hospital effects are random, the effects of other baseline factors are fixed, and that end points such as OS and PFS are determined by prognostic factors, treatment arms, baseline risk (ie, deviation of each hospital from the overall baseline risk in the standard treatment, ie, not explained by other prognostic factors), and treatment effects (ie, deviation of each hospital from the overall effect of treatment arms). The adjusted prognostic factors were gender, age (continuous variable), performance status (0 vs 1, 2), disease status (recurrent vs unresectable), history of gastrectomy (– vs +), macroscopic type (0, 1, 2 vs 3, 4, 5 according to Japanese classification), histology (intestinal vs diffuse), target lesion (– vs +), and number of metastatic sites (0, 1 vs 2 or more). To evaluate the baseline risk of the standard regimen, the predicted OS and PFS for each hospital were converted to median durations to facilitate the interpretation of our results.

The heterogeneity in the incidences of severe adverse events was estimated using a mixed effects logistic

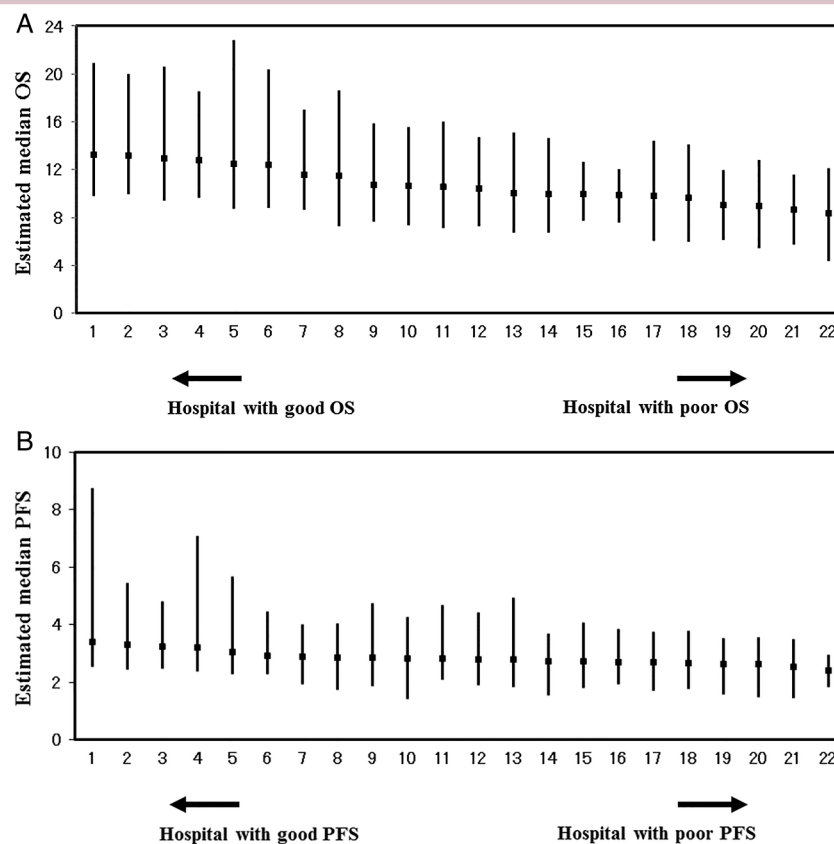


Figure 2 Estimated median overall survival (OS) (A) and progression-free survival (PFS) (B) for fluorouracil alone at the 22 hospitals.

regression model. In this model, institutional effect was considered to be random while the effect of treatment arms and other prognostic factors mentioned above was considered to be fixed.

To investigate the reasons for the observed inter-institutional heterogeneity, Spearman's correlation coefficients were calculated for associations between estimated outcomes and hospital volume or median years of medical oncology clinical experience. All statistical analyses were performed with SAS software (V.9.1, 9.2) and WinBUGS software (V.1.4.2).

RESULTS

A patient flow diagram for the JCOG9912 trial is shown in [figure 1](#). Excluding 46 of the 704 randomised patients due to low enrolment at certain institutions, 658 patients enrolled at 22 hospitals were included in this analysis.

The characteristics of the patients in this study are shown in [table 1](#). In each regimen group, approximately two-thirds of patients had an ECOG performance status of zero and three-fourths had at least one target lesion.

[Figure 2A](#) shows the estimated median OS for fluorouracil alone in each hospital after adjusting for nine background factors. A large heterogeneity in median OS was observed (range, 8.3–13.3 months). On the other hand, the difference between the longest (3.4 months) and shortest (2.4 months) median PFS for fluorouracil alone was only 1.0 month ([figure 2B](#)).

[Figures 3A, B](#) show the estimated HRs for OS and PFS, respectively, for irinotecan plus cisplatin compared with fluorouracil alone at the 22 hospitals. Although some heterogeneity in the treatment effect of irinotecan plus cisplatin was observed in OS (range, 0.81–0.91) and PFS (range, 0.62–0.82), the estimated HRs did not exceed 1.00 in any hospital. [Figures 4A, B](#) show the estimated

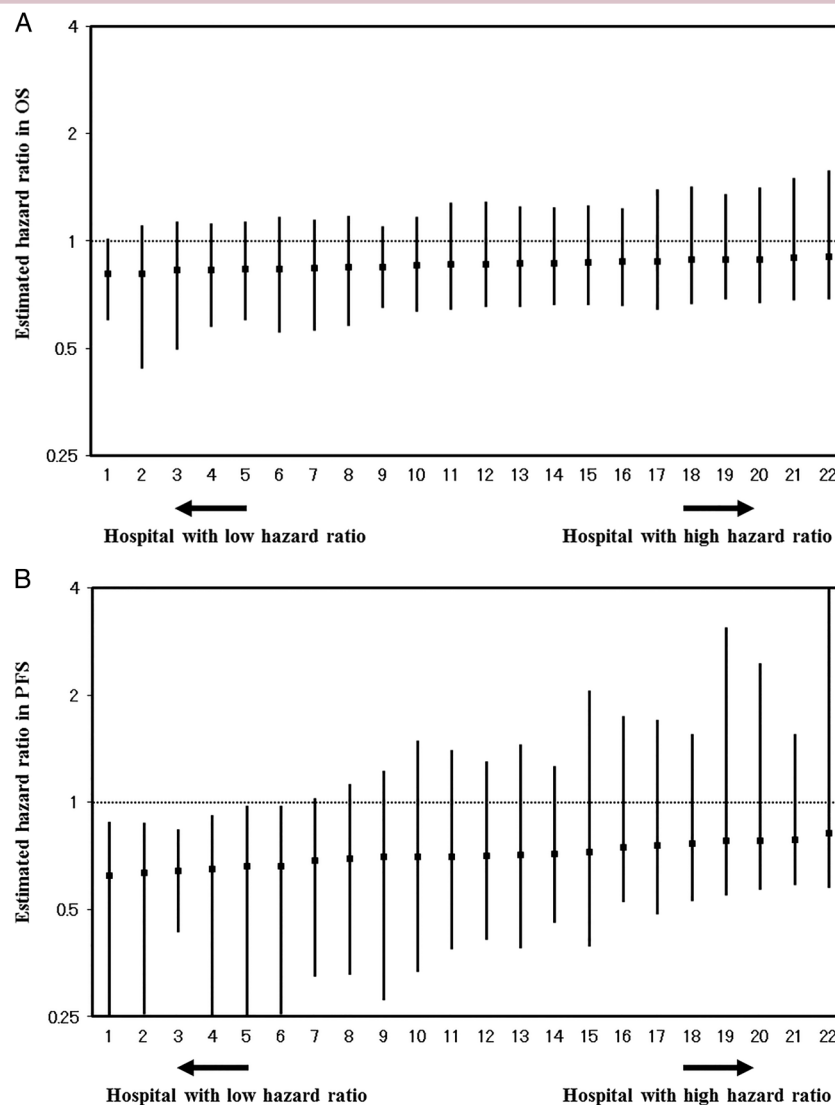


Figure 3 Estimated HRs for overall survival (OS) (A) and progression-free survival (PFS) (B) for irinotecan plus cisplatin compared with fluorouracil alone at the 22 hospitals.

HRs for OS and PFS for S-1 alone in each hospital. The inter-institutional heterogeneity in OS (range, 0.75–0.80) and PFS (range, 0.77–0.90) for S-1 alone was also small.

The difference between the highest (44.8%) and lowest (41.4%) incidences of severe adverse events for fluorouracil alone was only 3.4%. There was also little heterogeneity in the risk ratio of severe adverse events for irinotecan plus cisplatin (range, 1.90–1.94) or S-1 alone (range, 0.94–0.96) versus fluorouracil alone.

Correlations between estimated outcomes (OS and PFS) and hospital volume and medical oncology clinical experience are shown in table 2. There was no correlation between hospital volume and any outcome. In contrast, greater medical oncology clinical experience showed trends towards correlation with better OS after fluorouracil alone and a lower HR for OS after irinotecan plus cisplatin, but these were not statistically significant.

DISCUSSION

JCOG9912 was a landmark phase III trial intended to demonstrate the clinical benefits of S-1 as first-line chemotherapy for metastatic gastric cancer.⁵ According to international statistical guidelines (ICH-E9),⁷ exploring the heterogeneity in treatment effects is desirable to evaluate the generalisability of the conclusions of positive phase III trials such as JCOG9912. We therefore evaluated the inter-institutional heterogeneity in treatment effects of irinotecan plus cisplatin or S-1 alone in this correlative study. Our results showed only small heterogeneity in the HRs for OS and PFS of irinotecan plus cisplatin or S-1 alone compared to fluorouracil, indicating that the final results of JCOG9912 can be generalised to their respective target population, regardless of institution.

Surprisingly, regarding the baseline risk of participating institutions estimated in the outcomes of the

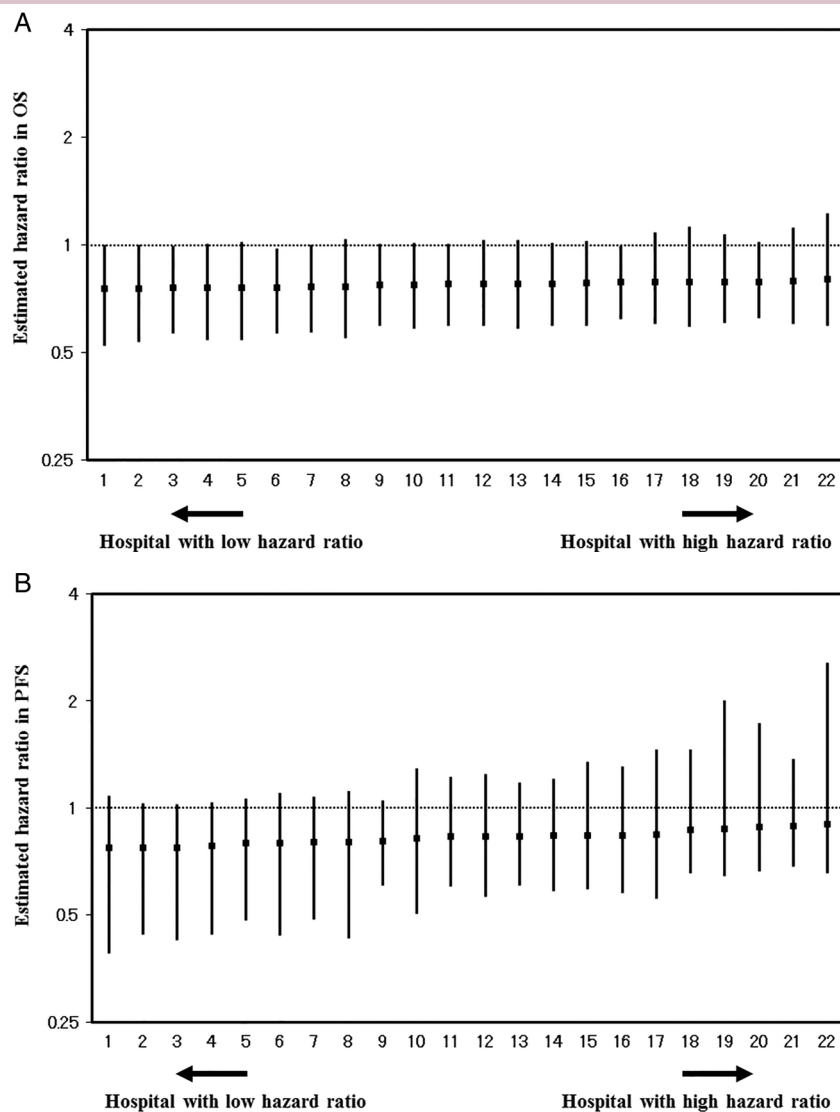


Figure 4 Estimated HRs for overall survival (OS) (A) and progression-free survival (PFS) (B) for S-1 alone compared with fluorouracil alone at the 22 hospitals.

Table 2 The correlations between estimated outcomes and both hospital volume and medical oncology clinical experience

	Hospital volume	Medical oncology clinical experience
OS for fluorouracil alone	r=0.122 (p=0.590)	r=0.376 (p=0.085)
PFS for fluorouracil alone	r=0.143 (p=0.525)	r=0.237 (p=0.289)
HR in OS for irinotecan plus cisplatin	r=0.027 (p=0.907)	r=-0.361 (p=0.099)
HR in PFS for irinotecan plus cisplatin	r=0.014 (p=0.952)	r=-0.196 (p=0.382)
HR in OS for S-1 alone	r=-0.071 (p=0.753)	r=0.315 (p=0.154)
HR in PFS for S-1 alone	r=0.015 (p=0.947)	r=-0.119 (p=0.599)

OS, overall survival; PFS, progression-free survival.

standard regimen, the difference in estimated median OS between the hospitals with the highest and lowest values reached 5.0 months, while the difference in the estimated median PFS was only 1.0-month. While clinical trials such as JCOG9912 enrol relatively homogeneous patient populations due to eligibility criteria, and in JCOG9912 there were no prognostic factors for PFS shared among the three treatment arms,⁸ survival outcomes are still affected by various background prognostic factors before enrolment to the trial, such as age, sex, performance status, tumour macroscopic and histological type, presence or absence of target lesions, and number of metastatic sites.⁹ Although heterogeneity in patient background among the participating institutions might explain the differences in OS, we adjusted for these prognostic factors using the mixed effects model to minimise their impact. The results of this study indicated that the large degree of inter-institutional heterogeneity in OS was mainly due to the difference in survival after first-line chemotherapy. In several multinational phase III trials for metastatic gastric cancer, a substantial difference in survival after chemotherapy among nations or regions has been reported,¹⁰⁻¹⁴ and it is suggested that this is due to variations in the proportions of patients receiving subsequent chemotherapy. JCOG9912 did not prespecify subsequent treatment, including second-line or third-line chemotherapy regimens. As a result, physician management choices, including those related to subsequent treatment, might have contributed significantly to the heterogeneity among participating hospitals, including the large gap in estimated OS between hospitals with the largest and smallest values.

A strong correlation between hospital volume and postoperative outcomes has been observed in many studies.¹⁵⁻²⁰ However, to the best of our knowledge, there have been no studies investigating the relationship between hospital volume or medical oncology clinical experience and outcomes after chemotherapy for metastatic gastric cancer. Although we did not find any

associations between hospital volume and postchemotherapy outcomes in this study, there was a marginal relationship between medical oncology clinical experience and both the OS after the standard regimen and the HR for OS after irinotecan plus cisplatin. Furthermore, medical oncology clinical experience was significantly correlated with the risk ratio of severe adverse events for irinotecan plus cisplatin (data not shown). It is suggested that physicians with enough clinical experience in medical oncology might choose the proper treatments after first-line chemotherapy, as well as provide appropriate management to reduce the toxicity of intensive chemotherapies such as irinotecan plus cisplatin.

In conclusion, although the difference between participating institutions in terms of PFS was very small, there was large heterogeneity in OS. This heterogeneity was possibly caused by differences in the treatments subsequent to first-line chemotherapy, which in turn may have been due to variations in medical oncology clinical experience. The heterogeneity in the HR for irinotecan plus cisplatin and S-1 alone compared with fluorouracil alone was small, indicating that the final results of the JCOG9912 trial can be generalised to the target population. Finally, this study provided evidence of the high reliability of the JCOG gastric cancer study group.

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Competing interests YK has received honoraria from Taiho and Yakult. NB has received honoraria from Taiho and Yakult and research funding from Taiho.

Patient consent Obtained.

Ethics approval The JCOG Clinical Trial Review Committee and the institutional review boards of all participating hospitals.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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