reported testing sorafenib in combination with capecitabine and cisplatin as a first-line treatment in patients with advanced gastric cancer [14]. In addition, sorafenib in combination with docetaxel and cisplatin was tested for metastatic or advanced gastric cancer in a phase II trial (ECOG 5203) and demonstrated an encouraging efficacy profile with a median overall survival of 13.6 months [9]. These studies and our present trial support the use of sorafenib in combination with other chemotherapeutic agents against advanced gastric cancer.

Table 10 Pharmacokinetics parameters of cisplatin (CDDP) on day 8 CDDP

CDDP		Total platinum	Free platinum
C_{max}	*n*	13	13
	mg/l	3.065 (14.5)	1.246 (15.8)
AUC_{0-tn}	*n*	13	12
	mg·h/l	152.282 (14.8)	4.472 (39.6)
t_{max}	*n*	13	13
	h	1.98 (1.93–2.32)	1.98 (1.93–2.32)

Geometric mean (% coefficient of variation)

t_{max} is given as median (range)

The most common adverse events observed in this study were anorexia, rash/desquamation, neutropenia, thrombocytopenia, hand-foot reaction, nausea, leukopenia, fatigue, and elevation of lipase. All these adverse events were already reported in the SPIRITS trial (S-1 plus CDDP regimen for gastric cancer) or the TARGET study (sorafenib monotherapy for renal cell carcinoma). There was no specific or serious adverse event newly reported in this study, suggesting that the combination of the three drugs may cause no serious drug interaction. In terms of elevation of lipase, this was reported in TARGET study [15] as one of the most common laboratory abnormalities

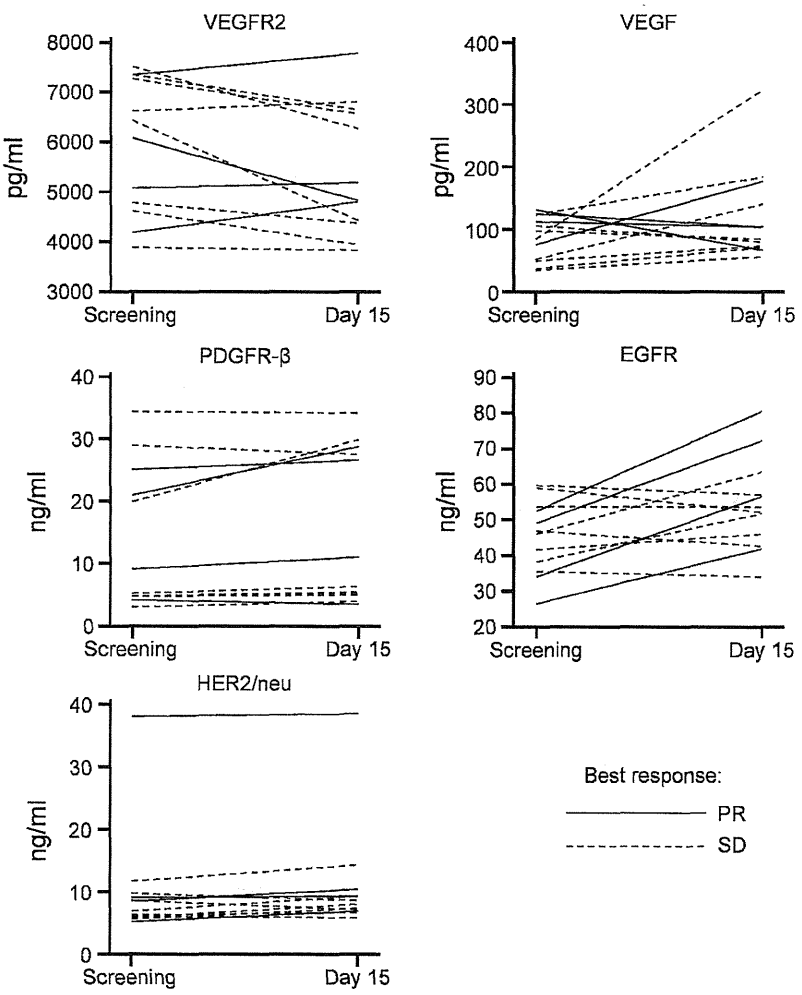

Fig. 5 Changes in plasma concentrations of various biomarkers [before treatment (screening) and on day 15]. *VEGFR2* vascular endothelial growth factor receptor-2, *PDGFR* platelet-derived growth factor receptor, *EGFR* epidermal growth factor receptor

Table 11 Summary of immunohistochemical staining (percent positive)

Patient ID	BR	Treatment	VEGFR-2	*H* score					
			% Positive	AKT	pAKT (clone D9E)	pAKT (clone 14-5)	ERK	pERK (clone MAPK-YT)	pERK (clone D13.14.4E)
20001-1008	PR	Screening	20.22	5	0	23	0	10	5
		End of C2				30			
20003-1003	SD	Screening		1	100	72	265	1	1
		End of C2	15.49	20	10	33	130	10	21

Blank spaces indicate that no tumor was present and the percentage could not be evaluated

BR best response

Table 12 Gene ontology classification of the top ten probes

affy_id	Gene symbol	Gene name	Direction	Indicative GO classification (component)	Indicative GO classification (function)
213953_at	KRT20	Keratin 20	Down	Cytoskeleton part Intermediate filament cytoskeleton	Structural constituent of cytoskeleton
217564_s_at	CPS1	Carbamoyl-phosphate synthase 1, mitochondrial	Down	Mitochondrial part Mitochondrial inner membrane	Amino acid binding Glutamate binding
209816_at	PTCH1	Patched 1	Down	Plasma membrane Integral to plasma membrane	Transmembrane receptor activity Signal transducer activity
243018_at		Unidentified	Down	Not annotated	Not annotated
232315_at	ZNF880	Zinc finger protein 880	Up	Intracellular	Zinc ion binding Nucleic acid binding
213843_x_at	AC133561.1	Solute carrier family 6 (neurotransmitter transporter, creatine), member 8	Down	Not annotated	Not annotated
37892_at	COL11A1	Collagen, type XI, alpha 1	Down	Extracellular region part Extracellular matrix part Collagen	Extracellular matrix structural constituent Structural molecule activity
206828_at	TXK	TXK tyrosine kinase	Up	Cell part	Protein tyrosine kinase activity
234973_at	SLC38A5	Solute carrier family 38, member 5	Up	Integral to membrane Plasma membrane	Active transmembrane transport activity Amino acid transmembrane transport activity
214712_at		Unidentified	Up	Not annotated	Not annotated

of grade 3 or 4. Thus, toxicity observed in this study was consistent with the known side effects of S-1 plus CDDP combination therapy and sorafenib monotherapy. The frequency of common adverse events, however, tended to be higher in the present study than that in the SPIRITS trial and TARGET study.

In the present study, preliminary evaluations showed an encouraging efficacy profile, although the sample size of this study was small. Overall, 5 patients (38.5 %) showed partial response (PR) and the remaining 8 (61.5 %) showed stable disease (SD) whereas none of the patients showed progressive disease (PD). The ratio of PR in this study was lower than the SPIRITS trial [2]; however, the number of patients was relatively small for PK evaluation in the combination treatment, so it might be hard to compare this result with other studies and to obtain conclusions. It is noteworthy that all 12 patients having a target lesion for evaluation showed reduction of the target lesion after study treatment.

The median RDI of sorafenib (50.0 %) was relatively lower than those of S-1 (89.3 %) and CDDP (92.0 %), and in median RDI from cycles 1 to 4, RDI of sorafenib was decreasing gradually, whereas on the other hand those of S-1 and CDDP were sustained more than 80 %. One of the causes for this was the different dose reduction between these drugs (50 % reduction for sorafenib versus 20 % for S-1 and 25 % for CDDP at level 1). In terms of adverse events that eventually led to discontinuation permanently, namely, diarrhea, elevation of transaminase, myelosuppression, and skin toxicities (e.g., hand-foot skin reaction and rash), care should be taken.

In the present study, because of the negative results of the FLAGS study, a one-dose regimen based on the SPIRITS study was administered. In the future, therefore, considering these points such as dose reduction criteria in the protocol and adverse events that caused discontinuation in this study, efficacy should be confirmed in large-scale cohort studies using the combination regimen in this study.

The plasma concentration of 5-FU peaked at 4 h and gradually decreased thereafter both in patients who received S-1 alone (day 1) and in those who received the combination of three drugs (day 8) (Fig. 4). Geometric means of plasma 5-FU concentrations were slightly higher when 5-FU was administered in combination with two other drugs (day 8) than that when administered alone (day 1). In addition, mean ratios (day 8/day 1) of C_{max} and AUC_{0-tn} of 5-FU were 1.64 and 1.56, respectively, in 13 patients in whom these measurements were obtained on both day 1 and day 8 (Table 6).

In a previous pharmacokinetic study [16], the day 5/day 1 ratio of C_{max} and AUC_{0-10} of 5-FU when S-1 was administered alone for 5 days was 1.60 (230/144 ng ml^{-1}) and 1.59 (1364/857 ng h ml^{-1}), respectively. This finding suggested that plasma 5-FU concentration increased to day 2 and achieved steady state after multiple administration of S-1. The observed ratios (day 5/day 1) in that study were similar to those (day 8/day 1) in our present study.

In our study, the influence of accumulation by repeated administration of S-1 cannot be ruled out as a cause of increased 5-FU exposures on day 8.

Among the biomarkers tested in this study, plasma concentration of EGFR tended to increase more during treatment in patients showing PR than in those showing SD, although there was no difference in baseline plasma EGFR level between patients grouped by best response. Although the sample size here was small, it is interesting to speculate as to possible mechanisms of this phenomenon whose clinical relevance remains unknown. The ectodomain (ECD) of EGFR is detected in serum from patients with gastric cancer [17] and is thought to be shed from the cell surface via proteolytic cleavage and released into circulation. An in vitro study suggested that a disintegrin and metalloproteinase (ADAM) is involved in proteolytic release of ECD of EGFR [18]. Interestingly, it is also reported that colorectal cancer tumors responded to 5-FU treatment by activating ADAM17, which resulted in increased shedding of a EGFR ligand such as transforming growth factor (TGF)-α [19]. Simultaneous monitoring of soluble EGFR and its ligands such as EGF and TGF-α in plasma could provide further insights into clinical implication of change in plasma EGFR after chemotherapy treatment including 5-FU.

Results of histological and gene expression analysis should be interpreted cautiously because matched samples with tumors both before and after treatment were available only in limited patients. Although the samples for IHC analysis and gene expression analysis were collected during gastroscopy and therefore with visual inspection of the sampling sites, the fraction of tumor material was variable and about half of the samples for IHC analysis were found to consist of only normal gastric epithelium. Thus, differences detected between the pre- and post-treatment samples in gene expression analysis may also reflect differences between normal and tumor tissue as well as effects of therapy. Despite these caveats, the results from the GO classification seem to show a general trend in that the major expression changes were seen in genes required for maintaining tissue integrity and gastric epithelial function, rather than effects on genes involved in tumor pathogenesis.

In conclusion, the present phase I study demonstrates the acceptable toxicity and preliminary efficacy of combined treatment with S-1, CDDP, and sorafenib. Pharmacokinetic results suggested that combination of S-1 and CDDP did not affect the PK of sorafenib. It is important to further investigate the mechanism underlying the efficacy of this combination therapy in a large-scale cohort study in the future.

Acknowledgments This study was funded by Bayer Yakuhin Ltd., Osaka, Japan. Hironobu Minami has received honoraria from Bayer Yakuhin Ltd., Osaka, Japan. Kensei Hashizume, Yoshihiro Kuroki, and Yuichiro Ito are employees of Bayer Yakuhin Ltd., Osaka, Japan. The other authors have no disclosures.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
2. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
3. Jin M, Lu H, Li J, et al. Randomized 3-armed phase III study of S-1 monotherapy versus S-1/CDDP (SP) versus 5-FU/CDDP (FP) in patients (patients) with advanced gastric cancer (AGC): SC-101 study. J Clin Oncol 2008;26:15s(supple;abstr4533)
4. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004;64:7099–109.

5. Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer. 2003;3:11–22.
6. McCubrey JA, Steelman LS, Chappell WH, et al. Roles of the Raf/MEK/ERK pathway in cell growth, malignant transformation and drug resistance. Biochim Biophys Acta. 2007;1773:1263–84.
7. Boku N, Ohtsu A, Nagashima F, Shirao K, Koizumi W. Relationship between expression of vascular endothelial growth factor in tumor tissue from gastric cancers and chemotherapy effects: comparison between S-1 alone and the combination of S-1 plus CDDP. Jpn J Clin Oncol. 2007;37:509–14.
8. Lieto E, Ferraraccio F, Orditura M, et al. Expression of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) is an independent prognostic indicator of worse outcome in gastric cancer patients. Ann Surg Oncol. 2008;15:69–79.
9. Sun W, Powell M, O'Dwyer PJ, Catalano P, Ansari RH, Benson AB 3rd. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. J Clin Oncol. 2010;28:2947–51.
10. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28:1547–53.
11. Kloft C, Appelius H, Siegert W, Schunack W, Jaehde U. Determination of platinum complexes in clinical samples by a rapid flameless atomic absorption spectrometry assay. Ther Drug Monit. 1999;21:631–7.
12. Gentleman RC, Carey VJ, Bates DM, et al. Bioconductor: open software development for computational biology and bioinformatics. Genome Biol. 2004;5:R80.
13. Boyle EI, Weng S, Gollub J, et al. GO: TermFinder—open source software for accessing gene ontology information and finding significantly enriched gene ontology terms associated with a list of genes. Bioinformatics (Oxford, England). 2004;20:3710–5.
14. Kim C, Lee JL, Choi YH, et al. Phase I dose-finding study of sorafenib in combination with capecitabine and cisplatin as a first-line treatment in patients with advanced gastric cancer. Invest New Drugs. 2012;30:306–15.
15. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125–34.
16. Yamada Y, Hamaguchi T, Goto M, et al. Plasma concentrations of 5-fluorouracil and F-beta-alanine following oral administration of S-1, a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, as compared with protracted venous infusion of 5-fluorouracil. Br J Cancer. 2003;89:816–20.
17. Choi JH, Oh JY, Ryu SK, et al. Detection of epidermal growth factor receptor in the serum of gastric carcinoma patients. Cancer (Phila). 1997;79:1879–83.
18. Sanderson MP, Keller S, Alonso A, Riedle S, Dempsey PJ, Altevogt P. Generation of novel, secreted epidermal growth factor receptor (EGFR/ErbB1) isoforms via metalloprotease-dependent ectodomain shedding and exosome secretion. J Cell Biochem. 2008;103:1783–97.
19. Kyula JN, Van Schaeybroeck S, Doherty J, Fenning CS, Longley DB, Johnston PG. Chemotherapy-induced activation of ADAM-17: a novel mechanism of drug resistance in colorectal cancer. Clin Cancer Res. 2010;16:3378–89.

Gastrointestinal Cancer

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Determination of Prognostic Factors in Japanese Patients With Advanced Gastric Cancer Using the Data From a Randomized Controlled Trial, Japan Clinical Oncology Group 9912

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Prognostic index • Prognostic factor • Advanced gastric cancer • Chemotherapy

ABSTRACT

Background. In advanced gastric cancer (AGC), no globally accepted prognostic scoring system has been developed. Therefore, we explored baseline prognostic factors in Japanese AGC patients using the data from a randomized controlled trial, Japan Clinical Oncology Group (JCOG) 9912, which investigated the efficacy of systemic chemotherapy as a first-line treatment.

Patients and Methods. Prognostic factors and prognostic indices for overall survival were screened and evaluated in patients enrolled in JCOG9912 using the Cox proportional hazard model. The Royal Marsden Hospital prognostic model was also applied to the JCOG9912 trial.

Results. A total of 650 (92.3%) of the 704 patients randomized in the JCOG9912 trial, for whom complete data were available for multivariate analyses, was included in the present study (5-fluorouracil arm, $n = 215$; irinotecan plus cisplatin arm, $n = 216$; S-1 arm, $n = 219$). The median survival time (MST) for all patients was 11.8 months. To construct a prognostic index, we selected four risk factors by multivariate analysis: performance status ≥ 1, number of metastatic sites ≥ 2, no prior gastrectomy, and elevated alkaline phosphatase. MSTs were 17.0 months for patients categorized into the low-risk group, who had zero or one risk factor ($n = 225$); 10.4 months for patients in the moderate-risk group, who had two or three risk factors ($n = 368$); and 5.0 months for patients in the high-risk group, who had all four risk factors ($n = 57$).

Conclusion. In the present study, we propose a new prognostic index for patients with AGC. This can be used for more appropriate patient stratification in future clinical trials. ***The Oncologist*** 2014;19:1–9

Implications for Practice: Prognostic indices are useful not only to estimate the prognosis of each patient but are also applicable for stratification of patients for clinical trials. By using patient data from the Japan Clinical Oncology Group (JCOG) 9912 trial, we explored baseline prognostic factors and prognostic index. In the results, a novel prognostic index consisting of four risk factors (performance status ≥1, metastatic sites ≥2, no prior gastrectomy, and elevated ALP), which can classify patients into three risk groups, is proposed. This index can be used for more accurate patient stratification in future clinical trials.

INTRODUCTION

Despite a steady decrease in the mortality rate of gastric cancer (GC) in recent years, GC remains a major health problem, causing approximately 738,000 deaths worldwide in 2008 [1]. For advanced gastric cancer (AGC) patients, the primary treatment is systemic chemotherapy, which improves survival and quality of life [2, 3]. Whereas fluoropyrimidine plus

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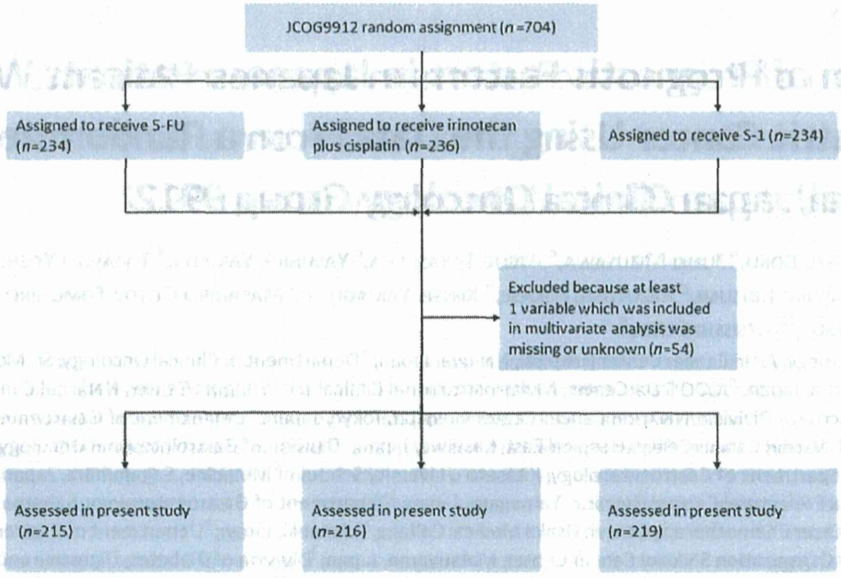


Figure 1. CONSORT diagram.
Abbreviations: 5-FU, 5-fluorouracil; JCOG, Japan Clinical Oncology Group.

platinum has been regarded as the standard first-line chemotherapy for AGC worldwide, there are some regional variations in chemotherapy regimens. The most popular chemotherapy is epirubicin plus cisplatin plus 5-fluorouracil (5-FU) or epirubicin plus oxaliplatin plus capecitabine [4] in the U.K., docetaxel plus cisplatin plus 5-FU (DCF) [5] or 5-FU, leukovorin, and oxaliplatin (FOLFOX) in Europe, cisplatin plus 5-FU or DCF in the U.S., and S-1 plus cisplatin in Japan [6].

Recently, new drugs have been developed globally, and a multinational phase III trial named AVAGAST has been conducted [7] to evaluate the efficacy of adding bevacizumab to capecitabine plus cisplatin as a first-line chemotherapy for AGC. In this trial, substantial differences in the prognosis of AGC patients from Western and Asian countries, especially Japan, were observed. These results suggest some interaction between treatment effects and regions. However, before investigating the reasons for regional differences, it is first necessary to identify common prognostic factors between Asian and Western populations and to compare them after adjusting for the patients' backgrounds.

Prognostic indices are now available for several cancer types, including non-Hodgkin lymphoma [8], multiple myeloma [9], breast cancer [10], prostate cancer [11], renal cancer [12], and colorectal cancer [13]. In several cancers, such as non-Hodgkin lymphoma and renal cancer, prognostic indices are not only useful to estimate the prognosis of each patient but also are applicable for determination of the optimal treatment strategy and stratification of patients for clinical trials. In AGC, a prognostic index based on clinical trials conducted in the 1990s was proposed by Royal Marsden Hospital (RMH) in 2004; this index consists of four independent risk factors for survival: Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\geq$ 2, liver metastasis, peritoneal metastasis, and serum alkaline phosphatase (ALP) $\geq$ 100 μ/L [14]. To formulate this index, patients were classified into three groups by the number of risk factors: low risk (no risk factors), moderate risk (one or two risk factors), and high risk (three or four risk factors), resulting in significant survival differences across the groups. However, the RMH index was developed using only data from Western patients, and 30% of the patients had esophageal cancer. In Asia, a few reports have investigated the prognostic factors and indices in Korean populations [15–17]; however, all of these studies were based on retrospective data. From Japan, prognostic factors based on clinical trials conducted in the 1990s have been reported [18]. However, recent clinical trials have been conducted globally, and regional differences, such subsequent chemotherapy, are recognized as a substantial problem. Recently, active new agents for gastric cancer have contributed to the prognosis not only in the first-line but also in the subsequent lines. Thus, new prognostic scoring systems for AGC, including Asian patients, should be proposed.

Japan Clinical Oncology Group (JCOG) 9912 was a large randomized trial investigating the superiority of irinotecan plus cisplatin (IP) and the noninferiority of oral S-1 compared with continuous infusion of 5-FU for patients with metastatic or recurrent gastric cancer [19]. In this trial, it was demonstrated that S-1 was not inferior to 5-FU (hazard ratio [HR]: 0.83 [95% confidence interval (CI): 0.68–1.01]; $p = .0005$ for noninferiority) in terms of overall survival (OS), but IP was also not superior (HR: 0.85 [95% CI: 0.70–1.04]; $p = .0552$ for superiority).

In the present study, we first investigated whether the RMH index could be applicable to Japanese patients with AGC. Next, we tried to establish a new prognostic index in AGC using the data from JCOG9912.

Patients and Methods

Between 2000 and 2006, 704 patients were enrolled in JCOG9912, which was registered with ClinicalTrials.gov, number NCT00142350. The details of the inclusion/exclusion criteria and treatment regimen for patients enrolled in JCOG9912 were published previously [19]. The patients analyzed in the present study were those having complete data available for multivariate analyses using the Cox proportional hazard model. Metastatic sites were reported by each investigator according to the

Table 1. Patient characteristics

Characteristics		5-FU ci	Irinotecan + cisplatin	S-1	Total
No. of patients		215	216	219	650
Median age, years (range)		63 (24–75)	63 (32–75)	64 (39–75)	64 (24–75)
Age	<65	112	120	110	342
	>65	103	96	109	308
Sex	Male	158	165	162	485
	Female	57	51	57	165
ECOG PS	0	140	137	140	417
	1	73	76	76	225
	2	2	3	3	8
No. of metastatic sites	0, 1	94	94	95	283
	≥2	121	122	124	367
Target lesion	No	52	52	54	158
	Yes	163	164	165	492
Gastrectomy	No	151	148	150	449
	Yes	64	68	69	201
Disease status	Unresectable	177	173	177	527
	Recurrent	38	43	42	123
Macroscopic type	0, 1, 2	62	76	68	206
	3, 4, 5	153	140	151	444
Histologic type	Intestinal	103	91	103	297
	Diffuse	112	125	116	353
Peritoneal metastasis	No	134	146	157	437
	Yes	81	70	62	213
Liver metastasis	No	112	113	117	342
	Yes	103	103	102	308
Lung metastasis	No	202	220	200	602
	Yes	13	16	19	48
Bone metastasis	No	204	209	210	629
	Yes	11	7	9	31

Abbreviations: ci, continuous infusion; ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil; PS, performance status.

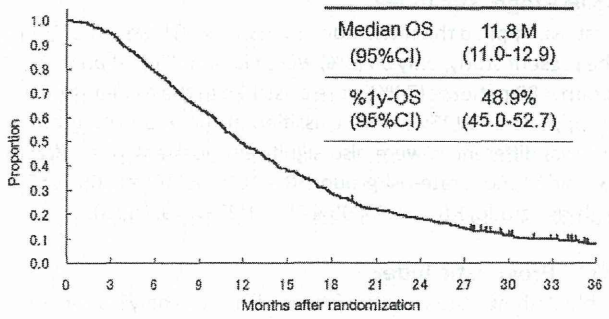


Figure 2. Survival curve of the 650 patients with complete data for baseline factors and laboratory tests for the multivariate analysis.

Abbreviations: %1y-OS, 1 year overall survival; CI, confidence interval; OS, overall survival.

Response Evaluation Criteria in Solid Tumors version 1.0, specifying all target and nontarget lesions in the case report form of each enrolled patient, in which the investigator checked prospectively the presence or absence of the metastatic sites, such as cervical, mediastinal, abdominal and superficial lymph nodes, lung, liver, peritoneum, ovary, adrenal gland, bone, skin, and others listed. For the total number of metastatic sites of each patient, each organ was counted separately; all lymph node metastases, regardless the regions, were counted as one site.

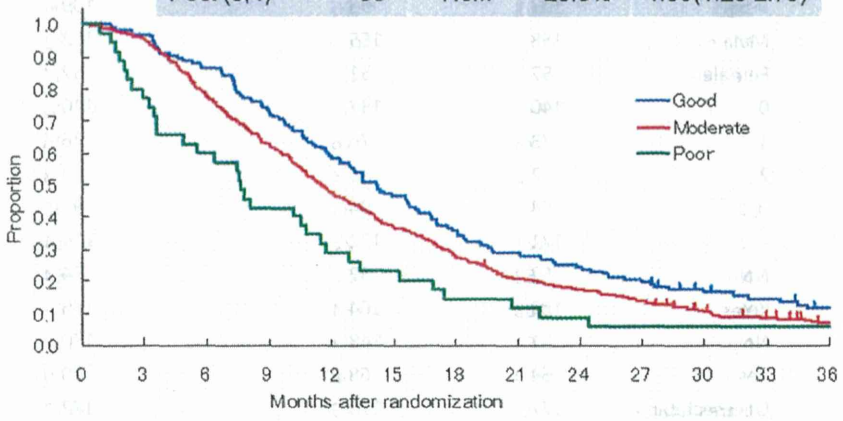
Statistical Analysis

OS was measured from the date of randomization to the date of death and censored at the date of last contact for a surviving patient.

To investigate whether the RMH index could be applicable to Japanese patients with AGC, regression analysis was performed using the Cox proportional hazard model, including the same factors as those proposed by the RMH index.

An exploration of the potential prognostic index model was carried out within the model, including four factors. The number of factors was determined by taking into account the applicability of the results to clinical practice and to avoid an over-fit model. To construct a prognostic index, we performed multivariate analysis with the Cox proportional hazard model by using PROC PHREG in SAS 9.1 (SAS Institute, Cary, NC, http://www.sas.com) and selected five models based on their score χ^2 values from all possible models, which included four factors

	n	MST	%1-year	HR(95%CI)
Good (0)	132	14.2M	59.1%	1
Moderate (1,2)	483	11.5M	47.6%	1.28(1.05-1.57)
Poor (3,4)	35	7.6M	28.6%	1.90(1.29-2.79)



H_0: $S_G(t) = S_M(t) = S_P(t)$

p for log-rank test = .0025, two-sided

Figure 3. *Survival curves of the three groups in the present study classified according to the Royal Marsden Hospital prognostic index.* Good (0), no risk factors; moderate (1,2), 1 or 2 risk factors; poor (3,4), 3 or 4 risk factors.

Abbreviations: CI, confidence interval; HR, hazard ratio; MST, median survival time.

by specifying the SELECTION = SCORE option in the MODEL statement. When there were substantial differences among those five possible models in terms of statistical adequacy, that is, score χ^2 values, the model with the largest score χ^2 values was to be selected. Otherwise, model selection was to be performed based on clinical aspects.

Factors included in these analyses were as follows: age (<65/≥65), sex (male/female), PS (0/1, 2), disease status (metastatic/recurrent), number of metastatic sites (0, 1/≥2), target lesion (−/+), macroscopic type (0, 1, 2/3, 4, 5) [20], histological type (intestinal/diffuse), prior gastrectomy (−/+), and laboratory data at the date of enrollment in the trial, such as hemoglobin (Hb), white blood cell (WBC), platelets (Plt), Na, K, Ca, albumin, ALP, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), C-reactive protein (CRP), carcinoembryonic antigen, and creatinine clearance (CCr). Each of these laboratory variables, except for Hb, WBC, Plt, and CCr, was dichotomized with the cutoff point at the limit of its normal range at each institution. Hb, WBC, Plt, and CCr were dichotomized with the cutoff points at 11 g/dL, 4000/μL, 10.0 × 10^4/μL, and 60 mL/min, corresponding to grade 1 adverse events in the National Cancer Institute Common Toxicity Criteria (version 2.0).

Survival curves were estimated by the Kaplan-Meier method and compared for statistical differences using the log-rank test. All p values are two-sided.

Results

Data Collection

All data for baseline factors and laboratory tests for the multivariate analysis were available in 650 (5-FU arm, n = 215; irinotecan plus cisplatin arm, n = 216; S-1 arm, n = 219) of 704 patients enrolled in JCOG9912 (Fig. 1). Table 1 shows the baseline characteristics of the subjects in the present study. A total of 417 patients (64%) showed PS 0, 283 patients (44%) had 0 or 1 metastatic sites, and 123 (19%) had recurrent disease after curative surgery. A total of 607 (93%) of 650 patients did not survive until the final data cutoff in April 2008. The median survival time (MST) for all analyzed patients was 11.8 months (Fig. 2).

RMH Prognostic Index

First, we applied the RMH index to our data. Of the patients in the present study, only 35 (5%) were classified in the poor-risk group, 483 patients (74%) were classified in the moderate-risk group, and 132 (21%) were classified in the good-risk group. Survival differences were also significant (log-rank p = .0025, two-sided; moderate-risk group, HR = 1.28, 95% CI = 1.05–1.57; high-risk group, HR = 1.90, 95% CI = 1.29–2.79; Fig. 3).

JCOG Prognostic Index

Table 2 shows the results of the univariate analyses for survival using baseline characteristics and laboratory tests. The following parameters were strongly related to poor prognosis: PS≥1, unresectable disease, number of metastatic sites≥2, having target lesions, no prior gastrectomy, metastasis of bone and lymph nodes, elevated ALP, elevated LDH, and elevated CRP (p < .001 for each factor).

To construct the prognostic index, we proposed five models whose χ^2 values were the highest in all possible models (Table 3). Because the six risk factors in the five selected models (PS ≥1, number of metastatic sites ≥2, no prior gastrectomy, elevated ALP, LDH, and CRP) had similar HRs, risk scores were assigned

Table 2. Univariate analyses of survival

Factors	Category	Hazard ratio	95% CI	*P* value (two-sided)
Age	≥65 (vs. <65)	0.99	0.85–1.17	.9434
Sex	Female (vs. male)	1.21	1.01–1.46	.0380
PS	1 (vs. 0)	1.52	1.29–1.80	<.0001
	2 (vs. 0)	1.32	0.63–2.79	.4658
	1, 2 (vs. 0)	1.51	1.28–1.79	<.0001
	2 (vs. 0, 1)	1.16	0.55–2.46	.6897
Tumor status	Unresectable (vs. recurrent)	1.50	1.22–1.84	<.0001
No. of metastatic sites	1 (vs. 0)	1.33	0.55–3.22	.5288
	≥2 (vs. 0)	2.31	0.96–5.60	.0631
	≥2 (vs. 0, 1)	1.75	1.49–2.06	<.0001
Target lesion	Yes (vs. no)	1.46	1.20–1.76	.0001
Gastrectomy	No (vs. yes)	1.71	1.43–2.04	<.0001
Macroscopic type	3, 4, 5 (vs. 0, 1, 2)	1.14	0.96–1.35	.1471
Histologic type	Diffuse (vs. intestinal)	1.06	0.90–1.24	.4837
Peritoneal metastasis	Yes (vs. no)	1.07	0.90–1.26	.4681
Liver metastasis	Yes (vs. no)	1.30	1.11–1.53	.0013
Lung metastasis	Yes (vs. no)	0.93	0.68–1.26	.6211
Bone metastasis	Yes (vs. no)	2.34	1.52–3.65	.0001
Lymph node metastasis	Yes (vs. no)	1.44	1.19–1.73	.0002
Hemoglobin	<11g/dL (vs. ≥11g/dL)	1.06	0.90–1.26	.4836
White blood cell	<4000/μL (vs. ≥4,000/μL)	0.68	0.47–0.98	.0369
Sodium	<LLN (vs. ≥LLN)	1.40	1.05–1.85	.0201
Potassium	<LLN (vs. ≥LLN)	2.21	0.99–4.96	.0534
Hypocalcemia	<LLN (vs. ≥LLN)	1.15	0.80–1.64	.4510
Hypercalcemia	≥ULN (vs. <ULN)	0.97	0.66–1.43	.8897
Albumin	<LLN (vs. ≥LLN)	1.11	0.95–1.31	.1853
ALP	≥ULN (vs. <ULN)	1.36	1.16–1.61	.0002
Total bilirubin	≥ULN (vs. <ULN)	0.78	0.55–1.10	.1604
AST	≥ULN (vs. <ULN)	1.33	1.10–160	.0029
ALT	≥ULN (vs. <ULN)	1.14	0.93–1.39	.2051
LDH	≥ULN (vs. <ULN)	1.48	1.25–1.76	<.0001
CRP	≥ULN (vs. <ULN)	1.47	1.25–1.73	<.0001
CCr	<60 mL/min (vs. ≥60 mL/min)	0.75	0.52–1.09	.1295

Platelets were not included in the analysis because there were no patients under the cutoff point.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CCr, creatinine clearance; CI, confidence interval; CRP, C-reactive protein; LDH, lactate dehydrogenase; LLN, lower limit normal; PS, performance status; ULN, upper limit normal.

based on HRs with one point for each factor. Moreover, because score χ^2 values of these five models were statistically nearly equal, taking into account clinical aspects, we selected the fifth model as the JCOG prognostic index (JCOG index), which included PS ≥1, number of metastatic sites ≥2, no prior gastrectomy, and elevated ALP as prognostic factors.

Figure 4A shows survival according to the number of risk factors, from 0 to 4, as determined by the JCOG index. There were significant survival differences among five groups (log-rank $p <$ .0001, two-sided). Furthermore, for clinical convenience, we divided patients into three groups, rather than the five groups proposed by the authors of the RMH index. Patients with zero or one risk factor were categorized into the low-risk group (n = 225), those with two or three risk factors were categorized into the moderate-risk group (n = 368), and those with four risk factors were categorized into the high-risk group (n = 57). MSTs for the low-, moderate-, and high-risk groups were 17.0, 10.4, and 5.0 months, respectively. Compared with the low-risk group, the moderate-risk group had a nearly 2-fold increased risk of death (HR = 1.84, 95% CI = 1.55–2.20), and the high-risk group had a 3.4-fold increased risk of death (HR = 3.38, 95% CI = 2.50–4.58; Fig. 4B). Although statistically significant interaction between prognostic index and treatment was shown (p = .0002), a similar trend was observed in each of the three treatment arms. HRs of the moderate and high-risk groups compared with the low-risk group were 1: 2.04 (95% CI = 1.51–2.76): 10.00 (95% CI = 5.69–17.59 in the 5-FU arm); 1: 1.99 (95% CI = 1.46–2.72): 2.24 (95% CI = 1.39–3.59 in the irinotecan and cisplatin arm); 1: 1.65 (95% CI = 1.22–2.24): 4.66 (95% CI = 2.54–8.56) in the S-1 arm.

Table 3. The five best models to construct a prognostic index

Covariates	category	HR	95% CI	P
1st model: Scoreχ^2=88.292				
PS	1, 2 (vs. 0)	1.47	1.24-1.73	< .001
Number of metastatic sites	≥2 (vs. 0, 1)	1.48	1.24-1.76	< .001
Prior gastrectomy	No (vs. yes)	1.36	1.12-1.65	.002
LDH	≥ULN (vs. <ULN)	1.31	1.10-1.57	.003
2nd model: Scoreχ^2=86.992				
PS	1, 2 (vs. 0)	1.41	1.19-1.66	< .001
Number of metastatic sites	≥2 (vs. 0, 1)	1.50	1.26-1.78	< .001
Prior gastrectomy	No (vs. yes)	1.36	1.12-1.65	.002
CRP	≥ULN (vs. <ULN)	1.28	1.08-1.51	.004
3rd model: Scoreχ^2=86.667				
PS	1, 2 (vs. 0)	1.45	1.23-1.72	< .001
Number of metastatic sites	≥2 (vs. 0, 1)	1.60	1.35-1.89	< .001
LDH	≥ULN (vs. <ULN)	1.29	1.08-1.55	.006
CRP	≥ULN (vs. <ULN)	1.27	1.07-1.50	.007
4th model: Scoreχ^2=86.311				
PS	1, 2 (vs. 0)	1.46	1.23-1.72	< .001
Number of metastatic sites	≥2 (vs. 0, 1)	1.47	1.23-1.75	< .001
Prior gastrectomy	No (vs. yes)	1.45	1.20-1.75	< .001
AST	≥ULN (vs. <ULN)	1.30	1.08-1.57	.007
5th model: Scoreχ^2=86.085				
PS	1, 2 (vs. 0)	1.43	1.21-1.69	< .001
Number of metastatic sites	≥2 (vs. 0, 1)	1.47	1.23-1.76	< .001
Prior gastrectomy	No (vs. yes)	1.42	1.17-1.71	< .001
ALP	≥ULN (vs. <ULN)	1.25	1.06-1.47	.009

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; HR, Hazard ratio; LDH; lactate dehydrogenase; PS, performance status.

Discussion

To the best of our knowledge, this is the first report of a prognostic index limited to patients with only AGC in an Asian population based on data from a single large prospective randomized controlled trial. We adopted four risk factors for survival (PS ≥1, metastatic sites≥2, no prior gastrectomy, and elevated ALP) and used these factors to develop the JCOG index. By classifying patients into three risk groups (low, zero to one risk factor; moderate, two to three risk factors; high, four risk factors), OS curves for our three risk groups indicated significantly good separation in JCOG9912. We believe that the JCOG index can be used for more accurate patient stratification in future clinical trials.

We selected these four prognostic factors to construct the prognostic index because there were no remarkable differences in the score χ^2 values between the prognostic indices consisting of four and five factors. In terms of metastatic sites, to avoid confounding with other factors (such as bone metastasis and ALP), we adopted a factor that considered the number of metastatic sites rather than selecting each metastatic site individually. It seems reasonable to consider that the number of metastatic sites can reflect the tumor burden in the entire body.

To select the most optimal of our five candidate models, three of the four factors (PS ≥1, number of metastatic sites ≥2, and no prior gastrectomy), excluding elevated ALP and LDH, were included in all models, and we selected elevated ALP from the point of consistency in previous reports [14, 15, 17]. Both LDH and ALP commonly represent liver function, bone metastasis, and other abnormal conditions; however, there were no previous reports of prognostic models, including LDH. Finally, we decided to select the fifth model, which included the risk factors PS ≥1, number of metastatic sites ≥2, no prior gastrectomy, and elevated ALP, for the JCOG index.

In the late 1990s, Yoshida et al. [18] also reported prognostic factors from the old JCOG trials; PS, number of metastatic sites, and scirrhous-type tumor were found to be prognostic factors. Moreover, a few reports have described prognostic factors for GC from Korean patients [15–17]. Lee et al. [15] reported ECOG PS ≥2, no prior gastrectomy, peritoneal metastasis, bone metastasis, elevated ALP, and decreased albumin as independent prognostic factors; Kim et al. [16] reported ECOG PS ≥2, peritoneal metastasis, bone metastasis, metastatic sites ≥2, and elevated total bilirubin as prognostic factors; and Koo et al. [17] reported ECOG PS ≥2, no prior gastrectomy, peritoneal metastasis, bone metastasis, lung metastasis, elevated ALP, decreased albumin, and elevated total bilirubin as prognostic factors. Only PS was a common prognostic factor in all four studies, and peritoneal and bone metastasis were shared among three studies. Whereas the Korean reports were retrospective studies based on data from clinical practice populations that contained patients who were in poor condition, the present