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Can S-1 replace fluorouracil for advanced gastric cancer? A PRISMA-compliant systematic review and meta-analysis

Xiao-Dong Chen (MD, PhD)[a], Fu-Qian He (MD, PhD)[b], Mi Chen (BM)[a], Ling-Chao Tang (BM)[a], Xiao-Li Tang (BM)[a,*]

Abstract

It remains to be seen whether S-1 can be a replacement for infusional fluorouracil (5-FU) for advanced gastric cancer (AGC). The aim of this study was to compare the efficacy and safety of S-1 with 5-FU in AGC.

PubMed and Cochrane Library were searched. Randomized controlled trials and meta-analyses comparing S-1 with 5-FU for AGC were eligible. Meta-analysis was performed using RevMan 5.2.

Seven trials involving 2443 patients were included. Compared with 5-FU, S-1 showed no significant prolongation of overall survival (OS) (hazard ratio [HR] = 0.91, 95% confidence interval [CI] [0.83–1.01], $P = 0.07$) and progression-free survival (HR = 0.89, 95% CI [0.70–1.13], $P = 0.35$), but longer time to treatment failure (HR = 0.74, 95% CI [0.56–0.97], $P = 0.03$). The objective response rates were comparable (risk ratio [RR] = 1.36, 95% CI [0.95, 1.96], $P = 0.10$). Regarding treatment-related deaths and hematological toxicities, there was significant heterogeneity between Asian and non-Asian trials, and subgroup analysis was applied. In Asian patients, there was a significant increase in hematological toxicities such as leukopenia (grade 1–4: RR = 1.22, 95% CI [1.08, 1.37], $P = 0.001$; grade 3–4: RR = 2.21, 95% CI [1.52, 3.21], $P < 0.0001$), neutropenia (grade 1–4: RR = 1.29, 95% CI [1.11, 1.48], $P = 0.0005$; grade 3–4: RR = 1.87, 95% CI [1.11, 3.17], $P = 0.02$), and thrombocytopenia (grade 1–4: RR = 1.71, 95% CI [1.22, 2.41], $P = 0.002$) in S-1-containing regimens compared with 5-FU-containing regimens, but without significant difference in treatment-related mortality rate (risk difference [RD] = 0.00, 95% CI [−0.01, 0.01], $P = 0.68$). In non-Asian patients, S-1-containing regimens were, however, associated with significantly fewer treatment-related deaths (RD = −0.02, 95% CI [−0.05, −0.00], $P = 0.04$), as well as less all grade 1–4 and grade 3–4 hematological toxicities except anemia. There was no significant heterogeneity in nonhematologic toxicities between Asian and non-Asian trials. Lower incidence of grade 1–4 nausea, diarrhea, mucositis, grade 3–4 mucositis, increased creatinine, and decreased calculated creatinine clearance was observed in S-1-containing regimens.

S-1 could not improve OS, but increase some hematological toxicities in Asian patients. Therefore, special attention on hematological toxicities should be paid to Asian patients because S-1 is administered on an outpatient basis.

Abbreviations: 5-FU = fluorouracil, AEs = adverse events, AGC = advanced gastric cancer, CI = confidence interval, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, QOL = quality of life, RCTs = randomized controlled trials, RD = risk difference, RR = risk ratio, TTF = time to treatment failure, TTP = time to progression

Keywords: Efficacy, fluorouracil, heterogeneity, meta-analysis, S-1, stomach neoplasms, toxicity

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1. Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer mortality worldwide.[1] Because an early detection strategy through population-based screening is not yet widely practiced, the majority of patients are diagnosed with advanced disease. Surgical resection is the only treatment modality that is potentially curative for patients with local or locoregional disease. However, palliative chemotherapy should be considered for patients with unresectable locally advanced, metastatic, or recurrent disease, as it prolongs overall survival (OS) and improves quality of life (QOL) compared with best supportive care alone.[2]

At present, infusional fluorouracil (5-FU) remains the mainstay for the treatment of advanced gastric cancer (AGC) due to its broad antitumor activity, as well as its synergism with other anticancer drugs.[3] Nevertheless, its efficacy is relatively low, whereas its hematological and gastrointestinal toxicities are relatively common. S-1 is a novel oral fluoropyrimidine, comprising tegafur, gimeracil, and oteracil in a molar ratio of 1:0.4:1. Tegafur is a pro-drug of 5-FU and converted into 5-FU after absorption; gimeracil prolongs the half-life of 5-FU by

decreasing its degradation in the liver; and oteracil improves gastrointestinal tolerability through decreasing 5-FU phosphorylation in the gastrointestinal tract.[4]

Data from a series of phase II studies of S-1-containing regimens showed promising efficacy and favorable toxicity profiles.[4] Based on the evidence obtained by the Japan Clinical Oncology Group trials, S-1 plus cisplatin has been recommended as the first-line regimen for AGC in Japan.[5] In addition, more randomized trials outside of Japan comparing S-1 with 5-FU in mono or combined therapies have been carried out in recent years, with not completely consistent results regarding the efficacy and safety of these 2 treatments. It remains to be seen whether S-1 can be a replacement for infusional 5-FU.

A published meta-analysis of 4 trials indicated that S-1-based therapy showed better OS and nearly equivalent objective response rate (ORR) and safety profiles, compared with 5-FU-based therapy.[6] After careful reading of the full text, we, however, found that this meta-analysis contained duplicate material, which led to unreliable results and conclusions. During our preparation of this manuscript, another meta-analysis including 6 trials reported similar results to the previous one.[7] However, a few trials were not included and some pivotal information, such as heterogeneity between Asian and non-Asian, has been neglected in these analyses. In addition, the results of some trials have been updated recently. Therefore, we considered that it was deemed important to finish this meta-analysis to clarify the issue.

2. Materials and methods

Because no individual patient data were involved in this systematic review and meta-analysis, ethical approval from an ethics committee was not required.

2.1. Search strategy

Two reviewers (X-DC and F-QH) independently searched the following online electronic databases: PubMed and Cochrane Library using the following search terms: ((((((((((gastric cancer) OR gastric carcinoma) OR gastric adenocarcinoma) OR stomach cancer) OR stomach carcinoma) OR stomach adenocarcinoma)) OR ((((((esophagogastric junction cancer) OR esophagogastric junction carcinoma) OR esophagogastric junction adenocarcinoma) OR gastroesophageal junction cancer) OR gastroesophageal junction carcinoma) OR gastroesophageal junction adenocarcinoma))) AND fluorouracil) AND ((S-1[Title/Abstract]) OR TS-1 [Title/Abstract])) AND random*. Searches were updated until December 2015. After identifying relevant citations, the abstracts of these studies were read to decide if the studies were eligible. The full text was retrieved when the information in the title and/or abstract seemed to meet the objective of this review. A manual search of reference lists of studies was conducted to identify any relevant articles not found in the computerized search.

2.2. Inclusion and exclusion criteria

Randomized controlled trials (RCTs) comparing S-1-containing chemotherapy with 5-FU-containing chemotherapy, mono or combined chemotherapy with S-1 versus 5-FU, and not confounded by additional agents or interventions (i.e., the experimental and control arms in the combined chemotherapy differed only in S-1 and 5-FU) were eligible for inclusion. Abstracts or unpublished work with sufficient information were also included. Included

patients were diagnosed with histologically confirmed unresectable, recurrent, or metastatic gastric or esophagogastric junction carcinoma. Reports of survival outcomes, response rates, or toxicities were mandatory for inclusion. Studies containing duplicate material were excluded, and the studies containing the best documented data were included for analysis.

2.3. Selection, quality assessment, and data extraction

Two reviewers (X-DC and F-QH) independently read the title and abstract of each searched citation to select eligible studies for further assessment. The full text of potentially eligible citations was retrieved and evaluated for inclusion. The Jadad scale was used to assess the quality of the selected studies.[8] Two reviewers independently extracted all relevant information in a data collection form, including study characteristics (author, country, sample size, regimen details, and methodological characteristics), efficacy, and safety data.

2.4. Outcomes of interest

The primary efficacy endpoint used for this study was OS. Secondary efficacy measures were endpoints based on tumor assessments, including ORR, defined as the sum of partial and complete response rates assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), progression-free survival (PFS), time to treatment failure (TTF), and time to progression (TTP). Safety analysis was based on adverse events (AEs), including treatment-related deaths and toxicities graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE).

2.5. Statistical analysis

Statistical analyses of the pooled hazard ratio (HR) for OS, PFS, and TTF, the risk ratio (RR) or risk difference (RD) for ORR and AEs were calculated using Review Manager (RevMan) Version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012). We also compared the pooled estimates of OS and ORR for subgroups stratified by region (Asia vs non-Asia) and regimen (different combined cytotoxic drugs). Statistical heterogeneity was evaluated by the χ^2 test and the I^2 statistic and was considered high when $P < 0.1$ or $I^2 > 50\%$. In meta-analysis, the fixed-effects method was used when the statistical heterogeneity was low, and the random-effects model and subgroup analysis were applied when it was high. The result stability was evaluated by performing a sensitivity analysis, in which one study was removed at a time. The presence of publication bias was evaluated by using the Begg and Egger tests in StataSE version 12.0 (Stata Corporation, College Station, TX).[9,10] An HR < 1 indicated a favorable outcome of S-1-containing regimens for OS, PFS, and TTF. A RR > 1 or RD > 0 indicated a favorable ORR or more AEs in S-1-containing regimens. A 2-tailed $P < 0.05$ was considered statistically significant.

3. Results

The literature search and selection procedure are shown in Figure 1. A total of 7 RCTs were eligible for analysis, including 5 full texts,[11–15] 1 abstract from ASCO Annual Meeting,[16] and 1 abstract from the ECCO/ESMO Congress.[17] The main characteristics of the included trials were shown in Table 1. Six studies were performed in East Asia (3 in Japan[12,14,17] and 3
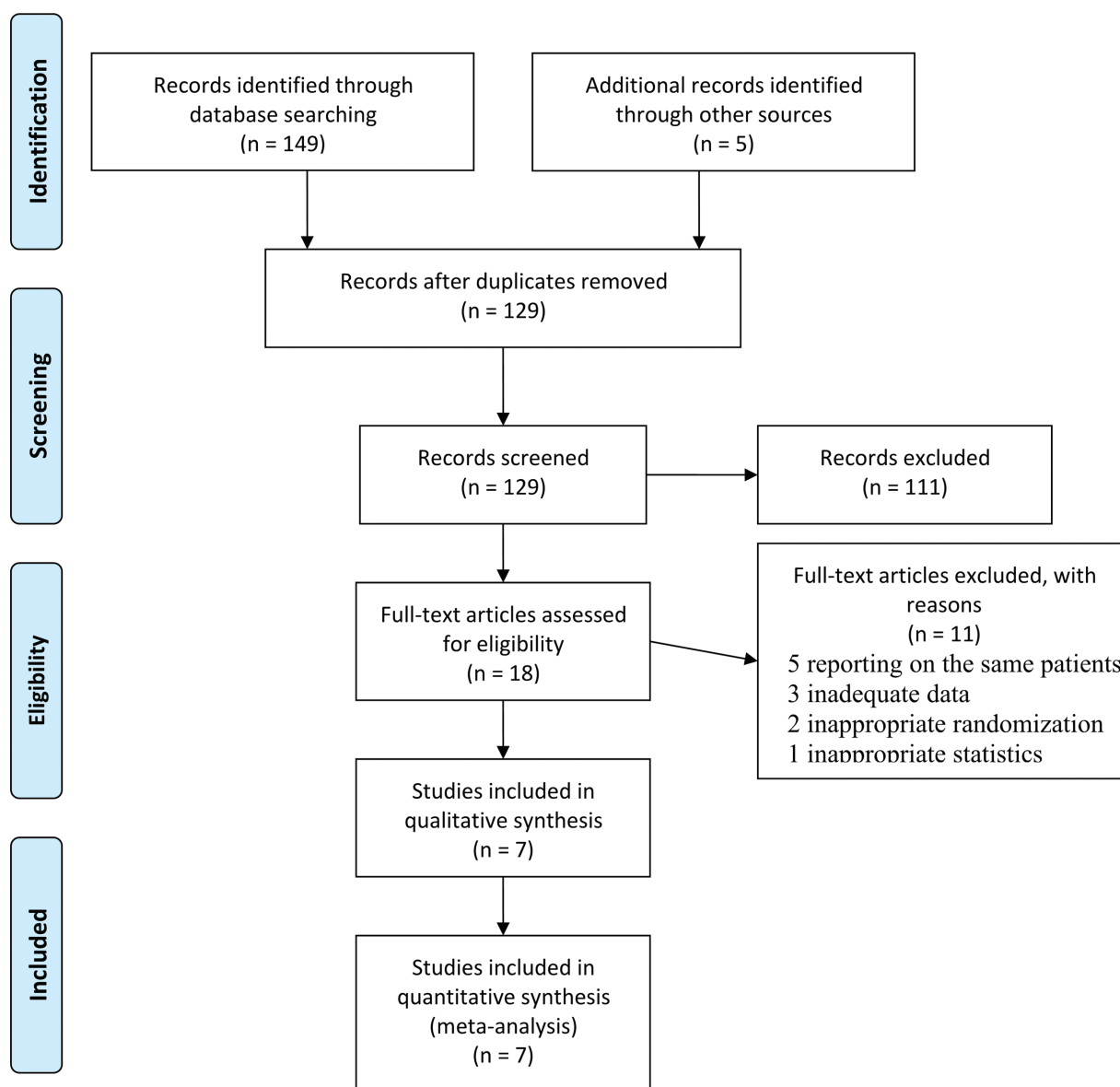
Figure 1. Flow diagram of literature search and selection procedure.

in China[11,15,16]), and the remaining study was a non-Asian global phase III trial performed in 24 countries.[13] All studies were multicenter in nature, involving 8 to 146 centers. Of the 2443 patients in those studies, 1236 patients received S-1-containing chemotherapy and 1207 patients received 5-FU-containing chemotherapy. The sample size of individual trials ranged from 147 to 1029 patients. Two studies compared S-1 alone with 5-FU alone (S-1 vs 5-FU),[14,17] 3 compared S-1 plus cisplatin with 5-FU plus cisplatin (SP vs FP),[13,15,16] and 2 compared S-1 plus paclitaxel with 5-FU plus paclitaxel (SPtx vs FPtx).[11,12] Regimens were similar with respect to doses and schedules in every trial. There were no significant differences in the baselines between S-1-containing and 5-FU-containing groups in these studies as reported.

3.1. Efficacy
3.1.1. OS. Six studies reported OS data. Median OS ranged from 8.3 to 15.2 months in the S-1-containing groups and 7.9 to

14.2 months in the 5-FU-containing groups (Table 2).[12–17] Two studies reported that S-1-containing regimens were superior to 5-FU-containing regimens,[14,16] whereas the others reported that S-1-containing regimens were comparable or noninferior to 5-FU-containing regimens. The meta-analysis showed no statistically significant improvement of OS with S-1-containing regimens versus 5-FU-containing regimens (HR = 0.91, 95% confidence interval [CI] [0.83–1.01], $P = 0.07$; P of heterogeneity = 0.18, $I^2 = 34\%$; Fig. 2). The subgroup analyses of OS by region (Asia and non-Asia) and regimen (S-1 vs 5-FU, SP vs FP, and SPtx vs FPtx) found no differences, and tests for subgroup differences showed no significant difference in heterogeneity among subgroups (Figs. 3 and 4, respectively).

3.1.2. PFS. Four studies reported PFS, which ranged from 3.5 to 6.0 months in the S-1-containing groups and 2.9 to 5.5 months in the 5-FU-containing groups (Table 2).[11,13,14,17] Two Asian

Table 1

Characteristics of included trials.

Study	Country	Centers	Participants (M/F)	Intervention	Scheme of chemotherapy	Endpoints	Jadad scores
Huang et al (2013)[11]	China	14	119 (89/30)	SPtx (con.)	S-1 80–120 mg/d d1-14, PTX 60 mg/m^2 d1, 8, 15/q4w	DCR*, PFS, TTF, safety	3
			110 (76/34)	FPtx (con.)	5-FU 500 mg/m^2/d cvi d1-5, LV 20 mg/m^2 iv d1-5, PTX 60 mg/m^2 d1, 8, 15/q4w		
Nishikawa et al (2012)[12] (TASC trial)	Japan	8	40 (28/12)	SPtx (seq.)	S-1 80 mg/m^2 d1-28/q6w until progression, followed by PTX 80 mg/m^2 d1, 8, 15/q4w	OS*, TTF, ORR, safety	3
			38 (25/13)	FPtx (seq.)	5-FU 800 mg/m^2/d cvi d1-5/q4w until progression, followed by PTX 80 mg/m^2 d1, 8, 15/q4w		
			40 (32/8)	SPtx (con.)	S-1 80 mg/m^2 d1-14, PTX 50 mg/m^2 d1, 8/q3w		
			39 (28/11)	FPtx (con.)	5-FU 600 mg/m^2/d cvi d1-5, PTX 80 mg/m^2 d8, 15, 22/q4w		
Ajani et al (2010)[13] (FLAGS trial)	24 non-Asian countries	146	521 (382/139)	SP	S-1 50 mg/m^2/d d1-21, DDP 75 mg/m^2 iv d1/q4w	OS*, ORR, PFS, TTF, safety	3
			508 (347/161)	FP	5-FU 1000 mg/m^2/d cvi 120h, DDP 100 mg/m^2 iv d1/q4w		
Boku et al (2009)[14] (JCOG 9912)	Japan	34	234 (176/58)	S-1	S-1 40 mg/m^2 bid d1-28/q6w	OS*, ORR, NHS, PFS, TTF, safety	3
			234 (175/59)	5-FU	5-FU 800 mg/m^2/d cvi d1-5/q4w		
Li et al (2015)[15]	China	15	120	SP	S-1 80 mg/m^2/d d1-21, DDP 20 mg/m^2 iv d1-4/q5w	TTP*, ORR, OS, safety	2
			116	FP	5-FU 800 mg/m^2/d cvi 120h, DDP 20 mg/m^2 iv d1-4/q4w		
Jin et al (2008)[16] (SC-101 study)	China	15	74 (55/19)	SP	S-1 40–60 mg bid d1-21, DDP 60 mg/m^2 ivgtt d8/q5w	ORR*, TTF, OS, safety	2
			73 (61/12)	FP	5-FU 600 mg/m^2 cvi d1-5, DDP 20 mg/m^2 ivgtt d1-5/q4w		
Sawaki et al (2009)[17] (ISO-5FU10 trial)	Japan	60	88	S-1	S-1 40–60 mg bid d1-28/q6w	OS*, ORR, PFS, TTF, QOL, safety	2
			89	5-FU	I-LV 250 mg/m^2 2h iv, 5-FU 600 mg/m^2 iv bolus qw w1-6/q8w		

con. = concurrent, FP = 5-FU plus DDP, FPtx = fluorouracil (5-FU) plus PTX, I-LV = levo-leucovorin, LV = leucovorin, NHS = nonhospitalized survival, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, QOL = quality of life, seq. = sequential, SP = S-1 plus cisplatin (DDP), SPtx = S-1 plus paclitaxel (PTX), TTF = time to treatment failure, TTP = time to progression.
* Primary endpoint.

Table 2

Detailed information of OS, PFS, TTF, and TTP reported by some included trials.

Study	Participants		OS [95% CI], mo		PFS [95% CI], mo		TTF/TTP [95% CI], mo	
	S-1	5-FU	S-1-containing	5-FU-containing	S-1-containing	5-FU-containing	S-1-containing	5-FU-containing
Huang et al (2013)[11]	119	110	NR	NR	5.0	4.2	16 days*	20 days*
					HR = 0.641 [0.473–0.868], P = 0.004		HR = 1.449 [0.705–2.980], P = 0.229	
Nishikawa et al (2012)[12]	80	77	15.2 [11.4–19.0]	14.2 [9.6–18.7]	NR	NR	NR	NR
			HR = 0.96 [0.67–1.39], P = 0.83				"No difference"	
Ajani et al (2010)[13]	521	508	8.6 [7.9–9.5]	7.9 [7.2–8.5]	4.8 [4.0–5.5]	5.5 [4.4–5.8]	3.8	3.8
			HR = 0.92 [0.80–1.05], P = 0.20		HR = 0.99 [0.86–1.14], P = 0.92		HR = 0.87 [0.77–0.99], P = 0.03	
Boku et al (2009)[14]	234	234	11.4 (6.4–21.3)[†]	10.8 (5.7–17.8)[†]	4.2 (2.2–7.1)[†]	2.9 (1.7–5.7)[†]	4 (2.0–6.3)[†]	2.3 (1.4–5.4)[†]
			HR = 0.83 [0.68–1.00], P = 0.0233		HR = 0.77 [0.64–0.93], P = 0.0027		HR = 0.73 [0.61–0.88], P = 0.0004	
Li et al (2015)[15]	120	116	10.00 [8.59–14.52]	10.46 [8.92–13.84]	NR	NR	5.51[4.59–6.26][‡]	4.62 [4.00–6.33][‡]
			HR = 1.05 [0.71–1.54], P = 0.82				HR = 1.028 [0.758–1.394], P = 0.859	
Jin et al (2008)[16]	74	73	14.2 [12.0–]	10.2 [7.8–]	NR	NR	5.2 [4.8–7.2]	2.8 [2.2–3.5]
			HR = 0.52 [0.30–0.92], P = 0.038				HR = 0.37 [0.25–0.57], P < 0.001	
Sawaki et al (2009)[17]	88	89	8.3 [6.9–10.4]	10.3 [8.1–12.9]	3.5 [2.8–5.1]	4.0 [3.2–8.5]	2.8 [2.5–3.3]	3 [2.0–3.7]
			HR = 1.19 [0.85–1.67], P = 0.31		HR = 1.32 [0.94–1.82]		HR = 1.05 [0.76–1.45]	

NR = not reported, OS = overall survival, PFS = progression-free survival, TTF = time to treatment failure, TTP = time to progression.
* Data obtained through correspondence with the original investigators.
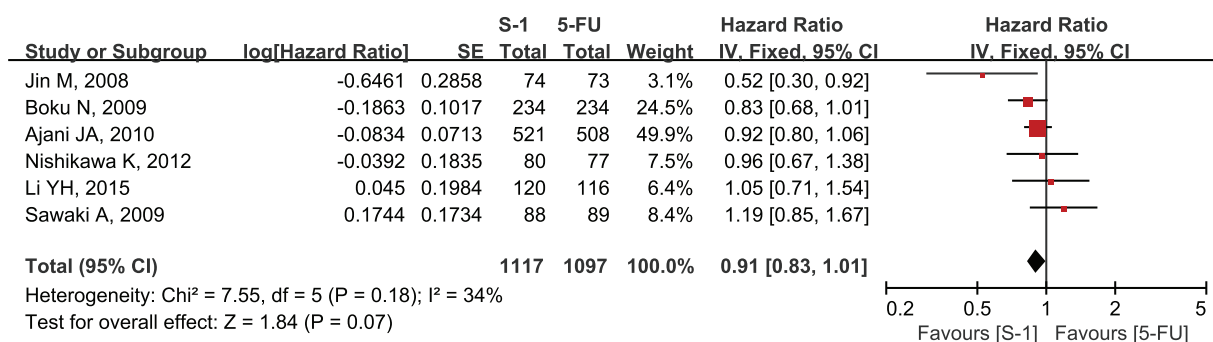† Interquartile range.
‡ TTP.

Figure 2. Forest plot of overall survival associated with the S-1-containing chemotherapy compared with the 5-FU-containing chemotherapy.
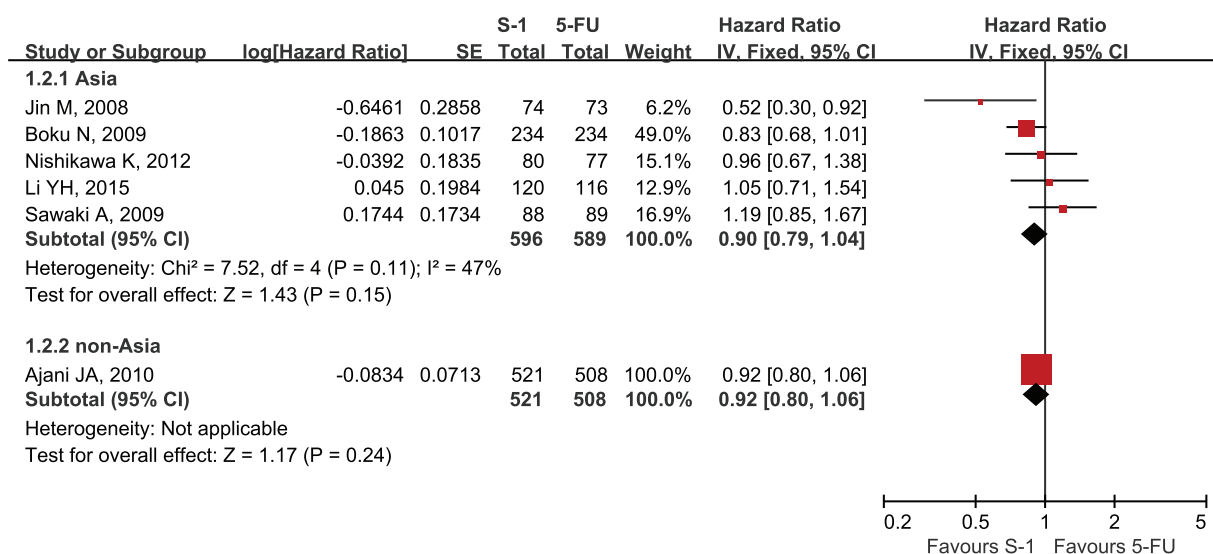

Figure 3. Forest plot of subgroup analysis of overall survival by region.

studies reported that S-1-containing regimens significantly prolonged PFS compared with 5-FU-containing regimens,[11,14] whereas the meta-analysis showed there were no significant benefits in PFS for the S-1-containing groups (HR = 0.89, 95% CI [0.70–1.13], P = 0.35; P of heterogeneity = 0.003, I^2 = 79%; Fig. 5).

3.1.3. TTF. Six studies reported TTF, which ranged from 2.8 to 5.2 months in the S-1-containing groups and 2.8 to 3.8 months in the 5-FU-containing groups (Table 2).[11–14,16,17] One study reported that no difference in TTF was observed between S-1-containing and 5-FU-containing regimens but did not provide exact data for meta-analysis.[12] Another study reported the Kaplan-Meier curve and HR of TTF; however, the median of TTF obtained through correspondence with the original investigators was only 16 days and 20 days which were observed in 17 patients and 19 patients of the S-1-containing and 5-FU-containing groups, respectively.[11] Consequently, these 2 studies were excluded from the meta-analysis. The pooled data of the remaining 4 studies by the random-effects model were significantly in favor of the S-1-containing group (HR = 0.74, 95% CI [0.56–0.97], P = 0.03; P of heterogeneity = 0.0004, I^2 = 84%; Fig. 6).

3.1.4. TTP. Only one study demonstrated no significant difference in TTP between the 2 groups.[15]

3.1.5. ORR. All studies provided information on response rate. ORR was 30.5% (310/1016) in the S-1-containing groups versus 24.4% (239/978) in the 5-FU-containing groups (Table 3). However, the meta-analysis showed no significant difference between the 2 groups (RR = 1.36, 95% CI [0.95, 1.96], P = 0.10; P of heterogeneity < 0.001, I^2 = 80%). The subgroup meta-analyses by region and regimen are shown in Table 3. The response rate in Asian patients seemed higher in S-1-containing groups than 5-FU-containing groups (31.4% vs 19.6%, RR = 1.48, 95% CI [1.00, 2.20], P = 0.05); however, no difference was observed in non-Asian patients. The comparisons between S-1 alone and 5-FU alone, SP and FP, SPtx and FPtx showed no significant differences.

3.2. Safety

We compared grade 1–4 and grade 3–4 toxicities in both groups according to reported information (Tables 4 and 5). The major toxicities of S-1-containing regimens were hematological toxicities including anemia, leukopenia, neutropenia, febrile
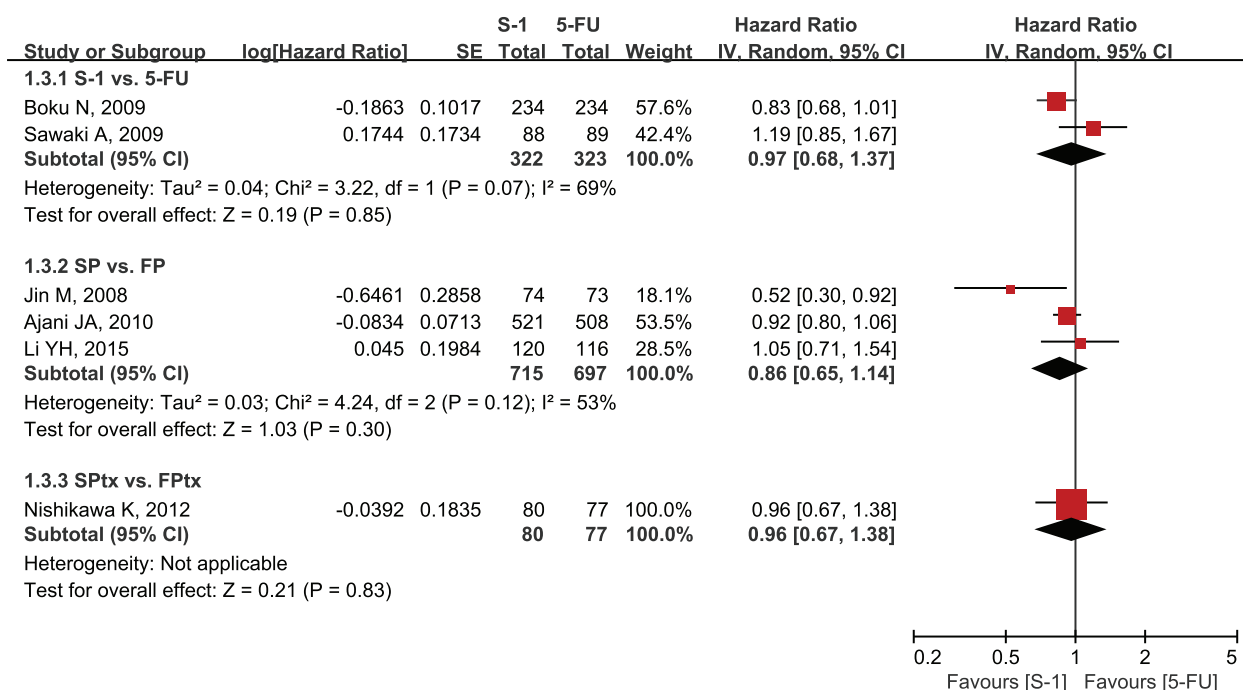
Study or Subgroup	log[Hazard Ratio]	SE	S-1 Total	5-FU Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
1.3.1 S-1 vs. 5-FU							
Boku N, 2009	-0.1863	0.1017	234	234	57.6%	0.83 [0.68, 1.01]	
Sawaki A, 2009	0.1744	0.1734	88	89	42.4%	1.19 [0.85, 1.67]	
Subtotal (95% CI)			322	323	100.0%	0.97 [0.68, 1.37]	
Heterogeneity: Tau² = 0.04; Chi² = 3.22, df = 1 (P = 0.07); I² = 69%							
Test for overall effect: Z = 0.19 (P = 0.85)							
1.3.2 SP vs. FP							
Jin M, 2008	-0.6461	0.2858	74	73	18.1%	0.52 [0.30, 0.92]	
Ajani JA, 2010	-0.0834	0.0713	521	508	53.5%	0.92 [0.80, 1.06]	
Li YH, 2015	0.045	0.1984	120	116	28.5%	1.05 [0.71, 1.54]	
Subtotal (95% CI)			715	697	100.0%	0.86 [0.65, 1.14]	
Heterogeneity: Tau² = 0.03; Chi² = 4.24, df = 2 (P = 0.12); I² = 53%							
Test for overall effect: Z = 1.03 (P = 0.30)							
1.3.3 SPtx vs. FPtx							
Nishikawa K, 2012	-0.0392	0.1835	80	77	100.0%	0.96 [0.67, 1.38]	
Subtotal (95% CI)			80	77	100.0%	0.96 [0.67, 1.38]	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.21 (P = 0.83)							

0.2   0.5   1   2   5
Favours [S-1]   Favours [5-FU]

Figure 4. Forest plot of subgroup analysis of overall survival by regimen. SP = S-1 plus cisplatin, FP = 5-FU plus cisplatin, SPtx = S-1 plus paclitaxel, FPtx = 5-FU plus paclitaxel.

Study or Subgroup	log[Hazard Ratio]	SE	S-1 Total	5-FU Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Huang D, 2013	-0.4447	0.1551	119	110	21.8%	0.64 [0.47, 0.87]	
Boku N, 2009	-0.2614	0.0943	234	234	27.8%	0.77 [0.64, 0.93]	
Ajani JA, 2010	-0.0101	0.0718	521	508	29.9%	0.99 [0.86, 1.14]	
Sawaki A, 2009	0.2744	0.1698	88	89	20.5%	1.32 [0.94, 1.84]	
Total (95% CI)			962	941	100.0%	0.89 [0.70, 1.13]	
Heterogeneity: Tau² = 0.05; Chi² = 14.29, df = 3 (P = 0.003); I² = 79%							
Test for overall effect: Z = 0.94 (P = 0.35)							

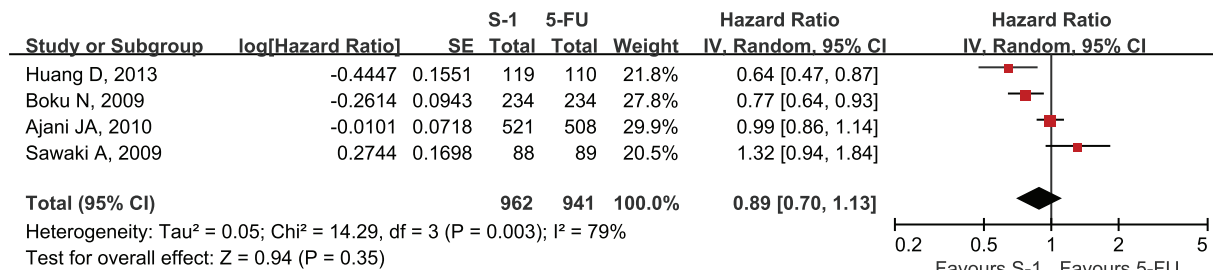0.2   0.5   1   2   5
Favours S-1   Favours 5-FU

Figure 5. Forest plot of progression-free survival associated with the S-1-containing chemotherapy compared with the 5-FU-containing chemotherapy.

neutropenia, thrombocytopenia, and gastrointestinal toxicities including nausea, vomiting, anorexia, diarrhea, constipation, and mucositis. Other relatively common toxicities were liver impairment (increased aminotransferases and bilirubin), renal impairment (increased creatinine and decreased calculated creatinine clearance), fatigue, infection, weight loss, and neuropathy.

3.2.1. Treatment-related deaths. Treatment-related deaths were reported in 4 studies.[11,13–15] The accumulated treatment-related mortality rate in Asian patients was 0.4% (2/473) in the S-1-containing group versus 0.2% (1/460) in the 5-FU-containing group, without significant difference (RD = 0.00, 95% CI [−0.01, 0.01], P = 0.68; Table 4); however, the mortality rate

Study or Subgroup	log[Hazard Ratio]	SE	S-1 Total	5-FU Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Jin M, 2008	-0.9859	0.2133	74	73	18.6%	0.37 [0.25, 0.57]	
Boku N, 2009	-0.3147	0.0916	234	234	28.4%	0.73 [0.61, 0.87]	
Ajani JA, 2010	-0.1393	0.0623	521	508	30.4%	0.87 [0.77, 0.98]	
Sawaki A, 2009	0.0513	0.1639	88	89	22.5%	1.05 [0.76, 1.45]	
Total (95% CI)			917	904	100.0%	0.74 [0.56, 0.97]	
Heterogeneity: Tau² = 0.06; Chi² = 18.36, df = 3 (P = 0.0004); I² = 84%							
Test for overall effect: Z = 2.15 (P = 0.03)							

0.2   0.5   1   2   5
Favours S-1   Favours 5-FU

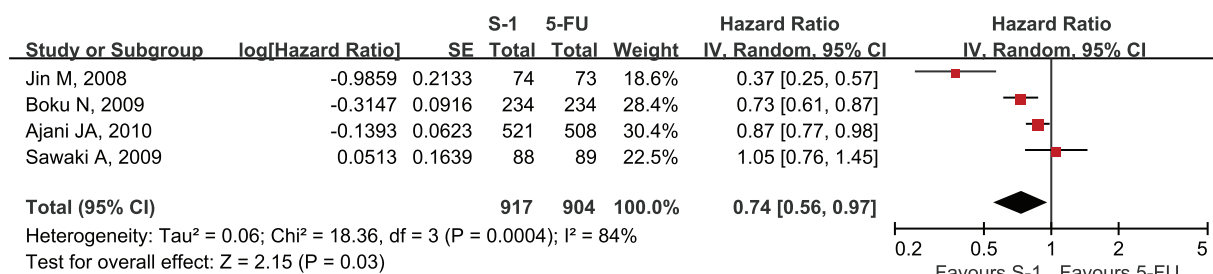**Figure 6.** Forest plot of time to treatment failure associated with the S-1-containing chemotherapy compared with the 5-FU-containing chemotherapy.

Objective response rate by region and regimen.

	Study counts	S-1-containing			5-FU-containing			Heterogeneity		Statistical method	Pooled effect	
		Events	Total	Incidence, %	Events	Total	Incidence, %	P	I², %		RR (95% CI)	P
Total	7	310	1016	30.5	239	978	24.4	<0.001	80	M-H, Random	1.36 [0.95, 1.96]	0.10
Regions												
Asia	6	193	614	31.4	116	593	19.6	0.002	73	M-H, Random	1.48 [1.00, 2.20]	0.05
Non-Asia	1	117	402	29.1	123	385	31.9	NA	NA	NA	0.91 [0.74, 1.13]	0.39
Regimens												
S-1 vs 5-FU	3	80	282	28.4	41	281	14.6	0.01	78	M-H, Random	1.62 [0.73, 3.60]	0.23
SP vs FP	3	172	596	28.9	162	574	28.2	0.04	70	M-H, Random	1.17 [0.76, 1.78]	0.48
SPtx vs FPtx	2	58	138	42.0	36	123	29.3	0.006	87	M-H, Random	1.05 [0.38, 2.95]	0.92

M-H = Mantel-Haenszel methods, NA = not available, RR = risk ratio.

in non-Asian patients was 2.5% (13/521) in the S-1-containing group versus 4.9% (25/508) in the 5-FU-containing group, which was a significant difference (RD = −0.02, 95% CI [−0.05, −0.00], P = 0.04; Table 4). Testing for subgroup differences was then performed, showing a significant difference in heterogeneity between Asian and non-Asian subgroups (P of heterogeneity = 0.04, I² = 76.5%).

3.3. Hematological toxicities

The profile of hematological toxicities was distinct between Asian and non-Asian trials (Table 4). Testing for subgroup differences demonstrated significant difference in heterogeneity between Asian and non-Asian subgroups. In Asian patients, there was a significant increase of hematological toxicities in S-1-containing

regimens such as leukopenia (grade 1–4: RR = 1.22, 95% CI [1.08, 1.37], P = 0.001; grade 3–4: RR = 2.21, 95% CI [1.52, 3.21], P < 0.0001), neutropenia (grade 1–4: RR = 1.29, 95% CI [1.11, 1.48], P = 0.0005; grade 3–4: RR = 1.87, 95% CI [1.11, 3.17], P = 0.02), and thrombocytopenia (grade 1–4: RR = 1.71, 95% CI [1.22, 2.41], P = 0.002). Conversely, in non-Asian patients, S-1-containing regimens were found to be associated with lower toxicities for leukopenia (grade 1–4: RR = 0.72, 95% CI [0.66, 0.79], P < 0.0001; grade 3–4: RR = 0.41, 95% CI [0.32, 0.53], P < 0.0001), neutropenia (grade 1–4: RR = 0.74, 95% CI [0.68, 0.80], P < 0.0001; grade 3–4: RR = 0.51, 95% CI [0.44, 0.59], P < 0.0001), febrile neutropenia (grade 1–4: RR = 0.28, 95% CI [0.14, 0.56], P = 0.0003; grade 3–4: RD = −0.05, 95% CI [−0.08, −0.03], P < 0.0001), and thrombocytopenia (grade 1–4: RR = 0.73, 95% CI [0.63, 0.84], P < 0.0001; grade 3–4:

Comparisons of treatment-related deaths and hematological toxicities between S-1-containing and 5-FU-containing regimens.

Toxicity (grade)		Study counts	S-1-containing			5-FU-containing			Heterogeneity		Statistical method	Pooled effect	
			Events	Total	Incidence, %	Events	Total	Incidence, %	P	I², %		RR/RD* [95% CI]	P
Treatment-related deaths													
	Asia	3	2	473	0.4	1	460	0.2	0.88	0	M-H, F	−0.01 [−0.01, 0.01]*	0.68
	Non-Asia	1	13	521	2.5%	25	508	4.9	NA	NA	NA	−0.02 [−0.05, −0.00]*	0.04
Hematological toxicities (1–4)													
Anemia	Asia	2	104	239	43.5	97	226	42.9	0.05	73	M-H, R	0.85 [0.39, 1.85]	0.67
	Non-Asia	1	421	521	80.8	393	508	77.4	NA	NA	NA	1.04 [0.98, 1.11]	0.18
Leukopenia	Asia	2	186	239	77.8	144	226	63.7	0.27	17	M-H, F	1.22 [1.08, 1.37]	0.001
	Non-Asia	1	284	521	54.5	383	508	75.4	NA	NA	NA	0.72 [0.66, 0.79]	<0.0001
Neutropenia	Asia	2	170	239	71.1	125	226	55.3	0.47	0	M-H, F	1.29 [1.11, 1.48]	0.0005
	Non-Asia	1	313	521	60.1	415	508	81.7	NA	NA	NA	0.74 [0.68, 0.80]	<0.0001
Febrile neutropenia	Asia	0	NR	NR	NR	NR	NR	NR	NA	NA	NA	NA	NA
	Non-Asia	1	10	521	1.9	35	508	6.9	NA	NA	NA	0.28 [0.14, 0.56]	0.0003
Thrombo-cytopenia	Asia	2	66	239	27.6	37	226	16.4	0.85	0	M-H, F	1.71 [1.22, 2.41]	0.002
	Non-Asia	1	190	521	36.5	254	508	50.0	NA	NA	NA	0.73 [0.63, 0.84]	<0.0001
Hematological toxicities (3–4)													
Anemia	Asia	5	94	629	14.9	67	609	11.0	0.02	65	M-H, R	1.48 [0.82, 2.66]	0.19
	Non-Asia	1	107	521	20.5	105	508	20.7	NA	NA	NA	0.99 [0.78, 1.26]	0.96
Leukopenia	Asia	5	80	629	12.7	34	609	5.6	0.20	34	M-H, F	2.21 [1.52, 3.21]	<0.0001
	Non-Asia	1	71	521	13.6	167	508	32.9	NA	NA	NA	0.41 [0.32, 0.53]	<0.0001
Neutropenia	Asia	5	136	629	21.6	64	609	10.5	0.01	69	M-H, R	1.87 [1.11, 3.17]	0.02
	Non-Asia	1	167	521	32.1	320	508	63.0	NA	NA	NA	0.51 [0.44, 0.59]	<0.0001
Febrile neutropenia	Asia	1	0	234	0	0	232	0	NA	NA	NA	0.00 [−0.01, 0.01]*	1.00
	Non-Asia	1	9	521	1.7	35	508	6.9	NA	NA	NA	−0.05 [−0.08, −0.03]*	<0.0001
Thrombo-cytopenia	Asia	4	29	395	7.3	16	377	4.2	0.07	57	M-H, F	1.75 [0.59, 5.15]	0.31
	Non-Asia	1	43	521	8.3	68	508	13.4	NA	NA	NA	0.62 [0.43, 0.89]	0.009

F = fixed effect, M-H = Mantel-Haenszel methods, NA = not available, NR = not reported, R = random effects, RR = risk ratio.
* RD, risk difference.

Table 5

Comparisons of nonhematological toxicities between S-1-containing and 5-FU-containing regimens.

Toxicity (grade)	Study counts	S-1-containing			5-FU-containing			Heterogeneity		Statistical method	Pooled effect	
		Events	Total	Incidence, %	Events	Total	Incidence, %	P	I^2, %		RR/RD* [95% CI]	P
GI toxicities												
Nausea (1–4)	3	419	760	55.1	471	734	64.2	0.03	72	M-H, R	0.80 [0.64, 1.00]	0.05
(3–4)	6	64	1150	5.6	81	1117	7.3	1.00	0	M-H, F	0.77 [0.56, 1.06]	0.11
Vomiting (1–4)	3	320	760	42.1	362	734	49.3	0.13	52	M-H, R	0.85 [0.67, 1.06]	0.15
(3–4)	5	53	916	5.8	70	885	7.9	0.81	0	M-H, F	0.74 [0.52, 1.04]	0.08
Anorexia (1–4)	3	252	760	33.1	265	734	36.1	1.00	0	M-H, F	0.92 [0.80, 1.05]	0.23
(3–4)	6	75	1150	6.5	73	1117	6.5	0.91	0	M-H, F	1.00 [0.74, 1.37]	0.98
Diarrhea (1–4)	2	178	640	27.8	217	618	35.1	0.18	44	M-H, F	0.79 [0.67, 0.94]	0.006
(3–4)	6	64	1150	5.5	34	1117	3.0	0.03	60	M-H, R	2.09 [0.85, 5.13]	0.11
Constipation (1–4)	1	9	119	7.6	17	110	15.5	NA	NA	NA	0.49 [0.23, 1.05]	0.07
(3–4)	3	0	315	0	2	300	0.7	0.69	0	M-H, F	−0.01 [−0.02, 0.01]*	0.36
Mucositis (1–4)	1	53	521	10.1	306	508	60.2	NA	NA	NA	0.17 [0.13, 0.22]	<0.0001
(3–4)	4	17	955	1.8	121	933	13.0	0.03	66	M-H, R	0.28 [0.08, 0.98]	0.05
Liver impairment (3–4)												
Aminotransferases	4	37	954	3.9	38	927	4.1	0.94	0	M-H, F	0.95 [0.61, 1.48]	0.83
Bilirubin	3	101	835	12.1	47	817	5.8	0.67	0	M-H, F	2.10 [1.51, 2.92]	<0.0001
Renal impairment (3–4)												
Creatinine	2	29	755	3.8	47	740	6.4	0.16	49	M-H, F	0.61 [0.39, 0.95]	0.03
Calculated CrCl	1	118	521	22.6	208	508	40.9	NA	NA	NA	0.55 [0.46, 0.67]	<0.0001
Fatigue (3–4)	5	78	1074	7.3	71	1043	6.8	0.33	14	M-H, F	0.00 [−0.02, 0.03]*	0.65
Infection (3–4)	2	30	755	4.0	51	740	6.9	0.005	87	M-H, R	0.73 [0.18, 2.96]	0.66
Weight loss (3–4)	3	21	721	2.9	33	701	4.7	0.09	58	M-H, R	−0.01 [−0.04, 0.01]*	0.31
Neuropathy (3–4)	3	5	433	1.2	2	419	0.5	0.70	0	M-H, F	0.01 [−0.01, 0.02]*	0.33

CrCl = creatinine clearance, F = fixed effect, M-H = Mantel-Haenszel methods, NA = not available, R = random effects, RR = risk ratio.
* RD, risk difference.

RR = 0.62, 95% CI [0.43, 0.89], P = 0.009). However, no significant difference in anemia was found in both subgroups.

3.4. Gastrointestinal toxicities

With regard to nonhematological toxicities, there was no significant heterogeneity between Asian and non-Asian subgroups. Gastrointestinal toxicities were frequent in both groups (Table 5). The incidence of nausea, vomiting, anorexia, diarrhea, and constipation demonstrated no significant differences between groups except that S-1-containing regimens were associated with a significantly decreased incidence of grade 1–4 nausea (RR = 0.80, 95% CI [0.64, 1.00], P = 0.05) and grade 1–4 diarrhea (RR = 0.79, 95% CI [0.67, 0.94], P = 0.006) (Table 4). Of note, S-1-containing regimens were associated with less frequent and less severe mucositis (stomatitis and/or mucosal inflammation), with an incidence of grade 1–4 mucositis of 10.1% versus 60.2% with 5-FU-containing regimens (RR = 0.17, 95% CI [0.13, 0.22], P < 0.001), and grade 3–4 of 1.9% versus 14.7%, respectively (RR = 0.23, 95% CI [0.06, 0.88], P = 0.03).

3.4.1. Other toxicities.
Liver impairment (increased bilirubin) was significantly more frequent in S-1-containing than 5-FU-containing regimens (12.1% vs 5.8%, RR = 2.10, 95% CI [1.51, 2.92], P < 0.001). However, the incidence of renal impairment was significantly less frequent in S-1-containing regimens, with 3.8% of patients exhibiting increased creatinine versus 6.4% in 5-FU-containing regimens (RR = 0.61, 95% CI [0.39, 0.95], P = 0.03) and 22.6% of S-1 patients having decreased calculated creatinine clearance versus 40.9% in 5-FU (RR = 0.55, 95% CI [0.46, 0.67], P < 0.001). Some toxicities, including fatigue, infection, weight loss, and neuropathy, were reported infrequently and had similar incidence in both groups (Table 5).

3.5. Sensitivity analysis

Sensitivity analysis showed that the corresponding pooled HRs and ORs were not significantly altered when one study was removed at a time, suggesting stability of the results.

3.6. Publication bias

Begg funnel plot and Egger test were performed to assess the publication bias of the analyzed studies. The shapes of the Begg funnel plots did not reveal evidence of obvious asymmetry (P = 1.00 and 0.76 for OS and ORR, respectively; Fig. 7). Egger test was then used to provide statistical evidence of funnel plot symmetry. The results still suggested no evidence of publication bias (P = 0.91 and 0.20 for OS and ORR, respectively).

4. Discussion

Five meta-analyses were identified in the literature search.[6,7,18–20] The main characteristics and results of these analyses were compared with the present study in Table 6. Although 2 published meta-analyses showed the superiority of S-1-containing regimens compared with 5-FU-containing regimens in terms of OS, one contained duplicate material[6] and the other missed a trial which was included in the present analysis.[7] In the present study, the pooled data revealed no significant improvement in OS for S-1-containing regimens (HR = 0.91, 95% CI [0.83–1.01], P = 0.07). It seems difficult to draw firm data-driven conclusion as to survival benefit of S-1. The median OS of S-1 monotherapy was approximately 11 months and the addition of other cytotoxic drugs, such as cisplatin,[16,21] oxaliplatin,[22] paclitaxel,[23] docetaxel,[24,25] or irinotecan[26,27] to S-1, even prolonged median OS beyond 12 months. Several trials comparing these doublets with S-1 monotherapy were conducted
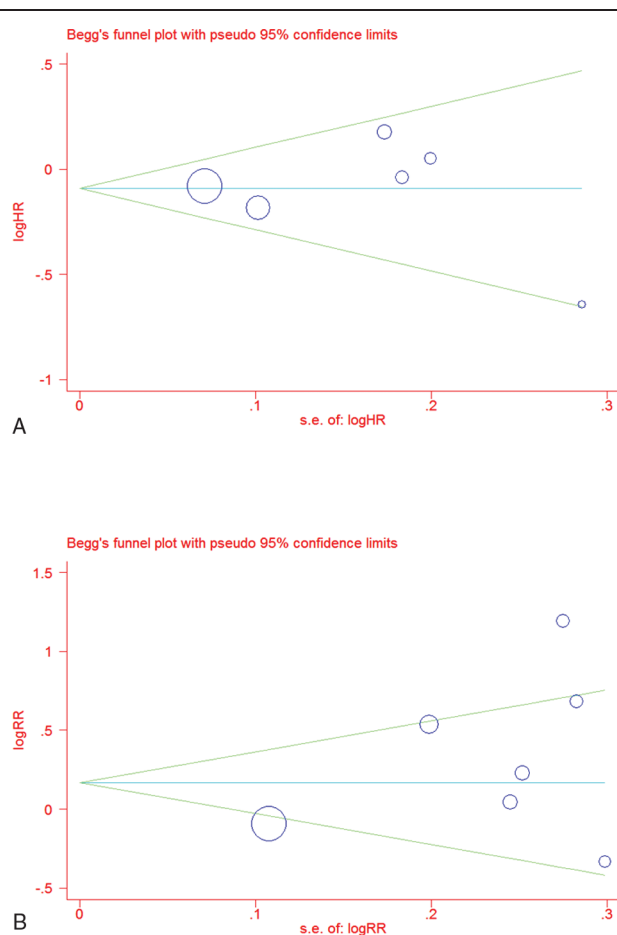
Figure 7. Begg funnel plot of publication bias test: (A) overall survival (OS) and (B) objective response rate (ORR). Each point represents a separate study for the indicated association; log = natural logarithm, s.e. = standard error.

and demonstrated that the doublets resulted in a longer OS than that resulting from S-1 monotherapy.[16,21,23,25] However, there are no data indicating which doublets are superior as first-line treatments for AGC.[28–30] Therefore, we suggest that the emphasis should be on further developing S-1 with different cytotoxic drugs and/or biologic agents to anticipate the prolongation of OS in patients with AGC.

Regarding endpoints based on tumor assessments, the pooled data showed that there were no significant differences in ORR and PFS between the 2 groups, whereas S-1-containing regimens were associated with much longer TTF than 5-FU-containing regimens. However, there was significant heterogeneity among trials; therefore, these results should be interpreted with caution. The subgroup meta-analyses showed that there was higher ORR in Asian patients with S-1-containing regimens than 5-FU-containing regimens, but no such difference was found in non-Asian patients. Different stage presentation may affect the efficacy; however, there was no obvious difference in the extent of disease between Asian and non-Asian patients. The profile of stage presentation was remarkably similar in all trials, that is, the majority (above 95%) of patients had metastatic disease and over two-thirds had more than one site of metastasis. In fact, according to the analyzed data in the present study (Tables 2 and 3), the efficacy of S-1 was closely comparable between Asian and non-Asian patients. The median OS was 8.6 months in non-Asian patients versus 8.3 to 15.2 months in Asian patients, PFS

4.8 months versus 3.5 to 5.0 months, TTF 3.8 months versus 2.8 to 5.2 months, ORR 29.1% versus 31.4%; nevertheless, the ORR of 5-FU-containing regimens was evidently high in non-Asian patients (31.9% vs 19.6%), which might be responsible for the difference.

With respect to safety profiles, S-1 monotherapy had a low incidence of grade 3–4 toxicities (usually <5% for each toxicity)[31]; however, the addition of other cytotoxic drugs significantly increased the incidence of grade 3–4 toxicities, which remained manageable.[16,21,23,25,27] It is noteworthy that there was significant heterogeneity in the incidence of treatment-related deaths and hematological toxicities between Asian and non-Asian patients. The reported treatment-related mortality was <1% in Asian patients, but was >2.5% in non-Asian patients. Treatment-related deaths were mainly caused by myelosuppression and infection.[11,13] Accordingly, the incidences of grade 3–4 leukopenia, neutropenia, and febrile neutropenia were markedly higher in non-Asian patients, especially in those assigned to 5-FU-containing regimens. Actually, according to the data from Table 4, the incidences of hematological toxicities for S-1-containing regimens were comparable between Asian and non-Asian patients; by contrast, the incidences for 5-FU-containing regimens were relatively low in Asian patients whereas remarkably high in non-Asian patients. As a result, the incidences of hematological toxicities in Asian patients were significantly higher in S-1-containing regimens than those in 5-FU-containing regimens. Conversely, the rates of hematological toxicities in non-Asian patients were significantly less frequent in S-1-containing regimens than 5-FU-containing regimens.

The reason for these differences is complicated and may be related to geographic region, dose, and schedule of cytotoxic drugs and gene polymorphism. A meta-analysis indicated that the Asian trials were associated with lower incidences of grade 3–4 neutropenia and febrile neutropenia, and concluded that geographic region was an independent predictor of safety in chemotherapy for gastric cancer.[32] The dose and schedule of cytotoxic drugs varied among studies due to the individual distinctions and practice culture in different regions. In every chemotherapy cycle, the daily dose of S-1 was usually $80\,mg/m^2$ in Asian patients versus $50\,mg/m^2$ in non-Asian patients; the total dose of 5-FU varied widely among studies, from $2500\,mg/m^2$ to $4000\,mg/m^2$ in Asian patients versus $5000\,mg/m^2$ in non-Asian patients. We observed that the non-Asian patients were administered noticeably lower single doses of S-1 but higher total doses of 5-FU. In addition, the total dose of cisplatin was lower, from $60\,mg/m^2$ to $80\,mg/m^2$ in S-1-containing arms versus $80\,mg/m^2$ to $100\,mg/m^2$ in 5-FU-containing arms; moreover, cisplatin was administered daily at a dose of $20\,mg/m^2/d$ intravenously over 4 to 5 days in Asian studies, whereas at the total dose was administered intravenously over 1 to 3 hours in non-Asian studies. However, the metabolic rate of conversion of tegafur to 5-FU differs in various ethnic populations,[33] Cytochrome P450 2A6 (CYP2A6) enzyme is now identified as the principal enzyme responsible for this conversion process.[34] The efficacy of CYP2A6 enzyme is higher in non-Asian patients than in Asian patients, which is attributed to different polymorphisms in the CYP2A6 gene.[35–37] Thus, the conversion rate of tegafur to 5-FU was faster in non-Asian patients, which would cause a lower dose of S-1 in non-Asian patients to achieve a comparable area under the curve of 5-FU with that in Asian patients and provide considerable improved safety without compromising efficacy. Taking all into consideration, the clinical heterogeneity of hematological toxicities between Asian and non-

Table 6

Comparisons of the main characteristics and results of the identified analyses with the present study.

Study	Huang et al (2011)[6]	Wu et al (2012)[18]	Cao et al (2014)[19]	Liu et al (2014)[20]	Li et al (2014)[7]	Present analysis
No. of trials	4	4	4	3	6	7
Abstract	3	1	2	0	2	2
Full text	1	3	2	3	4	5
No. of patients	2115	1263	1080 Asian patients	352	2264	2443
S-1 group	1065	641	547	182	1148	1236
5-Fu group	1050	622	533	170	1116	1207
Interventions	2 S-1 vs 5-Fu; 2 SP vs FP	4 SP vs FP	1 S-1 vs 5-Fu; 2 SP vs FP; 1 SPtx vs FPtx	3 SPtx vs FPtx	1 S-1 vs 5-Fu; 3 SP vs FP; 2 SPtx vs FPtx	2 S-1 vs 5-Fu; 3 SP vs FP; 2 SPtx vs FPtx
Efficacy measures						
OS	HR=0.87 [0.79–0.96], P=0.007; P_H=0.586, I^2=0.0%	NR	HR=0.87 [0.73–1.03], P=0.113; P_H=0.287, I^2=11.9%	—	HR=0.80 [0.80–0.99], P=0.03; P_H=0.28, I^2=21%	HR=0.91 [0.83–1.01], P=0.07; P_H=0.18, I^2=34%
PFS	NR	NR	HR=0.73 [0.62–0.86], P<0.001; P_H=0.313, I^2=1.6%	—	NR	HR=0.89 [0.70–1.13], P=0.35; P_H=0.003, I^2=79%
TTF	NR	NR	NR	—	HR=0.73 [0.53–1.00], P=0.05; P_H=0.0004, I^2=84%	HR=0.74 [0.56–0.97], P=0.03; P_H=0.0004, I^2=84%
ORR	OR=1.25 [0.31–5.09], P=0.754; P_H=0.001, I^2=90.5%	OR=1.58 [0.76–3.29], P=0.22; P_H=0.03, I^2=66%	OR=2.31 [1.29–4.13], P=0.005; P_H=0.020, I^2=69.5%	RR=1.08 [0.53–2.19], P=0.84; P_H=0.02, I^2=76%	OR=1.55 [0.87–2.77], P=0.14; P_H<0.0001, I^2=83%	RR=1.36 [0.95, 1.96], P=0.10; P_H<0.001, I^2=80%
Safety profiles						
Treatment-related deaths	OR=1.84 [0.95–3.54], P=0.068; P_H=0.279, I^2=14.6%	NR	OR=1.15 [0.39–3.45], P=0.798	—	NR	Asian: RD=0.00 [−0.01, 0.01], P=0.68; non-Asian: RD=−0.02 [−0.05, −0.00], P=0.04; P_{SD}=0.04, I^2=76.5%
Hematological	Less in S-1 group: grade 3–4 neutropenia (OR=0.33 [0.25–0.44]	Less in S-1 group: grade 3–4 thrombocytopenia (OR=0.58 [0.40–0.85], P=0.004)	More in S-1 group: grade 3–4 thrombocytopenia (OR=2.30 [1.40–3.77], P=0.001)	Equivalent	Less in S-1 group: grade 3–4 thrombocytopenia (OR=0.60 [0.42–0.88], P=0.008)	Significant difference in heterogeneity between Asian and non-Asian subgroups
Gastrointestinal	Equivalent	Less in S-1 group: grade 3–4 nausea/vomiting (OR=0.70 [0.52–0.95], P=0.02)	More in S-1 group: grade 3–4 diarrhea (OR=3.18 [1.54–6.57], P=0.002); less in S-1 group: grade 3–4 nausea (OR=0.69 [0.48–1.00], P=0.049)	Less in S-1 group: grade 1–4 nausea (RR=0.60 [0.43–0.82], P=0.001) and vomiting (RR=0.55 [0.33–0.91], P=0.02)	Less in S-1 group: grade 3–4 stomatitis (OR=0.22 [0.05–0.9], P=0.03)	Less in S-1 group: grade 1–4 nausea, diarrhea, mucositis

—=cannot be calculated, FP=fluorouracil (5-FU) plus DDP, FPtx=5-FU plus PTX, NR=not reported, ORR=objective response rate, OS=overall survival, PFS=progression-free survival, P_H=P of heterogeneity, P_{SD}=P of subgroup differences, SP=S-1 plus cisplatin (DDP), SPtx=S-1 plus paclitaxel (PTX), TTF=time to treatment failure.

Asian patients would be mainly attributed to higher doses of 5-FU and cisplatin in 5-FU-containing regimens.

With respect to the nonhematological toxicities, S-1-containing regimens significantly reduced the frequency and severity of mucositis compared with 5-FU-containing regimens. A grade 3–4 increase in total bilirubin was the only notable nonhematological toxicity observed more frequently in S-1-containing regimens. However, there were no differences with respect to grade 3–4 elevations in aminotransferases (ALT/AST) or reports of death due to drug-related hepatic toxicity, indicating that there was no evidence of direct hepatotoxicity by S-1.[31,38] Ajani et al acknowledged that the significantly lower rate of renal function abnormalities, such as elevated serum creatinine and impairment of renal clearance in the cisplatin/S-1 arm, could be attributed to lower cisplatin dose (75 mg/m^2) than in the cisplatin/infusional fluorouracil arm (100 mg/m^2).[13]

Although the data on QOL and cost-effectiveness analysis were limited, S-1-containing regimens seemed to be associated with longer nonhospitalized survival, fewer hospitalizations for drug administration, and lower monetary costs. One abstracts mentioned QOL as secondary endpoints, but no detailed data were reported.[17] Because infusional chemotherapy is commonly performed with hospitalization, we would presume that the nonhospitalized survival reflects a patient's benefit from a QOL point of view.[5] Boku et al reported that S-1 was associated with longer nonhospitalized survival compared with 5-FU (9.3 [interquartile range 4.2–18.0] vs 7.2 [2.7–13.3] months, HR = 0.77, 95% CI [0.63–0.92], $P = 0.0025$).[14] Moreover, Ajani et al reported that the total number of hospitalizations and percentage of patients hospitalized were lower and the median number of days hospitalized was shorter in S-1-containing arm.[38] In addition to efficacy and safety concerns, expenditure on chemotherapy drugs has recently become a main concern. Unfortunately, few trials compared S-1 with 5-FU from an economic point of view. Only Boku et al offered some information in their discussion section, reporting that in Japan, the cost of S-1 was cheaper than that of 5-FU.[14]

Some limitations should be considered when interpreting the data presented here. First, 2 included studies were abstracts from international conferences with insufficient data on methodological and patient characteristics. In addition, many important estimates, such as PFS, TTF, TTP, and some AEs, were not reported in many of the studies analyzed. These omissions might potentially limit detection of difference. Furthermore, heterogeneity problems were frequently found among the included studies and subgroups, which may have influenced our results. Therefore, we chose to use the random-effects model as well as subgroup analysis to calculate the estimates and explain the causes of heterogeneity, such as differences in geographic region, dose, and schedule of cytotoxic drugs. In addition, most of the studies included were performed in Asia, with only one non-Asian study. We noticed significant differences in efficacy and safety profiles, such as median OS, treatment-related mortality, and incidence of hematological toxicities. However, future studies are needed to determine the mechanism underlying this phenomenon.

In conclusion, S-1-containing regimens could not improve survival outcomes, but increase some hematological toxicities in Asian patients, compared with 5-FU-containing regimens. Therefore, special attention on hematological toxicities should be paid to Asian patients because S-1 is administered on an outpatient basis. Moreover, whether S-1 could provide advantages in terms of QOL and monetary costs needs to be clarified by further trials.

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