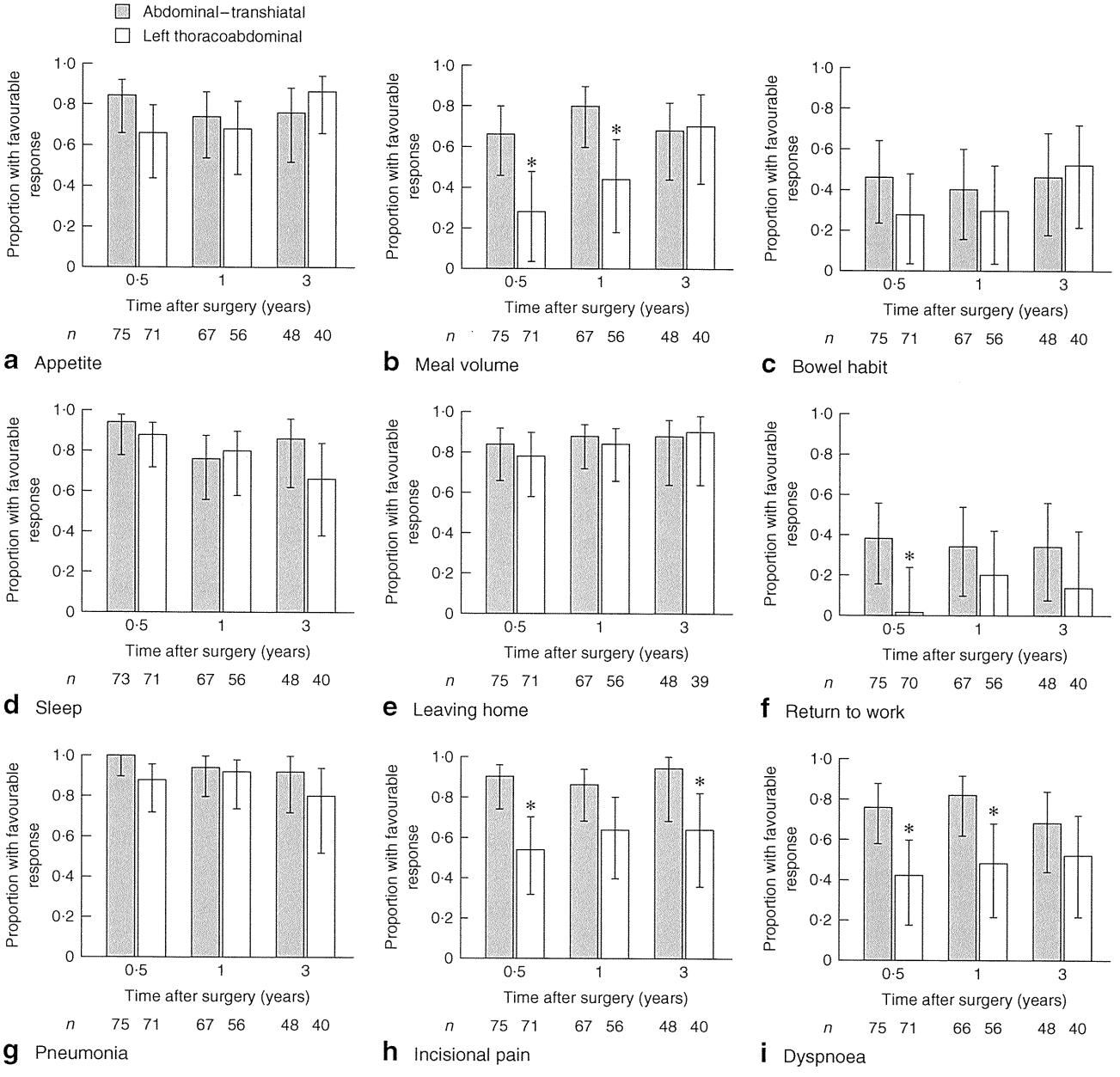

Fig. 2 Comparison of proportion of patients with a favourable response regarding nine symptoms between abdominal–transhiatal (TH) and left thoracoabdominal (LTA) groups: **a** appetite, **b** meal volume, **c** bowel habit, **d** sleep, **e** leaving home, **f** return to work, **g** pneumonia, **h** incisional pain and **i** dyspnoea. Group means are shown with 95 per cent confidence intervals. *$P < 0{\cdot}050$ *versus* TH (generalized estimating equations model)

plus PAND group at 6 months. At 1- and 3-year follow-up symptom scores were comparable between the two groups.

In the JCOG9502 trial, meal volume and respiratory status (dyspnoea) were better in the TH group than in the LTA group up to 1 year after surgery. The proportion of patients with incisional pain was significantly higher in the LTA group than in the TH group until the end of follow-up at 3 years.

Respiratory function in Japan Clinical Oncology Group 9502 trial

The LTA group showed a significantly greater decrease in vital capacity than the TH group at 1 and 6 months after

surgery (*Table 3*). There was no deterioration in FEV1 after surgery in either group. PaO_2 in the TH group did not change in the 6 months after surgery, whereas there was a transient decrease in the LTA group.

Discussion

The first randomized controlled trial compared two types of lymphadenectomy within the same surgical approach for gastric cancer, whereas the second trial compared two completely different surgical approaches, namely with and without thoracotomy. In the present study, secondary outcomes of patients without recurrence after gastrectomy were evaluated. Bodyweight was comparable after D2 and D2 plus PAND, whereas the difference in bodyweight between the TH and the LTA groups widened gradually owing to recovery in the TH group. This means that bodyweight change after gastrectomy is more dependent on surgical approach than on the extent of lymphadenectomy. Some of the clinical symptoms were particularly negatively affected by a LTA compared with a TH approach, whereas D2 and D2 plus PAND had comparable scores. The decrease in vital capacity was significantly greater after a LTA than a TH procedure.

Clinical symptoms in the D2 plus PAND group were limited to a short time after operation, and mostly related to changes in bowel habit. This may be due either to autonomic nerve damage or to lymphoedema of the jejunum caused by PAND. However, limited autonomic nerve dissection in PAND may not cause long-term impairment of intestinal function. A small-scale randomized controlled trial of PAND in patients with pancreatic cancer showed that dissection of such nodes frequently caused diarrhoea for up to 4 months after surgery[7]. Although changes in bowel habit may be the biggest disadvantage of PAND, these negative effects were limited to the early postoperative period and seemed to be acceptable clinically. Wu *et al.*[8] compared postoperative symptoms between D1 alone and D2 plus retropancreatic lymph node dissection in a single-institution randomized controlled trial[8]. They reported no significant difference in symptoms between the two groups and concluded that postoperative changes in symptoms were related largely to the scope of gastric resection, disease status and combined resection of the pancreas or spleen rather than the extent of lymph node dissection.

Pain and dyspnoea are well known sequelae of intercostal thoracotomy[9,10]. The negative impact of the thoracotomy procedure on symptoms within the first year agreed with the results of previous studies[11,12]. The difference in meal volume might arise from the location of the anastomosis, in the open thoracic cavity in LTA procedures *versus* the mediastinum in TH operations.

Although quality of life and symptoms are distinct entities, symptoms usually affect patients' quality of life quite strongly. Quality of life is usually assessed by questionnaire and is evaluated by the patients themselves to minimize information bias[13,14]. However, the Japanese versions of validated questionnaires such as the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) or the Functional Assessment of Cancer Therapy – General (FACT-G) were not available when these randomized controlled trials were conducted[14,15]. In the present study, the Gastric Cancer Surgical Study Group/JCOG Symptom Questionnaire, which consisted of only seven or nine queries, was used, because the more complicated the survey, the lower the compliance would have been. Moreover, this questionnaire evaluating patient-centred outcome such as symptom scores was completed by the doctor not the patient, which might have introduced observer bias.

The decrease in bodyweight and worsening of post-operative symptom scores following PAND was limited compared with D2 without PAND. Therefore, D2 plus PAND might be one option when R0 resection is impossible without dissection of such nodes. The LTA approach worsened both symptoms and respiratory function to a greater extent than the TH approach. Surgeons are advised to avoid the LTA approach based not only on previously published survival-related evidence but also on other parameters such as those evaluated in this study.

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Supporting information

Additional supporting information may be found in the online version of this article.

Fig. S1 CONSORT diagrams for **a** Japan Clinical Oncology Group (JCOG) 9501 and **b** JCOG9502 trials. PAND, para-aortic nodal dissection; TH, abdominal–transhiatal; LTA, left thoracoabdominal (Word file)

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ORIGINAL ARTICLE

Feasibility study of adjuvant chemotherapy with S-1 plus cisplatin for gastric cancer

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Abstract
Purpose To evaluate the feasibility of S-1 plus cisplatin as adjuvant chemotherapy for stage III gastric cancer after curative resection.
Methods Japanese patients with stage III gastric cancer who underwent gastrectomy with D2 lymph node resection were enrolled. Treatment consisted of 3 cycles of S-1 (80 mg/m^2/day, b.i.d.) for 21 days followed by a 14-day rest, and cisplatin (60 mg/m^2 iv) on day 8. After that, S-1 monotherapy was given on days 1–28 every 6 weeks until 1-year postsurgery. After protocol amendment, the first chemotherapy cycle consisted of S-1 monotherapy; cisplatin was added to cycles 2, 3, and 4, followed by S-1 monotherapy up to 1-year postsurgery. The primary endpoint was the completion rate of three cycles of S-1 plus cisplatin.

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Results A total of 63 enrolled patients have been evaluated. Grade 3/4 toxicities included neutropenia (40%), anorexia (28%), and febrile neutropenia (4%) before protocol amendment ($n = 25$), and neutropenia (37%), anorexia (8%), and febrile neutropenia (3%) after amendment implementation ($n = 38$). Excluding ineligible cases, treatment completion rates were 57% (12/21) before and 81% (30/37) after the protocol amendment.

Conclusions The amended S-1 plus cisplatin is more feasible than the original protocol because of early dose reduction of S-1 prior to cisplatin addition and greater recovery time from surgery prior to cisplatin. This treatment should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial.

Keywords Adjuvant chemotherapy · Gastric cancer · S-1 · Cisplatin

Introduction

Gastric cancer (GC) remains a major health problem with approximately 8,03,000 deaths worldwide in 2004, although the mortality rate has steadily decreased in recent years [1]. The primary treatment for GC is surgery, which is almost always curative in early GC (stage I) patients, who have a >90% 5-year survival rate. However, locally advanced (stage II–III) GC often recurs, even after curative resection is performed. Therefore, it is very important to develop adjuvant chemotherapy regimens that can improve survival in GC patients with stage II–III disease after surgical resection.

Until recently, several randomized controlled trials of postoperative adjuvant chemotherapy for GC were conducted [2–12]. Although most of them have failed to show clinical benefit in particular multi-agent anthracycline or cisplatin-based regimens, a recent meta analysis showed that postoperative adjuvant chemotherapy was associated with reduced risk of death compared with surgery alone [13].

S-1 (TS-1, Taiho Pharmaceutical Co.) is an orally active combination of tegafur (a prodrug that is converted by cells to fluorouracil), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil), and oteracil (inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the toxic gastrointestinal effects of fluorouracil) [14] approved in Japan, Korea, Singapore, and China for GC. In 2007, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial demonstrated the efficacy of S-1 for stage II–III GC patients who underwent curative resection with D2 lymphadenectomy [15]. S-1 improved the 3-year overall survival (OS) rate from 70.1% for surgery alone to 80.1%, with a low incidence of adverse events and good compliance with treatment for 3 months in 87.4% and for 6 months in 77.9%. However, the 3-year OS rates in stage IIIA and stage IIIB patients receiving S-1 were 77.4 and 63.4%, respectively, which are less satisfactory compared with the rate for stage II (90.7%). Therefore, further investigation into more effective treatments for patients with stage III GC is urgently needed.

Meanwhile, for metastatic or recurrent GC, the phase III trial comparing S-1 alone to S-1 plus cisplatin (S-1 Plus cisplatin vs. S-1 In RCT In the Treatment for Stomach cancer; SPIRITS trial) showed that S-1 plus cisplatin resulted in a significantly higher response rate, longer progression-free survival (PFS), and longer OS [16]. Another phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial) showed that S-1 plus cisplatin was associated with fewer toxic effects and demonstrated noninferiority compared with infusional fluorouracil and cisplatin [17]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent GC, as well as a candidate for an experimental arm in the next adjuvant chemotherapy trial.

Before comparing S-1 monotherapy with S-1 plus cisplatin in a phase III trial, we first evaluated the feasibility of S-1 plus cisplatin as adjuvant chemotherapy for stage III GC after curative resection, to confirm that S-1 plus cisplatin can safely be used.

Patients and methods

Eligibility criteria

The following eligibility criteria were employed: (1) histologically proven adenocarcinoma of the stomach; (2) ≥ D2 lymphadenectomy, with complete resection of the primary tumor (R0 surgery); (3) stage IIIA/IIIB disease (T2, N2; T3, N1–2; or T4, N0–1 [Japanese classification]); (4) ECOG performance status 0–1; (5) age 20–75 years; (6) no prior chemotherapy or radiotherapy; (7) able to be enrolled 4–8 weeks after surgery; (8) sufficient oral food intake; (9) adequate organ function (white blood cells [WBCs] $\geq 3{,}000/mm^3$ and $\leq 1{,}20{,}000/mm^3$, neutrophils $\geq 1{,}500/mm^3$, hemoglobin ≥8.0 g/dl, platelets $\geq 1{,}00{,}000/mm^3$, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels ≤100 IU/l, total serum bilirubin ≤2.0 mg/dl, serum creatinine concentration ≤1.2 mg/dl, estimated creatinine clearance ≤60 ml/min, normal electrocardiogram); and (10) written informed consent obtained from the patient. Disease stage was classified according to Japanese Gastric Cancer Association guidelines [18]. The protocol was approved by the institutional review board at each participating center.

Treatment and toxicity assessment

Treatment according to the original protocol was begun 4–8 weeks after surgery with 3 cycles of S-1 plus cisplatin ("S-1+ cisplatin [SP] step") followed by S-1 monotherapy ("S-1 step") up to 1 year after surgery. In the "SP step", each cycle consisted of 40 mg/m^2 of S-1 taken orally twice daily for 21 days plus a 2-hour infusion of 60 mg/m^2 of cisplatin on day 8. Each cycle was administered at 5-week intervals. In the "S-1 step", 40 mg/m^2 of S-1 was taken orally twice daily as monotherapy for 28 days at 6-week intervals. All patients received 5-HT3 antagonists and dexamethasone on administration of cisplatin as antiemetics.

Patients were assessed before registration, on days 1, 8, and 15 during the "SP step", and every 2 weeks during the "S-1 step". The baseline assessment included physical examination and laboratory tests. Patients were monitored for adverse effects throughout the treatment period, in addition to receiving follow-up for treatment-related adverse effects. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

For adverse effects, the subsequent chemotherapy cycle was delayed until patient recovery, which included the following parameters: WBCs $\geq$3,000/mm^3, neutrophils $\geq$1,500/mm^3, hemoglobin $\geq$8.0 g/dl, platelets >75,000/mm^3, AST or ALT levels $\leq$100 IU/l, total serum bilirubin level $\leq$2.0 mg/dl, and serum creatinine concentration <1.5 mg/dl. Nonhematological toxicities, excluding stomatitis, alopecia, pigmentation changes, nail changes, and watery eyes, were required to be grade 0/1. Cisplatin administration was delayed and administered within 1 day of recovery of the following parameters: WBCs $\geq$3,000/mm^3, neutrophils $\geq$1,500/mm^3, platelets >75,000/mm^3, and serum creatinine <1.5 mg/dl. Both S-1 and cisplatin doses were reduced in the event of grade 4 leukopenia or neutropenia, grade 3/4 thrombocytopenia, serum creatinine $\geq$1.5 mg/dl, or other drug-related nonhematological grade 3/4 toxicities. For level −1 dose reduction, S-1 was reduced from 120 to 100 mg/day, from 100 to 80 mg/day, or from 80 to 50 mg/day, while cisplatin was reduced from 60 to 50 mg/m^2. Dose reduction was permitted twice. When dose-limiting toxicities as described previously occurred again at level −2 (S-1 reduced from 100 to 80 mg/day or from 80 to 50 mg/day [if the −1 level of S-1 was already 50 mg, the patient was withdrawn from the study]; cisplatin administration reduced from 50 to 40 mg/m^2), the patient was withdrawn from the study. A patient was also withdrawn from the study whenever the beginning of the subsequent cycle was delayed by toxicity for more than 3 weeks. When cisplatin administration was delayed beyond day 15, the cisplatin portion of the cycle was skipped.

Protocol amendment

During enrollment, some toxicity was reported during the first cycle of SP, especially neutropenia and anorexia. To minimize patient risk, the Data and Safety Monitoring Committee recommended that patient enrollment be halted and that an interim analysis be conducted using the first 25 registered cases (see "Results"). After the analysis, we decided to amend the protocol.

Treatment according to the amended protocol was begun 4–6 weeks after surgery as in the ACTS-GC trial, and consisted of the following: (1) The first cycle of chemotherapy consisted of S-1 monotherapy, and cisplatin was added to cycles 2, 3, and 4. After that, S-1 monotherapy was administered up to 1 year after surgery; (2) The dose of S-1 in the first SP cycle was reduced in case of severe toxicity during the first cycle of S-1 monotherapy; (3) The criterion for delaying cisplatin administration was changed from a neutrophil count of <1,500/mm^3 to <1,200/mm^3; (4) Dexamethasone was recommended for treatment-induced nausea with 20 mg on day 8 (the day of cisplatin administration) and 16 mg on days 9 and 10.

Statistical analysis

The primary endpoint was the rate of completion of 3 cycles of S-1 plus cisplatin; secondary endpoints were the rate of completion of 2 cycles of S-1 plus cisplatin, the proportion of patients receiving treatment according to protocol, and adverse events. Treatment completion was defined as administration of S-1 for more than 14 days in each cycle plus administration of cisplatin. Completion rate of S-1 plus cisplatin was evaluated in all eligible patients. Toxicity was evaluated among patients who received more than one cycle of S-1 plus cisplatin.

In the present trial, the rate of treatment completion was expected to be lower than compliance in the ACTS-GC trial because of the addition of cisplatin. Moreover, if the rate of treatment completion using 3 cycles of S-1 plus cisplatin were lower than 50%, this regimen would be considered inappropriate for adjuvant therapy and would not be evaluated in a phase III trial. Assuming a null hypothesis of 50% for the rate of completion of 3 cycles and an alternative hypothesis of 70%, and using a 1-sided alpha of 0.1 and a statistical power of 0.1, it is necessary to enroll a minimum of 44 patients. Therefore, the target enrollment was 50 patients, in order to make accommodations for ineligible patients.

After protocol amendment, a minimum of 33 patients is needed for a 1-sided alpha of 0.1 and a statistical power of 0.2. Therefore, 38 more patients were added to allow for ineligible patients. Statistical analysis was performed independently for patients enrolled before and after amendment.

Table 1 Patient characteristics

Characteristic	Original ($n = 25$)	Amended ($n = 38$)
Median age, years (range)	60 (47–72)	62 (40–74)
Gender		
Male	16	25
Female	9	13
PS (ECOG)		
0	17	26
1	8	12
Pathological type		
Intestinal	14	5
Diffuse	11	33
Type of gastrectomy		
Total	8	13
Distal	16	25
Proximal	1	0
T stage		
pT1	2	0
pT2	8	9
pT3	14	28
pT4	1	1
N stage[a]		
pN0	1	0
pN1	10	8
pN2	14	30
Cancer stage[a]		
IB	1[b]	0
II	2[b]	0
IIIA	17	16
IIIB	5	21
IV	0	1[b]

Original before protocol amendment, *Amended* after protocol amendment, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group

[a] Japanese classification; [b] excluded after enrollment

Table 2 Toxicities

Toxicities	Original ($n = 25$)				Amended ($n = 38$)			
	All		Grade 3/4		All		Grade 3/4	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
(A) Hematological toxicities								
Leucopenia	19	(76)	1	(4)	26	(68)	2	(5)
Neutropenia	20	(80)	10	(40)	30	(79)	14	(37)
Anemia	23	(92)	5	(20)	35	(92)	3	(8)
Thrombocytopenia	10	(40)	1	(4)	17	(45)	1	(3)
Febrile Neutropenia	1	(4)	1	(4)	1	(3)	1	(3)
(B) Nonhematological toxicities								
Anorexia	23	(92)	7	(28)	34	(89)	3	(8)
Nausea	17	(68)	2	(8)	31	(82)	1	(3)
Vomitting	7	(28)	0	(0)	8	(21)	0	(0)
Diarrhea	13	(52)	0	(0)	24	(63)	1	(3)
Fatigue	17	(68)	0	(0)	34	(89)	2	(5)
Stomatitis	2	(8)	0	(0)	8	(21)	0	(0)
AST	5	(20)	0	(0)	10	(40)	0	(0)
ALT	5	(20)	0	(0)	8	(36)	0	(0)
Total bilirubin	6	(30)	0	(0)	22	(22)	0	(0)
Creatinine	5	(20)	0	(0)	11	(10)	0	(0)

Original before protocol amendment, *Amended* after protocol amendment, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Results

Patient characteristics

From August 2007 to July 2009, 63 patients (25 patients in the original protocol/38 patients in the amended protocol) were accrued from 5 Japanese hospitals. To date, all 63 patients have finished the "SP step" and have been evaluated. Clinical characteristics are summarized in Table 1. The median age was 60/62 (original/amended protocol) years (range, 47–72/40–74 years), and the following types of resection were performed: total gastrectomy ($n = 8/13$), distal gastrectomy ($n = 16/25$), and proximal gastrectomy ($n = 1/0$). In the original protocol, 17 patients had stage IIIA disease and 5 had stage IIIB disease; whereas 16 had stage IIIA and 21 had stage IIIB disease in the amended protocol. After enrollment, 4 patients were deemed ineligible during the original protocol because of confirmed stage II disease ($n = 2$), stage IB disease ($n = 1$), and cancer other than GC ($n = 1$), and 1 patient was considered ineligible during the amended protocol because of pathological stage IV ($n = 1$) disease.

Toxicity

A total of 202 cycles from the 63 cases were assessable for toxicity (Table 2). Under the original protocol ($n = 25$), neutropenia was the most common hematological toxicity, with grade 3/4 neutropenia observed in 10 patients (40%). Additional grade 3/4 hematological toxicities included anemia in 5 patients (20%), and leucopenia, thrombocytopenia, and febrile neutropenia in 1 patient (4%) each. Grade 3/4 anorexia was the most frequent nonhematological toxicity ($n = 7$ [28%]), followed by nausea ($n = 2$ [8%]). There was no grade 3/4 creatinine elevation seen.

Under the amended protocol ($n = 38$), the frequency of grade 3/4 neutropenia was similar to the original; it was seen in 14 patients (37%). Grade 3/4 anemia decreased to 3 patients (8%), and the frequencies of grade 3/4 leukopenia ($n = 2$

[5%]), thrombocytopenia ($n = 1$ [3%]), and febrile neutropenia ($n = 1$ [3%]) were also similar to the original. Among nonhematological toxicities, grade 3/4 anorexia was remarkably reduced to 3 patients (8%) and nausea also decreased to 1 patient (3%). The incidences of grade 3/4 fatigue and diarrhea slightly increased to 2 (5%) and 1 (3%) patients, respectively. There was no grade 3/4 creatinine elevation seen. There were no treatment-related deaths occurring within 30 days after completion of "SP step" treatment.

Compliance

As mentioned previously, 4 and 1 patients were determined to be ineligible after enrollment in the original and amended protocols, respectively, and therefore 21 and 37 patients were analyzed for compliance, respectively. Under the original protocol, 57% (12/21; 95% CI 34–78%) achieved treatment completion with 3 cycles of S-1 plus cisplatin, and 76% (16/21; 95% CI 53–92%) achieved treatment completion with 2 cycles. The proportion of patients receiving treatment according to protocol was 57% (12/21; 95% CI 34–78%). Of note, 6/21 (29%) patients did not complete the first cycle of the "SP step". Reasons for not completing the first cycle included neutropenia on the day of cisplatin administration (day 8) in 3 patients, anorexia in 2 patients, and infection in 1. Dose reductions of S-1 and cisplatin were required once in 9 (43%) and 8 (38%) patients, respectively, and twice in 1 (5%) and 1 (5%) patients, respectively. There were 6 patients (29%) withdrawn from treatment as follows: 3 because of toxicity (neutropenia), 2 because of patient refusal of additional treatment because of toxicity, and 1 because of refusal of additional treatment for other reasons.

Under the amended protocol, 81% (30/37; 95% CI 65–92%; $P < 0.001$ under the null hypothesis) achieved treatment completion with 3 cycles of S-1 plus cisplatin, and 95% (35/37; 95% CI 82–99%) achieved treatment completion with 2 cycles. The proportion of patients receiving treatment according to protocol was 78% (29/37; 95% CI 62–90%). The number of patients not completing the first cycle of the "SP step" was remarkably decreased to only 1 (3%) patient. There were 10 (27%) patients requiring S-1 dose reduction after the first chemotherapy cycle of S-1 monotherapy. Dose reductions of S-1 and cisplatin were required once in 12 (32%) and 8 (22%) patients, respectively, and twice in 7 (19%) and 6 (16%) patients, respectively. Withdrawal of treatment occurred in 2 (5%) patients as follows: one because creatinine elevation did not recover and the other because of patient refusal of additional treatment because of toxicity.

The relative dose intensities (RDIs) of S-1 were 0.67 in the original and 0.78 in the amended protocol, and for cisplatin were 0.65 and 0.81, respectively.

Discussion

To the best of our knowledge, this is the first report on a safety analysis of S-1 plus cisplatin treatment for stage III GC patients who have undergone curative resection with D2 lymphadenectomy. The overall frequencies of major toxicities under the original protocol were almost similar to those of the SPIRITS trial [16] (neutropenia 40 vs. 40%; anemia 20 vs. 26%; and anorexia 28 vs. 30% in this study and the SPIRITS trial, respectively). However, the completion rate of 3 cycles of S-1 plus cisplatin as a primary endpoint (57%) and RDI of S-1 or cisplatin were unexpectedly low in this study. Among the 9 patients who could not complete the 3 cycles of S-1 plus cisplatin, 6 patients could not complete treatment even during the first cycle, mainly because of neutropenia on day 8 and anorexia. We found that toxicity of chemotherapy was more likely to occur during the first cycle.

Therefore, to improve the completion rate of the treatment, we decided to amend the protocol by establishing S-1 monotherapy as the first cycle of chemotherapy, followed by 3 cycles of S-1 plus cisplatin. Although it might be possible that efficacy is decreased by changing the first cycle to S-1 monotherapy, we prioritized complying with postoperative adjuvant chemotherapy, which might also be important in improving survival [19, 20].

In our amended protocol, not only was cisplatin administration omitted in the first cycle, but also the dose of S-1 in subsequent combination cycles was reduced if there were severe toxicities during the "first-cycle" administration of S-1 monotherapy. In addition, the neutropenia count for delaying cisplatin administration was also changed, from $<1{,}500/mm^3$ to $<1{,}200/mm^3$. As a result, 81% of patients achieved treatment completion with 3 cycles of S-1 plus cisplatin with improved RDIs of both S-1 (0.78 from 0.65) and cisplatin (0.81 from 0.65). The frequency of grade 3/4 anorexia and nausea also decreased, from 28 to 8% and 8 to 3%, respectively, although we do not use Substance P inhibitor in both protocol because it was not approved in Japan at that time.

The actual cause of the poor compliance during the early post-gastrectomy course in this study was not discovered. There are several reports about the effect of gastrectomy on S-1 pharmacokinetics [21–23], although this issue remains controversial. Kim et al. reported that total gastrectomy significantly increased the maximum concentration and the areas under the curves of plasma fluorouracil and 5-chloro-2,4-dihydroxypyridine (CDHP) after S-1 administration, which may be one explanation for the toxicity seen in this study [23]. Additionally, there may be a hidden cause, such as relatively poor nutritional status due to gastrectomy, although this study included patients with sufficient oral intake and adequate organ function.

Although this was not a randomized study, in comparison with the original protocol, the amended protocol was more feasible, with a higher completion rate and higher RDIs. Relapse-free survival and overall survival were not reached in this study; therefore, it is difficult to speculate that the addition of 3 cycles of cisplatin might improve the prognosis compared with S-1 alone. Now in Japan, another feasibility study of S-1 plus docetaxel as postoperative adjuvant chemotherapy is ongoing [24]. The addition of any other agent to S-1 as an adjuvant chemotherapy needs to be validated in a randomized phase III trial with S-1 as the control arm.

In conclusion, the postoperative adjuvant S-1 plus cisplatin regimen of the amended protocol is more feasible than the original protocol, because of (1) early dose reduction of S-1 prior to cisplatin addition (2) greater recovery time from surgery prior to cisplatin. It should be regarded as a feasible experimental arm for the next adjuvant phase III trial comparing this S-1 plus cisplatin regimen and S-1 alone as adjuvant chemotherapy for stage III GC patients who have undergone curative resection with D2 lymphadenectomy.

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Conflicts of interest T. Sano has received lecture fees from Taiho Pharmaceutial (Tokyo, Japan). All other authors declared no conflicts of interest.

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ORIGINAL ARTICLE

Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer versus curative resection alone: final results of the Japan Clinical Oncology Group trial JCOG9206-2

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Abstract

Purpose To evaluate the survival benefit of adjuvant chemotherapy after curative resection in serosa-positive gastric cancer, a multicenter phase III clinical trial was conducted in Japan.

Patients and methods From January 1993 to March 1998, 268 patients were randomized to adjuvant chemotherapy (135 patients) or surgery alone (133 patients). All patients underwent gastrectomy with D2 or greater lymph node dissection. The chemotherapy regimen consisted of intraperitoneal cisplatin soon after abdominal closure, postoperative intravenous cisplatin (day 14) and 5-fluorouracil (day 14–16), and daily oral FU (UFT) starting 4 weeks after surgery for 12 months. The primary endpoint was overall survival. Relapse-free survival and site of recurrence were secondary endpoints.

Results Fifty-two patients (38.5%) in the adjuvant chemotherapy arm completed the chemotherapy regimen. There were 4 (1.49%) treatment-related deaths, 1 in the surgery-alone and 3 in the adjuvant chemotherapy arm (2 did not receive chemotherapy). Grade 4 toxicity was observed in 3 patients in the surgery-alone and 2 patients in the adjuvant chemotherapy arm. There was no significant difference in 5-year overall survival (62.0% adjuvant chemotherapy vs. 60.9% surgery-alone, $P = 0.482$) and 5-year relapse-free survival rates (57.5% adjuvant chemotherapy vs. 55.6% surgery-alone; $P = 0.512$).

Conclusion There was no benefit in overall and relapse-free survival with this adjuvant chemotherapy regimen for

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patients with macroscopically serosa-positive gastric cancer after curative resection.

Keywords Randomized clinical trial · Adjuvant chemotherapy · Serosa-positive gastric cancer · Intraperitoneal chemotherapy

Introduction

A large number of gastric cancers are still diagnosed in advanced stages worldwide [1, 2]. Once the primary tumor invades the subserosal or serosal layers of the gastric wall, cancer cells are more likely to spread into the abdominal cavity and implant on peritoneal surfaces, resulting in peritoneal dissemination [3, 4]. The most frequent cause of recurrence and subsequent cancer death in serosa-positive gastric cancer is peritoneal metastasis even after curative resection [5–7]. The main goal of adjuvant chemotherapy for resected gastric cancer is to prevent such a distant recurrence and increase the potential of cure.

In Japan today, adjuvant chemotherapy with single agent S-1 is considered the standard of care for patients with pathological stage II/III (Japanese Classification of Gastric Carcinoma 2nd English Edition [8, 9]) gastric cancer after potentially curative D2 dissection, based on the results of the ACTS-GC clinical trial [10–13]. However, subgroup analysis of the ACTS-GC data suggest that S-1 may be less effective for patients with more advanced gastric cancer such as serosa-positive cancer.

The present Japan Clinical Oncology Group (JCOG) trial, JCOG9206-2, is a randomized controlled phase III clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (FU). Thirteen institutions in Japan participated in this trial as members of the Gastric Cancer Surgical Study Group (GCSSG), a subgroup of JCOG [14]. We report here the final results with 6 years of follow-up.

Patients and methods

Patients

Patients had to fulfill the following eligibility criteria: macroscopically complete operation; histologically proven gastric adenocarcinoma, macroscopically serosa-positive (T3–4), with no metastases to level 3–4 lymph node stations (N0–2) [8, 9]; age 75 years or younger; no previous treatment for gastric cancer; negative peritoneal lavage cytology; adequate organ function as assessed by laboratory studies: leukocyte count of at least 4000/mm^3; hemoglobin of at least 11.0 g/dl; platelet count of at least 100000/mm^3; AST, ALT, total bilirubin, blood urea nitrogen and creatinine no higher than 1.25 times the upper limit of normal; creatinine clearance no lower than 70 ml/min. All patients provided written informed consent. Patients who had undergone any chemotherapy or radiotherapy, or those with synchronous or metachronous cancer of other organs were excluded.

Treatment assignment and evaluation

The patients were randomized using the minimization method to balance the adjuvant chemotherapy and surgery alone arms according to institution and the combination of the macroscopic depth of tumor invasion (T-category) and lymph node metastasis (N-category) according to the Japanese Classification of Gastric Carcinoma 2nd English Edition [9]. After the surgeon confirmed the above eligibility criteria, patients were randomly assigned to either arm by means of an intraoperative telephone call to the JCOG Data Center (Fig. 1).

The chemotherapy comprised intraperitoneal cisplatin (70 mg/m^2) soon after abdominal closure; intravenous cisplatin (70 mg/m^2) on postoperative day 14; intravenous 5-fluorouracil (5-FU) (700 mg/m^2) daily on postoperative days 14–16; and UFT (267 mg/m^2) daily, starting 4 weeks after surgery for 12 months. Intraperitoneal cisplatin (70 mg/m^2 with saline in total volume 1000 ml) was administered via drainage tubes that were clamped for following 2 h. Creatinine clearance was evaluated twice weekly before and after the administration of cisplatin. A full blood count was performed every week to assess for hematological toxicity during hospital stay. During UFT treatment, each patient was asked to visit the hospital every month for physical examinations and laboratory testing in both arms. Patients underwent upper gastrointestinal series, gastric endoscopy, ultrasonography, computed tomography or other investigations either as required or every 6 months

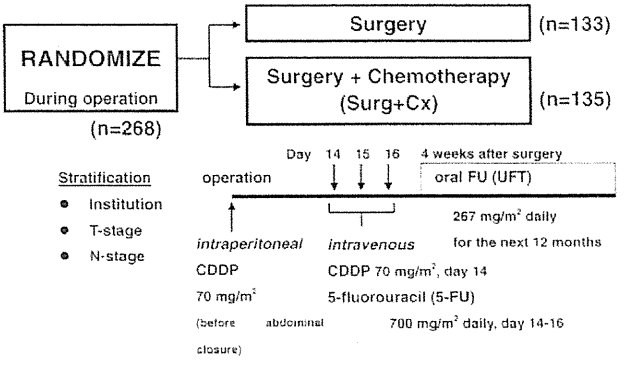

Fig. 1 Study scheme. All patients underwent gastrectomy with D2 or greater lymph node dissection. CDDP, *cis*-diamminedichloro-platinum (cisplatin)

to evaluate for recurrence. Adverse events were recorded according to the JCOG toxicity criteria [15]. Since some adverse events may occur after surgery even without chemotherapy, all potential adverse drug effects were compared with the adverse effects experienced by patients in the surgery-alone arm. Data on adverse events in the surgery-alone patients, except for postoperative morbidity and mortality, were collected retrospectively. Original case report forms were designed to collect adverse events during chemotherapy (only in the adjuvant chemotherapy arm). However, some adverse events happened even in the surgery-alone group. To keep the comparability between arms, we re-collected the data of adverse events from both arms at the final analysis. The surgery-alone arm received no additional treatment after surgery unless there was recurrence. The main prognostic factors, including age, gender, the depth of tumor invasion and nodal spread, operative procedures, and pathological findings, were described according to the general guidelines issued by the Japanese Research Society for Gastric Cancer Study [8, 9].

Study design and statistical analyses

This study was designed as a multicenter prospective randomized controlled phase III clinical trial. The study protocol was approved by the JCOG Clinical Trial Review Committee and the institutional review boards of all participating institutions. The primary endpoint was OS. Relapse-free survival and the site of recurrence were secondary endpoints. The original planned duration of accrual was 4 years with 5 years of follow-up. The planned sample size was 280 patients, with 140 patients in each arm to power the study at 80% to detect a 15% difference in 5-year OS rates between the surgery-alone arm (40%) and the chemotherapy arm (55%) with a two-sided significance level of 5%. The study design was amended to one projecting 5-year OS rates of 55% in the surgery-alone arm and 67% in the chemotherapy arm, with a 5-year accrual period and 6 years follow-up, because combined survival was better, and accrual poorer, than expected.

OS was measured from the date of random treatment assignment to the date of death or censored at the date of the last follow-up. Relapse-free survival was measured from the date of random treatment assignment to the date of the first observation of relapse or the date of death from any cause. If no progression was reported and if the patient remained alive, data on relapse-free survival were censored as of the date on which the absence of relapse was confirmed. OS and relapse-free survival were estimated by the Kaplan–Meier method and compared by the stratified log-rank test with the combination of the depth of the tumor invasion and lymph node metastasis as strata on the

Fig. 2 CONSORT diagram

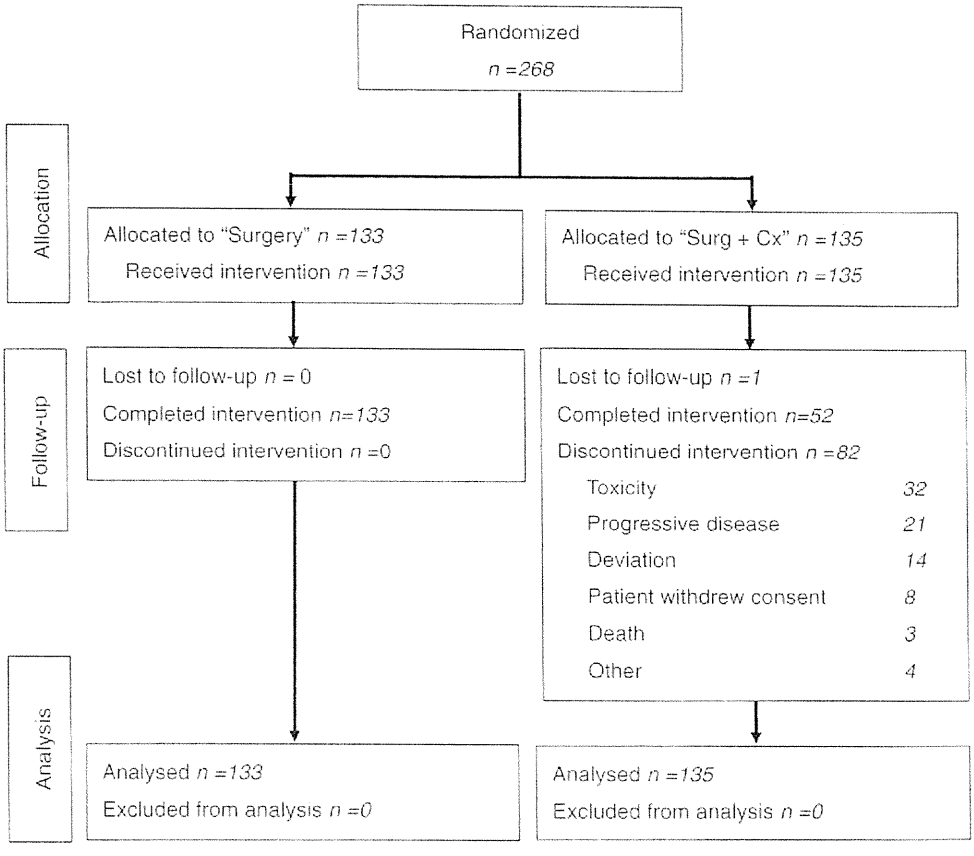

Table 1 Distribution of the main prognostic factors in the two treatment arms

No. of patients	Surgery ($n = 133$)	Surg + Cx ($n = 135$)	P*
Gender			0.601
Male	88	94	
Female	45	41	
Age (years)			0.043
Median	57	59	
Range	23–73	33–75	
Tumor diameter (cm)			0.324
Median	5.5	6.0	
Range	2.4–19.0	1.5–18.0	
Macroscopic type			0.603
0	0	0	
1	5	1	
2	31	32	
3	76	78	
4	14	15	
5	7	9	
Liver metastasis			–
Absent (H0)	133	135	
Present (H1)	0	0	
Peritoneal metastasis (macroscopic)			0.245
Absent (P0)	131	135	
Present (P1)	2	0	
Type of gastrectomy			1.000
Total	76	76	
Proximal	0	1	
Distal	57	58	
Combined resection			0.787
No	39	37	
Yes	94	98	
Spleen	73	74	
Pancreas	26	26	
Adrenal gland	7	5	
Colon	6	6	
Other	50	50	
Pathological depth of tumor invasion (T)			0.613
T1			
m, sm	2	3	
T2			
mp	5	7	
T2			
ss	34	41	
T3			
se	88	77	
T4			
si	4	7	
Pathological extent of lymph node metastasis (N)[a]			0.794
N0	32	41	
N1	51	49	
N2	38	35	
N3	5	4	
N4	7	5	
Involvement of the resection margin			
Proximal			1.000
Negative	133	134	
Positive	0	1	
Distal			0.498
Negative	133	133	
Positive	0	2	
Tumor histology			0.991
Common types			
Papillary	1	2	
Well differentiated	10	12	
Moderately differentiated	33	35	
Poorly differentiated	69	67	
Mucinous	6	5	
Signet ring cell	13	13	
Other types			
Carcinoid	1	0	
Unknown	0	1	

Surg + Cx Surgery plus adjuvant chemotherapy, *m* mucosa including muscularis mucosae, *sm* submucosa, *mp* muscularis propria, *ss* subserosal, *s* serosa, *si* serosa-infiltrating

* A *t*-test was used for continuous variables. Fisher's exact test was used for discrete variables

[a] Pathological extent of lymph node metastasis was classified based on the Japanese Classification of Gastric Carcinoma 1st English edition. Data are missing for one patient in the Surg + Cx arm

intention-to-treat basis. Analyses for toxicity were conducted for all of the randomly assigned patients. All statistical analyses were conducted with SAS software (version 8.1, SAS Institute, Cary, NC).

Results

From January 1993 to March 1998, 268 patients were enrolled in this phase III study. Of the 268 eligible patients enrolled, 133 patients were assigned to the surgery-alone arm and 135 patients to the adjuvant chemotherapy arm (Fig. 2). Distribution of the main prognostic factors across the two arms was well balanced (Table 1). There were no significant differences between the two groups in the

Table 2 Frequency of postoperative morbidity and mortality

	Surgery ($n = 133$)	Surg + Cx ($n = 135$)	P
Surgical morbidity			
Leakage	3	9	0.137
Pancreatic fistula	20	14	0.275
Peritoneal abscess	8	13	0.364
Pneumonia	3	1	0.369
Other infections	9	6	0.439
Stomal stenosis	2	1	0.621
Ileus	0	4	0.122
Miscellaneous	4	16	0.009
Non-surgical morbidity			
Creatinine ≥2.0	3	21	<0.001
AST, ALT ≥100	44	43	0.896
Hospital death	1	4	0.370

Surg + Cx Surgery plus adjuvant chemotherapy

institution and the combination of macroscopic T-category and N-category as stratification factors. There were also no significant differences in gender, but the surgery-alone group was younger than the adjuvant chemotherapy group ($P = 0.0426$). All patients underwent gastrectomy with D2 or greater lymph node dissection. The operative procedures were similar in the two groups. Seventy-six of 133 patients (57.1%) in the surgery-alone arm and 76 of 135 (56.3%) in the adjuvant chemotherapy arm underwent total gastrectomy, and all the other patients except one underwent distal gastrectomy. Similar numbers of patients in each group underwent combined resections involving the spleen, pancreas, adrenal gland, colon or other organs. There were no significant differences between the two groups in tumor diameter, macroscopic type, presence of liver or macroscopic peritoneal metastasis, depth of tumor invasion, extent of lymph node metastasis, involvement of the resection margins and histological type.

Of the 135 patients of the adjuvant chemotherapy arm, 82 patients discontinued chemotherapy as is shown in Fig. 2. Thirty-two patients discontinued chemotherapy because of toxicity, among whom 19 patients could not start intravenous chemotherapy. Therefore, only the remaining 13 patients terminated chemotherapy during intravenous CDDP/5-FU or oral UFT.

The perioperative mortality was low. There were 4 treatment-related deaths. One of 133 patients in the surgery-alone arm died because of postoperative complications, and 3 of 135 in the adjuvant chemotherapy arm died because of postoperative complications or chemotherapy toxicity (2 of 3 did not receive chemotherapy). There were no significant differences in the frequency of surgical morbidity except for miscellaneous events such as wound infection (Table 2). As for postoperative non-surgical morbidity, renal dysfunction (JCOG grade 3–4) within 3 months after surgery was observed only in 5 patients in the adjuvant chemotherapy group. Adverse events were generally mild. The frequencies of adverse events according to JCOG criteria are listed in Table 3. Grade 4 toxicity was observed in 3 patients in the surgery-alone and 2 patients in adjuvant chemotherapy arm.

Table 3 Adverse events

Arm	Grade[a]					% Grade 4	Total
	0	1	2	3	4		
Surgery							
Leukopenia	90	28	9	0	0	0	127
Anemia	58	31	34	4	–	–	127
Thrombocytopenia	125	1	1	0	0	0	127
Increase in bilirubin	83	–	32	11	1	0.8	127
Increase in AST	22	62	27	14	2	1.6	127
Increase in ALT	26	55	29	16	1	0.8	127
Increase in creatinine	109	13	4	1	0	0	127
Nausea or vomiting	110	16	4	0	0	0	130
Diarrhea	122	6	2	0	0	0	130
Stomatitis	129	1	0	0	0	0	130
Neuropathy (sensory)	130	0	0	0	0	0	130
Skin-other (pigmentation)	130	0	0	0	0	0	130
Surg + Cx							
Leukopenia	76	30	19	3	1	0.8	129
Anemia	31	24	56	18	–	–	129
Thrombocytopenia	123	4	1	0	1	0.8	129
Increase in bilirubin	67		43	15	1	0.8	126
Increase in AST	25	61	27	16	0	0	129
Increase in ALT	29	70	21	9	0	0	129
Increase in creatinine	70	38	16	5	0	0	129
Nausea or vomiting	80	31	19	1	0	0	131
Diarrhea	113	17	1	0	0	0	131
Stomatitis	126	4	1	0	0	0	131
Neuropathy (sensory)	128	3	0	0	0	0	131
Skin-other (pigmentation)	130	1	0	0	0	0	131

Surg + Cx Surgery plus adjuvant chemotherapy

[a] Toxicity graded according to JCOG criteria [13]

In 6 years of planned follow-up, there was no significant differences in OS (Fig. 3) and relapse-free survival (Fig. 4). The 5-year overall survival rate in the adjuvant chemotherapy arm was 62.0% (95% confidence interval 53.7–70.2) versus 60.9% (52.6–69.2) in the surgery-alone arm ($P = 0.482$, one-sided stratified log-rank test). The 5-year relapse-free survival rate was 57.5% (49.1–65.9) in the adjuvant chemotherapy group versus 55.6% (47.2–64.1) in the surgery-alone group ($P = 0.512$) one-sided stratified log-rank test). Sixty-six of 135 patients (48.9%) in the adjuvant chemotherapy arm and 64 of 133 patients

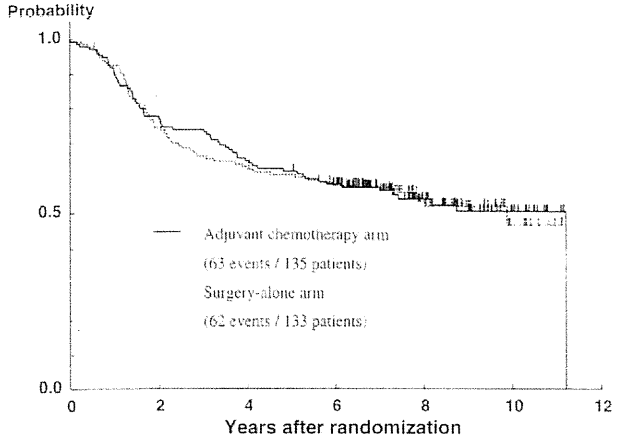

Fig. 3 Overall survival. There was no significant difference in overall survival: 5-year survival rate 62.0% (95% confidence interval 53.7–70.2) in the adjuvant chemotherapy group versus 60.9% (52.6–69.2) in the surgery-alone group, $P = 0.482$

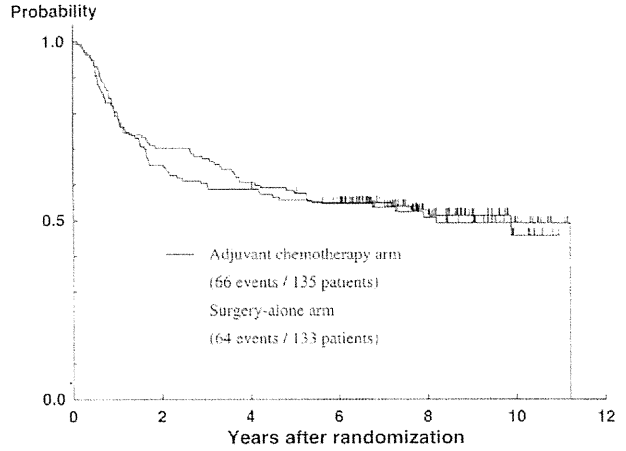

Fig. 4 Relapse-free survival. There was no significant difference in relapse-free survival: 5-year relapse-free survival rate 57.5% (95% confidence interval 49.1–65.9) in the adjuvant chemotherapy group versus 55.6% (47.2–64.1) in the surgery-alone group, $P = 0.512$

(48.1%) in the surgery-alone arm experienced cancer recurrence or death. The results for survival were not substantially changed after adjustment for age by Cox proportional hazards regression. Sites of recurrence, including peritoneal dissemination as the most common site, did not differ significantly between the two arms (Table 4).

Discussion

The present study is a prospective randomized controlled phase III clinical trial of adjuvant chemotherapy with cisplatin followed by UFT conducted by the GCSSG subgroup of JCOG to clarify the efficacy of adjuvant

Table 4 Site of cancer recurrence

Site of recurrence	Surgery ($n = 133$)	Surg + Cx ($n = 135$)	Total
Peritoneal dissemination	23	19	42
Liver metastases	9	16	25
Metastases to other organs	5	7	12
Local (remnant stomach)	0	2	2
Local (other sites)	4	2	6
Distant lymph nodes	10	6	16
Other	5	0	5
Death before recurrence	8	14	22
Total	64	66	130

Surg + Cx Surgery plus adjuvant chemotherapy

chemotherapy after curative resection with extended (D2 or greater) lymphadenectomy for macroscopically serosa-positive gastric cancer. There was no benefit in overall and relapse-free survival with this regimen, and there was no difference between the arms in the site of recurrence. The frequency of postoperative morbidity was similar in the two groups, suggesting that administration of intraperitoneal cisplatin does not affect postoperative morbidity [16].

The recent AMC 0101 trial demonstrated that adjuvant chemotherapy with intraperitoneal cisplatin and early mitomycin-C plus long-term doxifluridine plus cisplatin (iceMFP) improved survival of patients with grossly serosa-positive advanced gastric cancer when compared with mitomycin-C plus short-term doxifluridine (Mf) [17]. Another Korean randomized trial, AMC 0201, showed there was no benefit in survival with adjuvant mitomycin-C plus long-term doxifluridine plus cisplatin when compared with Mf [18]. Taken together, these two studies suggest that improved OS might have been due to intraperitoneal cisplatin and/or mitomycin-C when given early. However, the AMC 0101 trial could not definitively demonstrate whether intraperitoneal chemotherapy itself contributed to improved survival. The adjuvant chemotherapy in the present study might be insufficient because it consisted of just one single course of intravenous cisplatin/5-FU. However, in the AMC 0201 trial, repeated administration of doxifluridine plus cisplatin did not show any benefit over short-term mitomycin-C plus doxifluridine.

Only 39% in the adjuvant chemotherapy arm actually completed the chemotherapy regimen in the present study, although UFT toxicity was generally mild. Patients tend to suffer from gastrointestinal disturbances after gastrectomy even without postoperative chemotherapy. Compliance of highly toxic regimens significantly decreases if given in early postoperative period, as observed in the MAGIC trial, which demonstrated the superiority in overall survival of pre- and postoperative chemotherapy compared with

surgery-alone [19]. The MAGIC trial reported that 57% of patients in the chemotherapy group were able to receive postoperative chemotherapy and that only 43% of patients in the chemotherapy group actually completed the full 6 cycles, although 88% of patients completed the 3 cycles of neoadjuvant chemotherapy. Thus, special consideration should be given to compliance when choosing a regimen for postoperative adjuvant chemotherapy. Powerful regimens should be planned for neoadjuvant settings in more advanced disease and less toxic drugs for postoperative use for earlier stage disease, such as stage II [12, 20, 21].

In conclusion, there was no benefit in overall and relapse-free survival with adjuvant cisplatin followed by UFT for patients with macroscopically serosa-positive gastric cancer after curative resection. When recurrence occurs, there was no difference in the site between the two treatment groups. Therefore, we do not recommend adjuvant chemotherapy with this regimen for this patient population in clinical practice.

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ORIGINAL REPORT

Five-Year Outcomes of a Randomized Phase III Trial Comparing Adjuvant Chemotherapy With S-1 Versus Surgery Alone in Stage II or III Gastric Cancer

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See accompanying editorial on page 4348; listen to the podcast by Dr Mayer at www.jco.org/podcast

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ABSTRACT

Purpose
The first planned interim analysis (median follow-up, 3 years) of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer confirmed that the oral fluoropyrimidine derivative S-1 significantly improved overall survival, the primary end point. The results were therefore opened at the recommendation of an independent data and safety monitoring committee. We report 5-year follow-up data on patients enrolled onto the ACTS-GC study.

Patients and Methods
Patients with histologically confirmed stage II or III gastric cancer who underwent gastrectomy with D2 lymphadenectomy were randomly assigned to receive S-1 after surgery or surgery only. S-1 (80 to 120 mg per day) was given for 4 weeks, followed by 2 weeks of rest. This 6-week cycle was repeated for 1 year. The primary end point was overall survival, and the secondary end points were relapse-free survival and safety.

Results
The overall survival rate at 5 years was 71.7% in the S-1 group and 61.1% in the surgery-only group (hazard ratio [HR], 0.669; 95% CI, 0.540 to 0.828). The relapse-free survival rate at 5 years was 65.4% in the S-1 group and 53.1% in the surgery-only group (HR, 0.653; 95% CI, 0.537 to 0.793). Subgroup analyses according to principal demographic factors such as sex, age, disease stage, and histologic type showed no interaction between treatment and any characteristic.

Conclusion
On the basis of 5-year follow-up data, postoperative adjuvant therapy with S-1 was confirmed to improve overall survival and relapse-free survival in patients with stage II or III gastric cancer who had undergone D2 gastrectomy.

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INTRODUCTION

In 2008, there were 737,000 deaths from gastric cancer worldwide. Gastric cancer is the second leading cause of cancer-related death, with the highest mortality rates in East Asia, including Japan, Korea, and China (28.1 per 100,000 in males; 13.0 per 100,000 in females).[1] Approximately 60% of gastric cancers in the world are diagnosed in this area. The mainstay of treatment for gastric cancer is surgery. However, in stages II (excluding T1 disease) and III (moderately advanced), an appreciable proportion of patients have recurrence, even after curative resection. Consequently, various regimens for adjuvant chemotherapy have been implemented to prevent postoperative recurrence.

Although the results of many randomized, controlled studies conducted to verify the effectiveness of postoperative adjuvant chemotherapy for gastric cancer were negative on an individual study basis, meta-analyses of these results have suggested that postoperative adjuvant chemotherapy is therapeutically useful in patients with gastric cancer.[2-7] However, no regimens have been clearly recommended for adjuvant chemotherapy after gastrectomy with D2 lymphadenectomy (D2 gastrectomy), established as the standard procedure for advanced gastric cancer in East Asia.

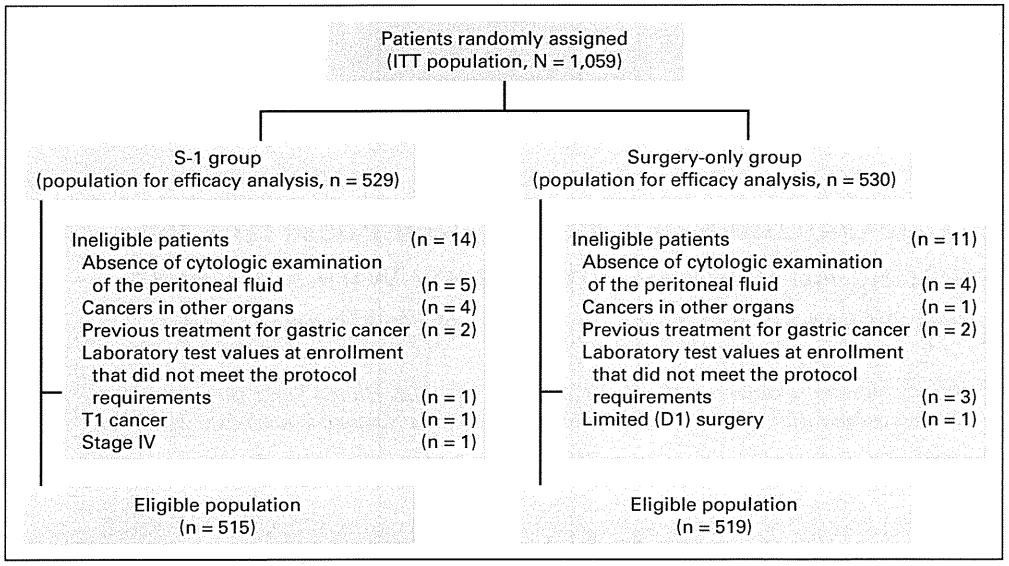

Fig 1. CONSORT diagram. D1 gastrectomy; ITT, intent-to-treat.

The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) is a randomized phase III trial to confirm the effectiveness of 1-year postoperative treatment with S-1 compared with surgery alone in patients with stage II or III gastric cancer who underwent D2 gastrectomy. S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) is a dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine preparation combining tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1.[8,9] Two phase II studies[10,11] in patients with advanced or recurrent gastric cancer obtained high response rates exceeding 40%. Postoperative adjuvant chemotherapy with S-1 was thus expected to be effective.

In this phase III trial, 1,059 patients with histologically confirmed stage II or III gastric cancer who underwent D2 gastrectomy were enrolled. A protocol-based interim analysis performed 1 year after the completion of enrollment (median follow-up, 3 years) confirmed that S-1 was effective. Because statistical analysis indicated that there was minimal probability that the results of this study would turn out to be negative after 5 years of follow-up, an independent data and safety monitoring committee recommended that the results should be disclosed at that time. An analysis of the results available at that time showed that the 3-year overall survival (OS) was 80.1% in the S-1 group compared with 70.1% in the surgery-only group. S-1 was demonstrated to reduce the risk of death by 32% (hazard ratio [HR], 0.68; 95% CI, 0.52 to 0.87; $P = .003$).[12] Although the study results were disclosed early because of these promising results, we considered it important to have 5-year follow-up data available. Such data would facilitate a comparison of our results for 5-year OS and other outcomes with those of previous trials. Moreover, this analysis may justify

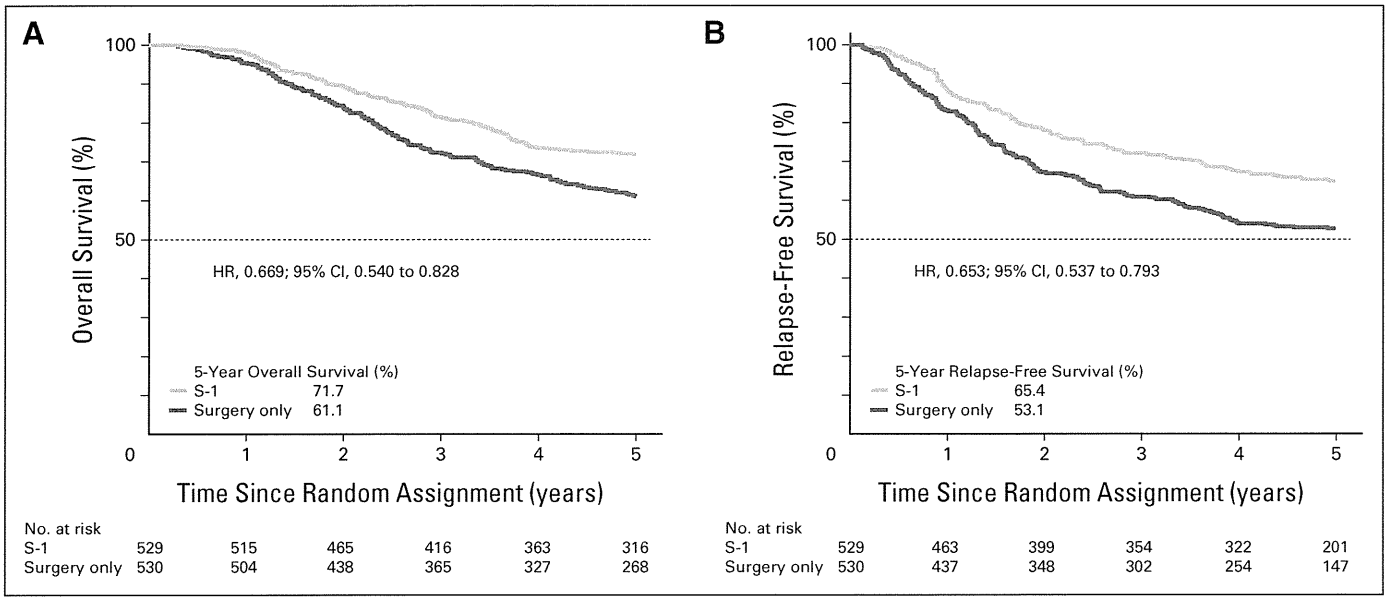

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for all randomly assigned patients. HR, hazard ratio.

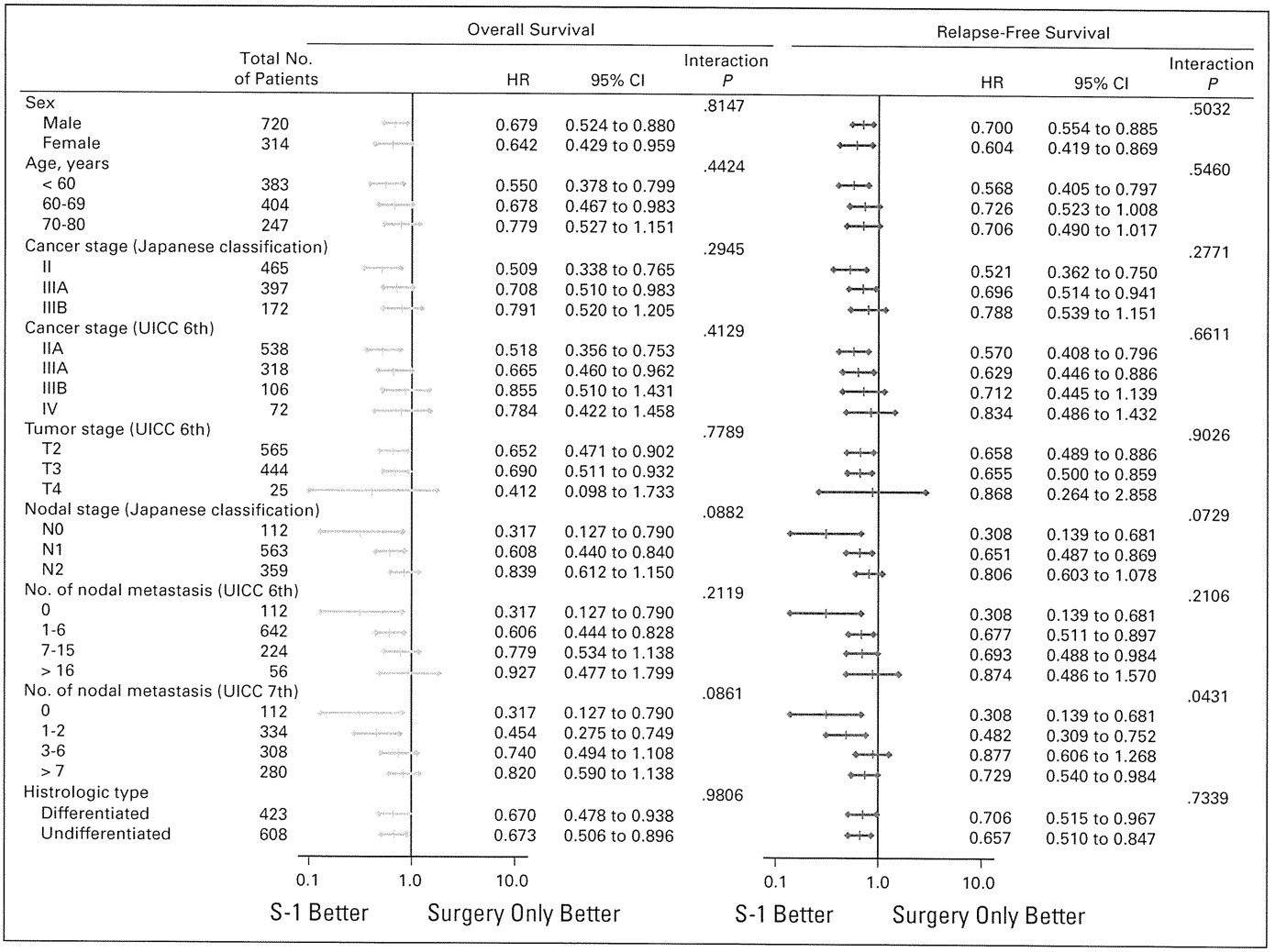

Fig 3. Subgroup analysis: overall survival and relapse-free survival for eligible population. In the surgery-only group, cancers in three patients could not be classified as differentiated or undifferentiated. HR, hazard ratio; UICC, International Union Against Cancer (UICC) TNM Classification of Malignant Tumours.

the present controversial use of 3-year relapse-free survival (RFS) as the primary end point in clinical trials of adjuvant chemotherapy for potentially curable gastric cancer.

PATIENTS AND METHODS

The trial was conducted in accordance with the World Medical Association Declaration of Helsinki and Japanese Good Clinical Practice guidelines. This protocol was approved by the institutional review board of each participating hospital (see Data Supplement). Written informed consent was obtained from all patients. Tumor stage classification and D classification were in accordance with the Japanese Classification of Gastric Carcinoma (Second English Edition).[13]

Patients and Treatment

Eligibility criteria were as follows: a histopathologically confirmed diagnosis of stage II (except for T1 disease), IIIA, or IIIB gastric cancer; R0 resection (with no tumor cells at the margin) with D2 or more extensive lymph node dissection; no evidence of hepatic, peritoneal, or distant metastasis; no tumor cells in peritoneal fluid on cytologic analysis; age 20 to 80 years; no previous treatment for cancer except for the initial gastric resection for the primary lesion; and adequate organ function. Patients were enrolled within 6 weeks after surgery over the telephone or by means of facsimile. Patients were randomly assigned to either the S-1 group or the surgery-only group. The assignments were made by the minimization method according to disease stage (II, IIIA, or IIIB) at the ACTS-GC data center.

Patients assigned to the S-1 group received S-1 in a daily dose of 80, 100, or 120 mg in two divided doses. The dose of S-1 was assigned on the basis of body surface area. S-1 was given for 4 weeks, followed by 2 weeks of rest. Treatment was continued for 1 year after surgery. Patients assigned to the surgery-only group received no anticancer treatment postoperatively until the confirmation of recurrence. The criteria for dose reduction and toxicity were described previously.[12]

Follow-Up

In the S-1 group, the results of blood tests and clinical findings were assessed at 2-week intervals during treatment with S-1. In the surgery-only group, patients came to the hospital for re-examination at least once every 3 months for the first year after surgery. From the second year onward, all patients were followed up in the same manner. Relapse was confirmed by imaging studies, including ultrasonography, computed tomography, and GI radiography, as well as endoscopy. Patients underwent at least one imaging study at 6-month intervals for the first 2 years after surgery and at 1-year intervals until 5 years after surgery. Individual patients were followed up for 5 years from the date of random assignment.

Statistical Analysis

The sample size was calculated as follows. Given that the 5-year survival rate would be 70% in the surgery-only group, with an HR of 0.70, $\alpha = .05$ (two-sided), and a statistical power of 80%, we estimated that 1,000 patients would be required. OS and RFS were estimated on the basis of all randomly assigned patients. The results in eligible patients were analyzed according to disease stage. OS was defined as the interval from the date of random assignment to the date of death from any cause. RFS was defined as the interval from the date of random assignment to the date of confirming recurrence or death from any cause, whichever came first. Data for up to 5 years from the date of random assignment were analyzed. Data obtained after 5 years were not included in this analysis. The survival rate was estimated by using the Kaplan-Meier method. The Cox proportional hazards model was used to calculate HRs. All statistical analyses were done with SAS, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients

From October 2001 through December 2004, a total of 1,059 patients were enrolled at 109 centers throughout Japan; 529 were assigned to the S-1 group and 530 to the surgery-only group (intention-to-treat population; Fig 1). In both groups combined, 474 patients (44.8%) had stage II disease, 409 (38.6%) had stage IIIA disease, and 175 (16.5%) had stage IIIB disease. The numbers of patients with each stage of disease were similar in the two treatment groups. The groups were also well balanced with respect to the type of gastrectomy performed, the combined resection of other organs, and other factors. Details of the patient demographics and baseline characteristics have been reported previously.[12]

Fourteen patients in the S-1 group and 11 in the surgery-only group were ineligible, as shown in Figure 1. In the S-1 group, 12 patients did not receive S-1. In the surgery-only group, four patients received adjuvant treatment at their strong request, violating the protocol.

Safety

Details of the safety analysis have been reported previously.[12] In brief, except for anorexia (incidence, 6%), grade 3 or 4 adverse events occurred in less than 5% of the patients in the S-1 group.

OS and RFS in All Randomly Assigned Patients

Among 1,059 patients, 145 and 199 died, 32 and 42 patients are alive with recurrence, and 352 and 289 patients are alive without recurrence in the S-1 and the surgery-only groups, respectively. Data on 131 patients lost to follow-up within 5 years from the date of random assignment were censored.

OS and RFS were analyzed in all 1,059 randomly assigned patients. The 5-year OS rate was 71.7% (95% CI, 67.8% to 75.7%) in the S-1 group and 61.1% (95% CI, 56.8% to 65.3%) in the surgery-only group. The HR for death in the S-1 group compared with the surgery-only group was 0.669 (95% CI, 0.540 to 0.828), indicating that S-1 reduced the risk of death by 33.1% (Fig 2A). The 5-year RFS rate was 65.4% (95% CI, 61.2% to 69.5%) in the S-1 group and 53.1% (95% CI, 48.7% to 57.4%) in the surgery-only group. The HR for relapse in the S-1 group compared with that in the surgery-only group was 0.653 (95% CI, 0.537 to 0.793). Treatment with S-1 thus reduced the risk of relapse by 34.7% (Fig 2B).

Subgroup Analysis

OS and RFS in eligible patients were analyzed according to sex, age, disease stage (Japanese Classification, 13th edition), and histologic type. There was no interaction between treatment and any of these factors (Fig 3). Kaplan-Meier estimates of OS and RFS are shown according to disease stage, which was used as a stratification factor when patients were randomly assigned (Figs 4, 5, and 6).

The 5-year OS rates of the patients with stage II disease were 84.2% (95% CI, 79.5% to 89.0%) in the S-1group and 71.3% (95% CI, 65.3% to 77.2%) in the surgery-only group, with an HR of 0.509 (95% CI, 0.338 to 0.765; Fig 4A). Their 5-year RFS rates were 79.2% (95% CI, 73.8% to 84.6%) in the S-1 group and 64.4% (95% CI, 58.1% to 70.7%) in the surgery-only group, with an HR of 0.521 (95% CI, 0.362 to 0.750; Fig 4B). The 5-year OS rates of stage IIIA patients were 67.1% (95% CI, 60.4% to 73.8%) in the S-1 group and 57.3% (95% CI, 50.3% to 64.2%) in the surgery-alone group, with an HR of 0.708 (95% CI, 0.510 to 0.983; Fig 5A). Their 5-year RFS rates were 61.4% (95% CI, 54.5% to 68.4%) in the S-1 group and 50.0% (95% CI, 42.9% to 57.0%) in the surgery-alone group, with an HR of 0.696 (95% CI,

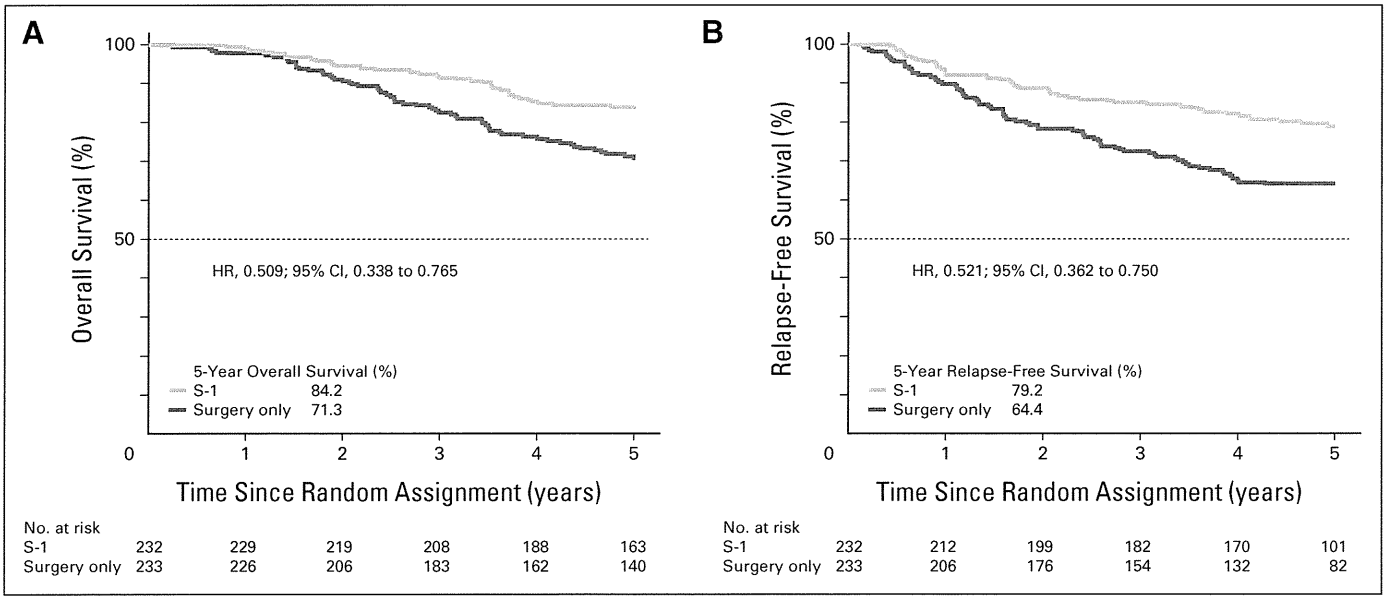

Fig 4. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage II gastric cancer. HR, hazard ratio.

