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Pharmacokinetics of Oxaliplatin in Gastrointestinal Cancer Patients with Malignant Ascites

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Summary

The pharmacokinetics of oxaliplatin in plasma and ascitic fluid was investigated in 5 gastrointestinal cancer patients with malignant ascites. Oxaliplatin was administered at 85 mg/m^2 by 2-hour infusion in the FOLFOX4 regimen, and the concentrations of total and free platinum were measured. There was a trend of lower plasma C_{max} values of total platinum in patients with a larger volume of ascitic fluid. The AUC_{0-t} values of mean concentration curves of total plasma platinum, total ascites platinum, free plasma platinum, and free ascites platinum were 31.15, 7.96, 4.93 and 2.93 μg·h/mL, respectively. The concentrations of free ascites platinum were similar to those of free plasma platinum at the last sampling time of 26 h in each patient. The decrease or disappearance of ascitic fluid was observed in 4 patients. These results suggest that oxaliplatin exerted a beneficial effect in gastrointestinal cancer patients with malignant ascites, even when administered intravenously.

***Key words*: Gastrointestinal cancer, ascites, oxaliplatin, FOLFOX4, pharmacokinetics.**

INTRODUCTION

The peritoneal dissemination of gastrointestinal cancer occurs mainly as a direct invasion of cancer cells [1]. It is more common in advanced gastric cancer and causes many serious complications including massive ascitic fluid, resulting in the poor prognosis of the patient [2]. For the treatment of malignant ascites, the antitumor activity and pharmacokinetics of intraperitoneal administration of cisplatin have been studied [3,4]. However, its usefulness still remains unclear. Oxaliplatin is a third-generation platinum consisting of the diaminocyclohexane carrier ligand and the leaving group of oxalate. Its antitumor spectrum in tumor models differs from that of cisplatin [5,6]. The combination treatment of oxaliplatin with leucovorin (LV) plus 5-fluorouracil (FU), designated as FOLFOX4 regimen, has been widely used for the first- and second-line therapy of metastatic colorectal cancer [7-9]. The effectiveness of such combination therapies including FOLFOX4 has also been reported against gastric cancers in phase II or III studies [10-13]. Oxaliplatin has also been used for the treatment of colorectal peritoneal carcinomas by intraperitoneal administration [14,15]. Recently the modified FOLFOX4 regimen was reported to be effective against gastric cancer patients with malignant ascites [16]. However, as far as we know, no clinical studies have been conducted to investigate the pharmacokinetics of oxaliplatin administered systemically in patients with malignant ascites. This study was planned to investigate the pharmacokinetics of oxaliplatin in both plasma and malignant ascitic fluid. Furthermore, the efficacy of the FOLFOX4 treatment was preliminarily examined against measurable lesion and ascites.

PATIENTS AND METHODS

This study was carried out in accordance with the Declaration of Helsinki, as amended in Edinburgh, Scotland, October 2000, and the good clinical practice. The study protocol was approved by the Institutional Review Board of Nihon University School of Medicine.

Inclusion criteria and study design: This study was a prospective and open clinical trial. The primary objective was to investigate the pharmacokinetics of oxaliplatin in both plasma and malignant ascites. Furthermore, the efficacy of FOLFOX4 treatment was preliminarily examined against measurable lesion and ascites. The inclusion criteria were: (1) histologically proven, unresectable gastrointestinal cancer with malignant ascites; (2) age 20-74 years old; (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2; (4) adequate organ functions defined as white blood cell count of 4-12 x 10^9/L, platelet count ≥100 x 10^9/L, serum transaminase (aspartate aminotransferase and alanine aminotransferase) levels ≤100 U, serum bilirubin level ≤1.5 mg/dL and serum creatinine ≤ upper limit of normal range; (5) no prior FOLFOX chemotherapy; (6) no other severe medical conditions; and (7) provision of written informed consent.

Treatment and sample collection: FOLFOX4 consisted of 2-h infusion of oxaliplatin, 85 mg/m^2 in 250 ml of 5% dextrose solution and *l*-LV 100 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and 22-h infusion of 5-FU 600 mg/m^2 on Day 1, and the same therapy without oxaliplatin on Day 2, and this was repeated every 2 weeks. A drain was implanted in the peritoneum of patients for the collection of ascitic fluid prior to FOLFOX4 treatment. The volume of ascitic fluid was estimated by applying the method reported for automated hepatic volumetry for living related liver transplantation [17]. Briefly, an experienced radiologist manually traced the contours of ascitic fluid on a Digital Imaging and Communications in Medicine viewer. The circumscribed areas were then multiplied by the CT section thickness. In Patient No.1, blood and ascitic fluid were collected at pre-dose, 15, 60 min, 2, 2.3, 2.75, 3.0 and 4.0 h after the initiation of the first oxaliplatin administration. In other patients, they were collected at pre-dose, 60 min, 2.0, 2.3, 4.0, 6.0 and 26 h similarly. Samples were collected into a heparinized tube at a volume of 8 mL at each sampling time, centrifuged at 1,050 × g for 10 min at 4°C, and 1 mL of each supernatant was stored at -20°C. The remaining samples were used for the ultrafiltration to measure free platinum concentration. Namely

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the plasma and ascites samples were centrifuged at 1,050 × g for 30 min at 4°C by using the Amicon MPSI micropartition system with YMT membranes (30,000 MW cut-off) [18]. The supernatant was stored at -20°C.

Drug assay: The platinum concentration of plasma, plasma ultrafiltrate, ascitic fluid, and ascitic fluid ultrafiltrate kept at -20°C was determined by flameless atomic absorption spectrophotometric analysis according to the method previously described [19]. The lower limit of quantification of platinum was 25 ng/mL for plasma ultrafiltrate, ascitic fluid, and ascitic fluid ultrafiltrate, and 100 ng/mL for plasma.

Pharmacokinetic parameters: Peak concentration (C_{max}) and time to reach peak concentration (T_{max}) were recorded directly from plasma/ascites concentration-time data. Area under the plasma/ascites concentration-time curve between 0 h and the last sampling time (AUC_{0-t}) was calculated by the linear trapezoidal method by using Microsoft Excel software.

Safety and efficacy: The adverse events were graded using the National Cancer Institute Common Toxicity Criteria version 3. The response of measurable and assessable disease sites was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.

RESULTS

From July 2006 to April 2009, FOLFOX4 was administered to a total of 5 patients, 2 with gastric cancer and 3 with colorectal cancer, who had malignant ascites. The patient demographics and characteristics are shown in *Table 1*. The patients consisted of 3 men and 2 women, with a median age of 58 years (range: 50-65 years). The median body surface area was 1.54 m^2 (range: 1.22-1.73 m^2), and the median dose of oxaliplatin was 134 mg/body/day (range: 100-150 mg).

Pharmacokinetics of oxaliplatin

Plasma and ascites concentrations of oxaliplatin in each patient are shown in *Figure 1*. From the results obtained in Patient N. 1, the last sampling time of 4 h measured was indicated to be not enough. Therefore, in Patients N. 2-5, the last sampling time was extended to 26 h. The mean plasma and ascites concentration curves of oxaliplatin in these patients are shown in *Figure 2*. The pharmacokinetic parameters of C_{max} and T_{max}, which are expressed as actual values observed in each patient or in a mean concentration curve, and AUC_{0-t} are shown in *Table 2*. There was a trend of lower plasma C_{max} values of total platinum in patients with a larger volume of ascitic fluid (Patients N. 1 and 2). The C_{max} values of the mean concentration curve and their ranges in the 5 patients of total plasma platinum, total ascites platinum, free plasma platinum, and free ascites platinum were 2.74 (1.10-2.95), 0.31 (0.18-0.51), 0.52 (0.25-1.37) and 0.12 (0.11-0.20) μg/mL, respectively. The T_{max} values of ascites platinum concentration were later than those of plasma platinum concentration. Among 4 patients excluding Patient N. 1, the AUC_{0-t} values of the mean concentration curve and their ranges of total plasma platinum, total ascites platinum, free plasma platinum, and free ascites platinum were 31.15 (18.30-37.31), 7.96 (5.43-10.44), 4.93 (3.58-6.33) and 2.93 (2.38-3.54) μg•h/mL, respectively. Although the difference in total platinum C_{max} values between plasma and ascites was considerable, that of free platinum AUC_{0-t} values was less than C_{max} values. This may be associated with the similar concentration of free platinum between plasma and ascites at the last sampling time (26 h) in each patient.

Clinical effect

In Patients N. 2, 3 and 5, malignant ascites decreased clearly and disappeared after 1 to 4 cycles of FOLFOX4 treatment (*Table 3*). The treatment was continued up to 10 to 17 cycles. According to RECIST, a partial response was observed in Patients N. 2, 3 and 5, stable disease in Patient N. 4, and progression disease in Patient N. 1.

Four adverse events were observed; one grade-3 neutropenia in Patient N. 4, one grade-2 nausea/vomiting in Patient N. 3, one grade-2 diarrhea and one grade-1 neuropathy in Patient N. 1. These were not critical and could be managed easily.

DISCUSSION

The recently modified FOLFOX4 regimen with 85 mg/m^2 of oxaliplatin has been reported to be effective against gastric cancer patients with malignant ascites [16]. Forty-eight patients with malignant ascites were enrolled in this study, and 22 patients (45.8%) received mFOLFOX4 therapy as first-line treatment. The disappearance or improvement of ascites was seen in 17 patients (35.4%). However, the pharmacokinetics of oxaliplatin in patients with malignant ascites remains undetermined.

The results of our study show that FOLFOX4 can be given safely to gastrointestinal cancer patients with malignant ascites. Although the total platinum C_{max} values of ascites are considerably lower than those of plasma (0.31 vs 2.74 μg/mL by mean value), the free platinum AUC_{0-t} values of ascites are close to those of plasma (2.93 vs 4.93 μg•h/mL by mean value) (*Table 2*). This may be associated with the similar concentration of free

TABLE 1 - *Patient demographics and characteristics*

Clinical features	Patient number No. 1	No. 2	No. 3	No. 4	No. 5
Gender	Male	Female	Female	Male	Male
Age (Year)	50	65	55	62	58
Cancers	Colorectal	Colorectal	Gastric	Gastric	Colorectal
Previous operation	Stoma	No	No	Stoma	No
Histological type Differentiation	Moderately	Moderately	Poorly	Poorly	Moderately
Organ involvement					
Lymph node	+	+	−	−	+
Liver	+	−	−	−	−
Skin	−	−	+	−	−
Prior chemotherapy	S-1+CPT-11	None	S-1+Docetaxel	S-1+Docetaxel	None
Ascites (mL)	5396	4856	340	1469	3299

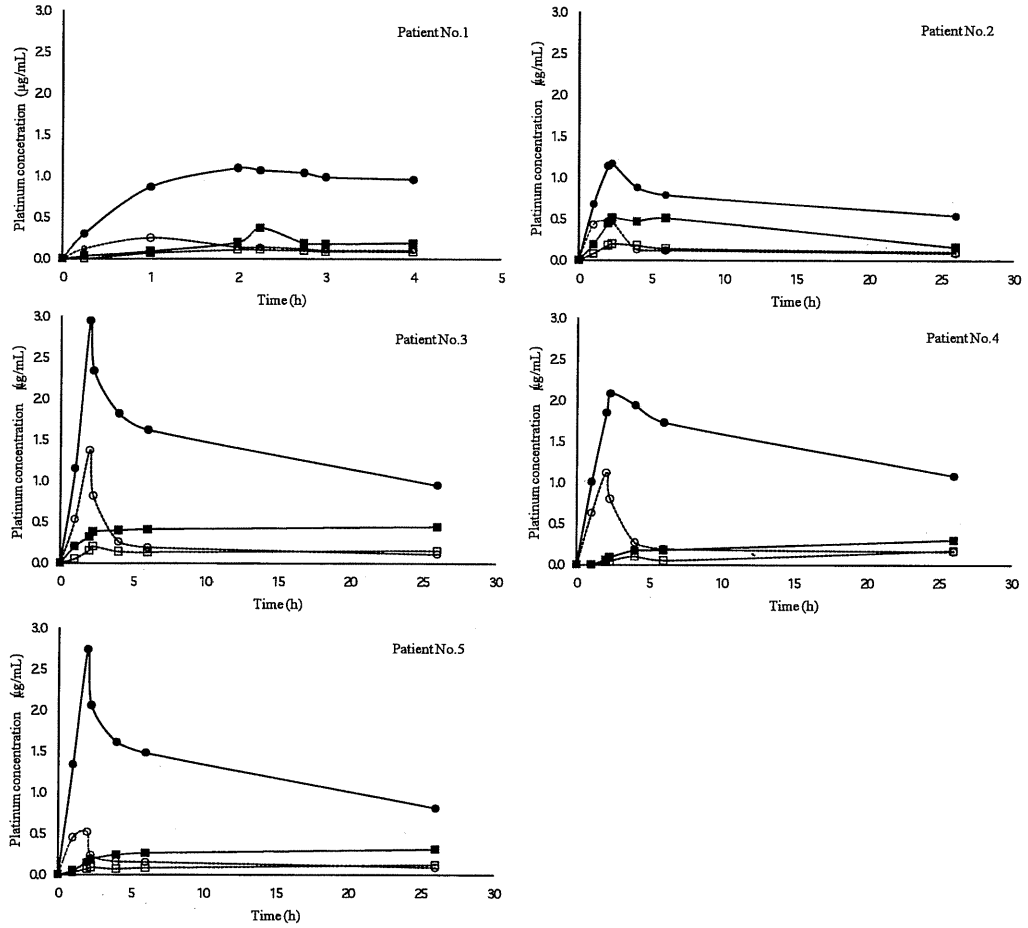

FIGURE 1 - Plasma and ascites concentration of platinum in each patient. Total platinum in plasma (filled circles, solid line), free platinum in plasma (open circles, dotted line), total platinum in ascites (filled squares, solid line), and free platinum in ascites (open squares, dotted line).

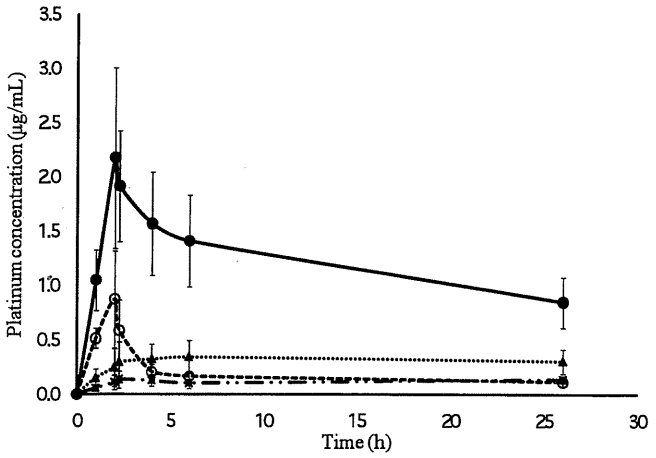

FIGURE 2 - Mean plasma and ascites concentration of platinum in Patients 2-5. Total platinum in plasma (filled circles, solid line), free platinum in plasma (open circles, dotted line), total platinum in ascites (filled squares, solid line), and free platinum in ascites (open squares, dotted line). Bars show the standard deviation.

platinum between plasma and ascites at the last sampling time (26 h) in each patient (*Figure 1*). Such a profile of free platinum concentration in both plasma and ascites after oxaliplatin administration may have resulted in its antitumor activity against malignant ascites (*Table 3*). Of the 5 patients enrolled, the ascitic fluid disappeared in 3 patients and decreased in 1 patient. It is speculated that oxaliplatin transferred from the plasma to the abdominal cavity after the intravenous administration and persisted in ascites. Then the ascites oxaliplatin concentration reached an equilibrium state with the plasma concentration, and oxaliplatin exerted an antitumor activity against peritoneal cancer cells.

Although the last sampling time in our study was 26 h, it was reported that free plasma platinum was detected even 21 days after the oxaliplatin administration of 130 mg/m^2 [20]. Furthermore, it was reported that the terminal half-life of free platinum after the oxaliplatin administration was long and its distribution volume was large [21]. Although the free platinum concentration detected by our method might include platinum bound to low molecular weight proteins or peptides [20,21], these pharmacokinetic profiles of oxaliplatin may be associated with its antitumor activity observed in our study. While it would have been ideal to investigate the pharmacokinetic profile of oxaliplatin in the plasma and ascitic fluid over a longer period, we limited the last sampling time to 26 h in this study to avoid the excessive burden caused by sampling procedure on the patients.

There was a trend of lower plasma C_{max} values of total platinum in patients with a larger volume of ascites (*Tables 1 and 2*). The volumes of ascitic fluid in Patients N. 1 and 2 were 5396 and 4856 mL, and the total plasma platinum C_{max} values were 1.10 and 1.17 μg/mL, respectively. On the other hand, the volumes of ascetic fluid in Patients N. 3 and 4 were 340 and 1469 mL, and the total plasma platinum C_{max} values were 2.95 and 2.08 μg/mL, respectively. Although the difference of C_{max} values between Patients N. 1/2 and 3/4 is not marked, it is noteworthy that the volume of ascitic fluid may affect the pharmacokinetics of oxaliplatin in plasma after FOLFOX4 treatment.

TABLE 2 - *Pharmacokinetic parameters of each patient and mean concentration.*

Patient Samples number		Total platinum			Ultrafiltrated platinum		
		C_{max} (μg/mL)	T_{max} (h)	AUC_{0-t} (μg•h/mL)	C_{max} (μg/mL)	T_{max} (h)	AUC_{0-t} (μg•h/mL)
1	Plasma	1.10	2.0	3.49	0.25	1.0	0.58
	Ascites	0.37	2.3	0.64	0.11	2.0/2.3*	0.31
2	Plasma	1.17	2.0	18.30	0.47	2.0/2.3*	3.58
	Ascites	0.51	2.3/6.0*	9.07	0.20	2.3	3.27
3	Plasma	2.95	2.0	36.07	1.37	2.0	5.88
	Ascites	0.44	26	10.44	0.15	2.0/26*	3.54
4	Plasma	2.08	2.3	37.31	1.12	2.0	6.33
	Ascites	0.18	6.0	5.43	0.17	26	2.50
5	Plasma	2.74	2.0	32.51	0.52	2.0	3.87
	Ascites	0.31	26	6.74	0.12	26	2.38
Mean	Plasma	2.74	2.0	31.15	0.52	2.0	4.93
	Ascites	0.31	26	7.96	0.12	26	2.93

T_{max} and C_{max} are actual values. AUC_{0-t} was calculated as described in "PATIENTS AND METHODS". Mean pharmacokinetic parameters were calculated from mean concentration data of Patients No. 2-5 in *Figure 2*. * The same C_{max} value was observed at two time-points.

TABLE 3 - *Antitumor activity.*

Site of tumor	Response	N. (%)	Patient N.
Ascites	Disappeared	3 (60)	2, 3, 5
	Decreased	1 (20)	4
	No change	1 (20)	1
	Increased	0	–
Measurable lesion	CR	0 (0)	–
	PR	3 (60)	2, 3, 5
	SD	1 (20)	4
	PD	0 (0)	1

CONCLUSION

The AUC_{0-t} values of free platinum in the ascitic fluid were relatively similar to those in the plasma in patients with gastrointestinal cancers treated with the FOLFOX4 regimen. The decrease in ascitic fluid was observed in 4 of 5 patients, suggesting that oxaliplatin exerts a beneficial effect in gastrointestinal cancer patients with malignant ascites. Further study is required to confirm the efficacy and safety of FOLFOX4 treatment in this patient population.

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JOURNAL OF CLINICAL ONCOLOGY 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.

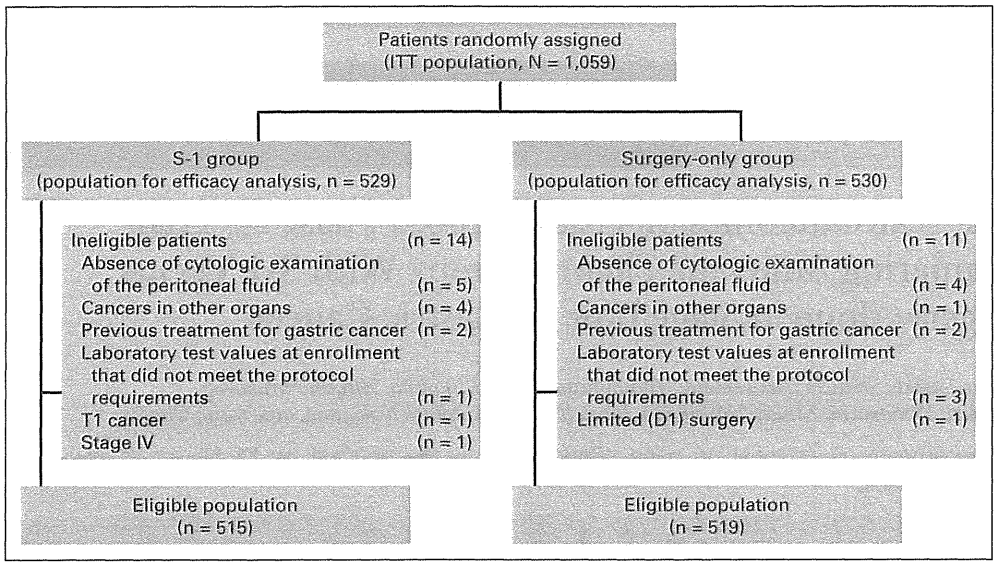

Fig 1. CONSORT diagram. D1 gastrectomy; ITT, intent-to-treat.

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

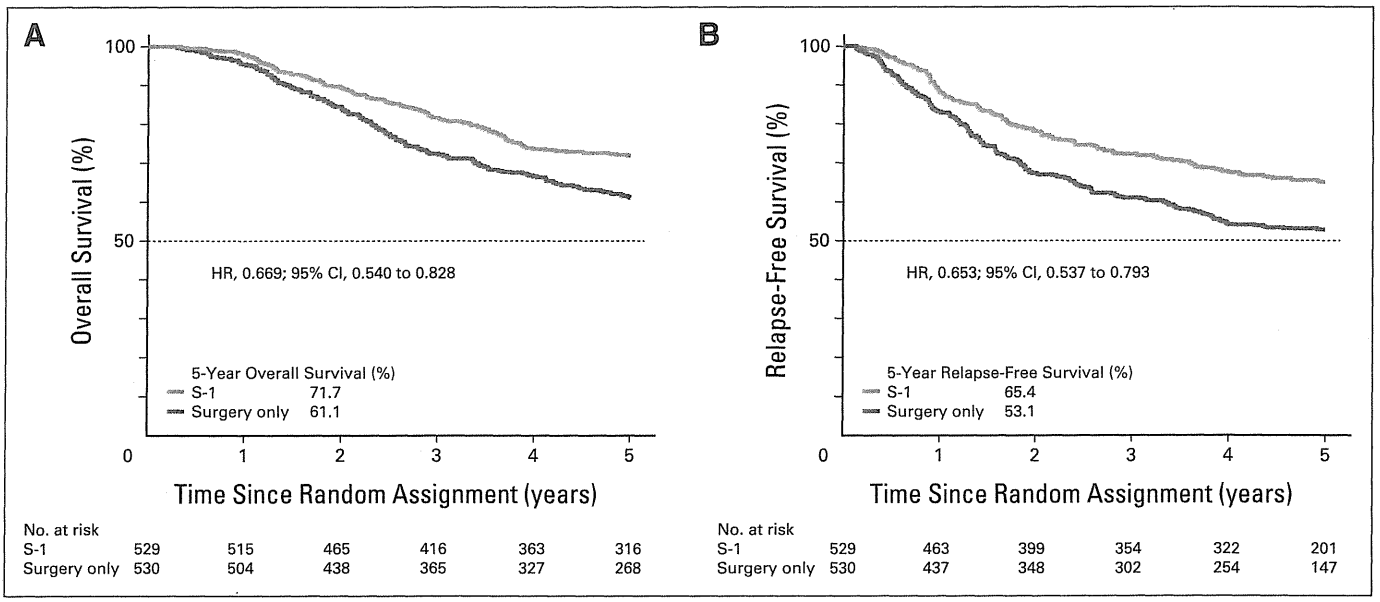

Fig 2. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for all randomly assigned patients. HR, hazard ratio.

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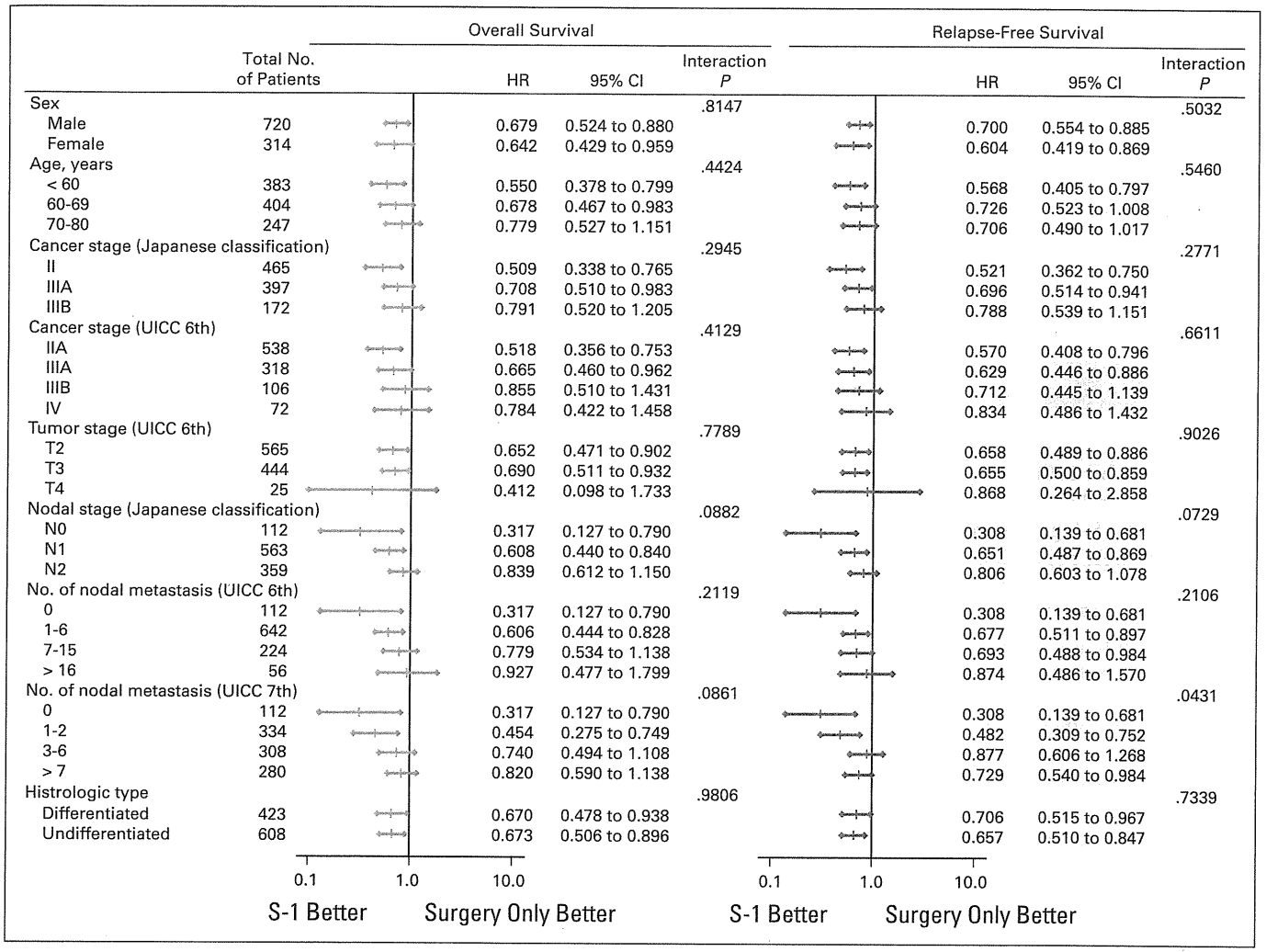

Fig 3. Subgroup analysis: overall survival and relapse-free survival for eligible population. In the surgery-only group, cancers in three patients could not be classified as differentiated or undifferentiated. HR, hazard ratio; UICC, International Union Against Cancer (UICC) TNM Classification of Malignant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

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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,

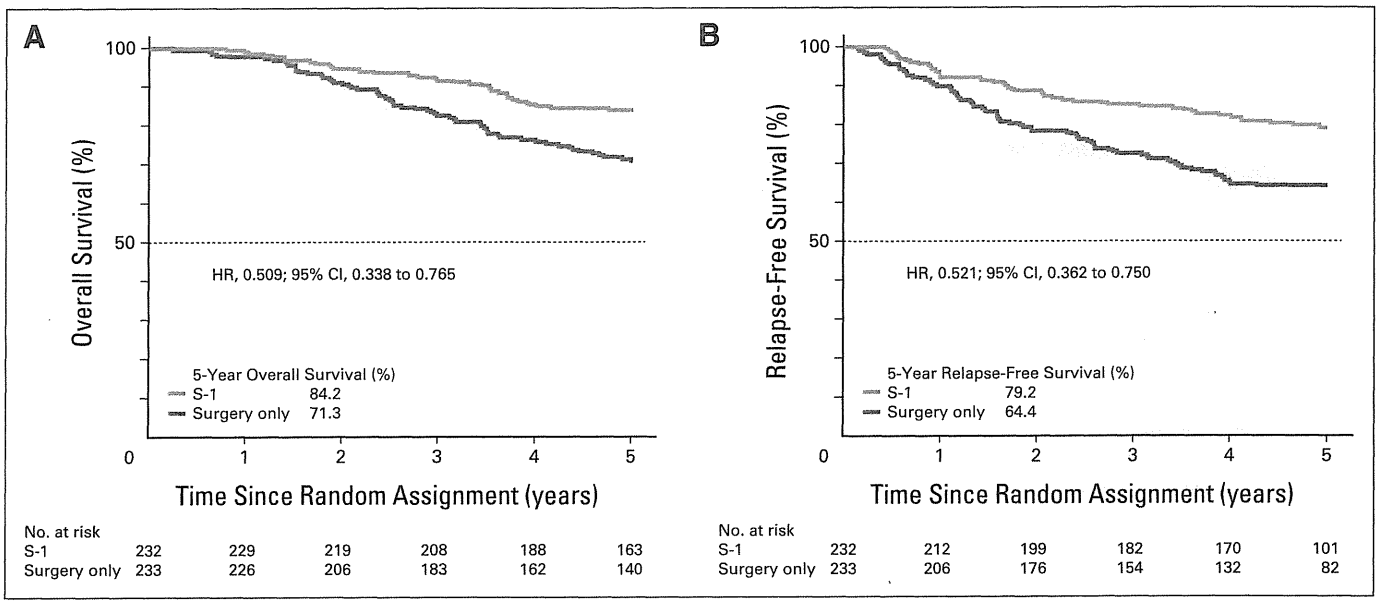

Fig 4. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage II gastric cancer. HR, hazard ratio.

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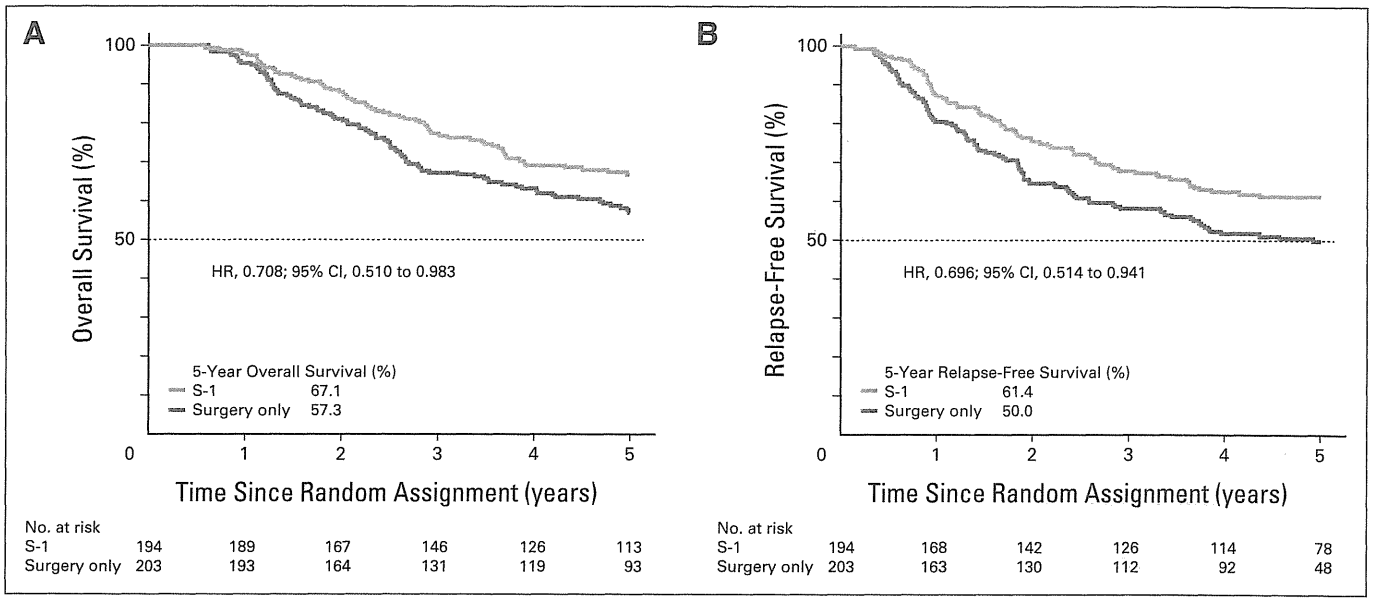

Fig 5. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage IIIA gastric cancer. HR, hazard ratio.

0.514 to 0.941; Fig 5B). As for stage IIIB disease, we enrolled 90 patients in the S-1 group and 85 in the surgery-only group; the 5-year OS rates were 50.2% (95% CI, 39.5% to 61.0%) in the S-1 group and 44.1% (95% CI, 33.1% to 55.0%) in the surgery-alone group, with an HR of 0.791 (95% CI, 0.520 to 1.205; Fig. 6A). Their 5-year RFS rates were 37.6% (95% CI, 27.0% to 48.2%) in the S-1 group and 34.4% (95% CI, 24.1% to 44.7%) in the surgery-alone group, with an HR of 0.788 (95% CI, 0.539 to 1.151; Fig 6B).

Site of First Relapse

Common sites of first relapse were the peritoneum, hematogenous sites, and lymph nodes (Table 1). Rates of metastasis and relapse were consistently lower in the S-1 group than in the surgery-only group for all sites. In particular, the rates of recurrence in lymph nodes and of peritoneal relapse were markedly lower in the S-1 group.

DISCUSSION

To the best of our knowledge, the ACTS-GC study is the first large clinical trial of adjuvant chemotherapy enrolling more than 1,000 patients who underwent D2 gastrectomy for gastric cancer. The results of this follow-up study showed that 1-year treatment with S-1 improved OS and RFS at 5 years compared with surgery alone, thus reconfirming the conclusions reached on early publication of the study results after a median follow-up of 3 years.

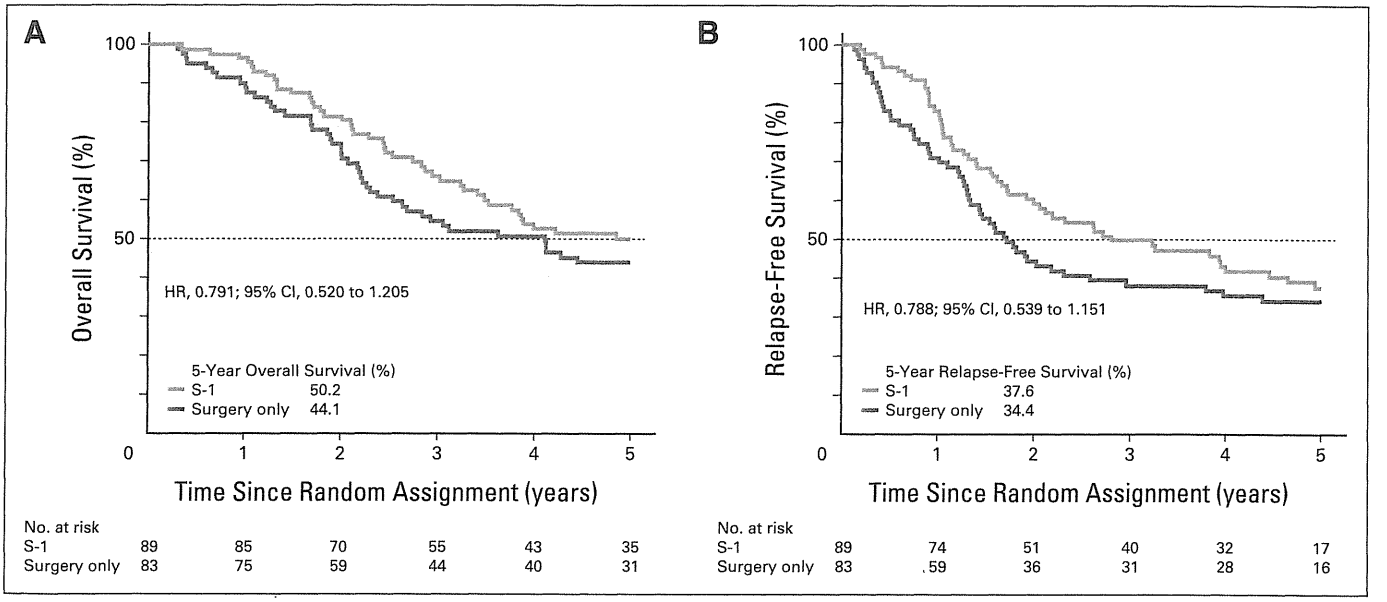

Fig 6. Kaplan-Meier estimates of (A) overall survival and (B) relapse-free survival for eligible patients with stage IIIB gastric cancer. HR, hazard ratio.

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Table 1. Site of First Relapse (all randomly assigned patients)*

Site	S-1 (n = 529) No.	S-1 (n = 529) %	Surgery Only (n = 530) No.	Surgery Only (n = 530) %	HR	95%CI
Total No. of relapses	162	30.6	221	41.7	—	—
Local	11	2.1	17	3.2	0.572	0.268 to 1.221
Lymph nodes	30	5.7	54	10.2	0.505	0.323 to 0.789
Peritoneum	77	14.6	100	18.9	0.687	0.511 to 0.925
Hematogenous	61	11.5	71	13.4	0.784	0.557 to 1.105

Abbreviation: HR, hazard ratio.
*Some patients had a first relapse at more than one site.

Our present results confirmed that postoperative adjuvant chemotherapy with S-1 alone reduced the risk of death by 33.1%, thereby demonstrating that effectiveness was maintained since the previous analysis. This reduction in the risk of mortality is comparable with that obtained with combined regimens for adjuvant chemotherapy in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial[14] and the Intergroup 0116 (INT-0116) trial.[15]

Whether the results of this study can be extrapolated to countries outside East Asia remains uncertain because of possible differences in pharmacokinetics of S-1 between whites and East Asians. If S-1 is used as adjuvant chemotherapy in whites, the dose should be carefully adjusted. A second reason is that all patients in this study underwent D2 gastrectomy although more limited surgery (D0/1) is commonly performed in the United States and some parts of Europe. In the surgery-only group, OS at 5 years was 61.1%, which was much better than that of patients undergoing D2 gastrectomy in Europe (33%) in a Dutch trial.[16] One of the reasons for this large difference may be the high level and widespread use of diagnostic technology in Japan, potentially leading to stage migration between Japan and Western countries.[17] Another important reason might be the high quality of D2 gastrectomy in Japan, whereas D0 or D1 gastrectomy remains the standard procedure in the United States and was the standard in Europe until recently. Although a Dutch trial comparing D1 with D2 gastrectomy reported negative results,[16,18] a 15-year follow-up study showed that the rate of mortality from gastric cancer was significantly lower in the D2 gastrectomy group.[19] Thus, the most recent European Society for Medical Oncology (ESMO) clinical practice guidelines recommend D2 gastrectomy as the standard procedure for curable advanced gastric cancer.[20]

The primary end point of this study was 5-year OS, although that of an ongoing adjuvant chemotherapy study in Korea and China is 3-year disease-free survival. The latter is designed to evaluate the efficacy of postoperative adjuvant chemotherapy with capecitabine and oxaliplatin compared with surgery alone. To justify the use of RFS or disease-free survival as the primary end point for adjuvant chemotherapy after curative resection of gastric cancer, more evidence is needed, but the results of this study may strongly suggest that RFS can be used as the primary end point of such studies. (In this follow-up analysis, the 3-year RFS rates were 72.4% and 61.1%, and the 5-year OS rates were 71.7% and 61.1% in the S-1 group and surgery-only group, respectively.)

To compare our results with those of other foreign studies, we also report the stage-specific 3- and 5-year OS and RFS according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours, Sixth Edition. Three-year OS rates according to UICC staging in the S-1 and surgery-only groups were 91.1% and 80.9% (stage II), 77.8% and 68.3% (stage IIIA), 66.6% and 56.8% (stage IIIB), and 59.1% and 45.7% (stage IV). Three-year RFS rates were 84.3% and 73.5% (stage II), 69.1% and 56.7% (stage IIIA), 44.8% and 28.9% (stage IIIB), and 46.0% and 37.1% (stage IV). Five-year OS rates were 83.4% and 70.8% (stage II), 68.9% and 56.2% (stage IIIA), 43.7% and 40.1% (stage IIIB), and 45.1% and 42.7% (stage IV). Five-year RFS rates were 77.9% and 65.4% (stage II), 64.3% and 48.7% (stage IIIA), 35.9% and 28.9% (stage IIIB), and 26.8% and 25.0% (stage IV).

The approach for adjuvant chemotherapy differs among East Asian countries, including Japan, in which D2 gastrectomy has long been the standard procedure, and Western countries, in which D0 or D1 gastrectomy used to be or currently is standard. As Cunningham and Chua[21] stated, "surgery alone" is no longer standard treatment anywhere in the world for advanced gastric cancer. Some type of adjuvant chemotherapy, including the use of radiotherapy after D0/1 resection, can thus be considered standard treatment at present.

A meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group[7] showed that some form of postoperative chemotherapy is associated with a higher survival rate than surgery alone; moreover, the use of monotherapy for postoperative adjuvant treatment resulted in good outcomes. The ACTS-GC trial demonstrated that S-1 monotherapy improved OS and RFS. In patients with early-stage (II and IIIA) tumors, the benefits of treatment with S-1 were considerable. However, the 5-year OS rate in patients with stage IIIB disease was 50.2% in the S-1 group and 44.1% in the surgery-only group, suggesting that there remains some room for improvement. Future studies should evaluate the effectiveness of intensive preoperative and/or postoperative chemotherapy with multiple agents in patients at high risk for relapse.

The results of the S-1 plus cisplatin versus S-1 in randomized controlled trial in the treatment for stomach cancer (SPIRITS) trial,[22] demonstrating that S-1 plus cisplatin is superior to S-1 alone with respect to survival in patients with unresectable or recurrent gastric cancer, and the V325 study [a randomized, multinational phase II/III trial of patients with untreated advanced gastric cancer],[23,24] showing that the addition of docetaxel to cisplatin plus fluorouracil prolongs survival, indicated that S-1 plus cisplatin and S-1 plus docetaxel are candidate regimens for postoperative adjuvant chemotherapy. These regimens were confirmed to be feasible in a postoperative setting,[25,26] and further studies should be performed to examine whether such regimens are superior to S-1 alone.

The Japan Clinical Oncology Group (JCOG) is now performing the JCOG 0501 study to compare S-1 plus cisplatin as neoadjuvant chemotherapy with surgery followed by S-1 monotherapy in patients with clinically resectable Borrmann type 4 (linitis plastica) and large type 3 gastric cancer. This trial is expected to be a landmark study, determining the future direction for preoperative chemotherapy in Japan.

The use of molecular targeted agents for gastric cancer has been studied extensively. In the Trastuzumab in Combination with Chemotherapy Versus Chemotherapy Alone for Treatment of HER2-Positive Advanced Gastric or Gastro-Esophageal Junction Cancer (ToGA) study, trastuzumab combined with cisplatin and either fluorouracil or capecitabine significantly prolonged OS in patients with HER2-positive gastric cancer.[27] The effectiveness of adjuvant chemotherapy with molecular targeted agents such as trastuzumab also needs to be assessed in patients with HER2-positive gastric cancer.

In conclusion, this 5-year follow-up study confirmed that adjuvant chemotherapy with S-1 given for 1 year after surgery improved

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OS and RFS at 5 years in patients with stage II or III gastric cancer who underwent D2 gastrectomy. Postoperative chemotherapy with S-1 can be recommended for patients with stage II or III gastric cancer who undergo D2 gastrectomy, at least in Asian populations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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特集 ……Stage Ⅳ胃癌における外科治療の有用性……

切除不能 stage Ⅳ進行胃癌に対する化学療法後の手術成績

三原良明*1　東風　貢*1　藤井雅志*1　金森規朗*1
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Evaluation of the Effectiveness of Surgery in Incurable Gastric Cancer Cases after Chemotherapy: Mihara Y*1, Kochi M*1, Fujii M*1, Kanamori N*1, Kaiga T*1, Hagiwara K*1, Funada T*1, Tamegai H*1, Watanabe M*1 and Takayama T*1 (*1Department of Digestive Surgery, Nihon University School of Medicine)

We retrospectively evaluated 86 patients with incurable gastric cancer. These patients were divided into chemotherapy alone group (n=59) and operation after chemotherapy group (n=27). The median survival time (MST) in the operation group and chemotherapy alone group were 21.3 and 11.3 months, respectively ($P \leq 0.001$). The operation group was further divided into 2 subgroups depending on whether the patients underwent curative or non-curative resection. The MST in the curative resection (n=16) group and non-curative resection (n=11) group were 35.6 and 16.2 months, respectively ($P \leq 0.005$). The main cause of non-curative resection was peritoneal metastasis. There was no significant difference between the MST in the non-curative resection group and that in the chemotherapy alone group. Our results suggest that curative resection after chemotherapy provides better survival benefit in incurable gastric cancer patients.

Staging laparoscopy may be useful for planning surgery after chemotherapy in patients with incurable gastric cancer.

Key words: Incurable gastric cancer, Chemotherapy, Curative resection

Jpn J Cancer Clin **56**(4): 311～315, 2010

はじめに

現在胃癌の術前化学療法は，切除可能な進行胃癌に対し down staging による根治性の向上を目指したものと，切除不能進行胃癌に化学療法が奏効し，結果的に切除可能となったものとに大きく2つに分けられる．前者の regimen は一般的に S-1/CDDP が用いられ，1～2クール施行後の切除が一般的であるが[1,2]，後者に関してはその regimen や施行クール数は確立されたものはなく，切除可能となるまで継続するのが現状である．

今回われわれは他臓器浸潤（T4），第3群リンパ節転移（N3），肝転移（H1），腹膜転移（P1），腹腔洗浄細胞診（CY1），遠隔転移陽性（M1）の因子の存在により，根治度 A,B が見込めない「切除不能 stage Ⅳ進行胃癌」に対する化学療法後の手術成績を，化学療法単独群と比較検討した．

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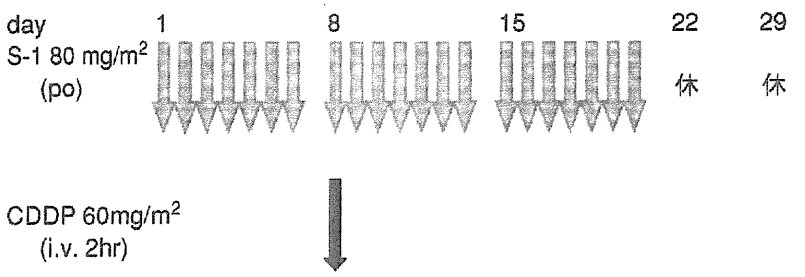

図1　化学療法の Regimen

1 対象と方法

1 対　象

検索対象は，当院における2008年3月より2009年8月までの化学療法を施行した初発の切除不能胃癌86例で，化学療法単独施行群59例と化学療法施行後手術施行群27例に分け比較検討，手術施行群をさらに根治切除施行群16例，非根治切除施行群11例に分けて，比較検討をした．

2 手術適応

切除不能進行胃癌に対する化学療法後に手術適応と判断した条件は1）遠隔リンパ節転移が画像上消失している，2）肝転移は画像上消失し，3カ月以上出現を認めない，3）腹膜転移が画像上腹水の出現が6カ月以上認めない．の3条件のいずれか認めた場合を手術適応条件とした．

3 化学療法

Regimen は S-1/CDDP を施行した．S-1 80 mg/m^2 を3週間内服し，CDDP を day 8 に 60 mg/m^2 で点滴加療し，その後2週間休薬とした（図1）．2コース以上施行後内視鏡で原発巣の残存を確認後，4週間休薬後手術を施行した．

4 検定方法

また2群間のデータ比較は student's t 検定または Mann-Whitney 検定，カイ二乗検定を用い，生存期間解析は Kaplan-Meier 法より行った．また $P<0.05$ を有意差ありとした．

表1　患者背景1

		n=86（%）
性	男性	67(77.9)
	女性	19(22.1)
年齢	中央値［Range］	65［30～84］
占拠部位	上部	15(17.4)
	中部	41(47.7)
	下部	30(34.9)
切除不能因子	N	28(32.6)
	P	16(18.6)
	H	16(18.6)
	SI	13(15.1)
	M	13(15.1)
化学療法	中央値［Range］	5［2～14］
奏効率	CR	1
	PR	44
		52.3%

2 結　果

患者背景を表1（全症例），表2（化学療法単独施行群，化学療法施行後手術施行群），表3（根治切除群，非根治切除群）に示した．化学療法単独群と化学療法施行後手術施行群及び根治切除群と非根治切除群の2群間の患者背景は共に有意差を認めなかった．

切除不能の要因は全体でリンパ節転移28例（32.6%），腹膜転移16例（18.6%），肝転移16例（18.6%），他臓器浸潤13例（15.1%），遠隔転移13例（15.1%）であった．化学療法の施行クールは中央値は5クール［2～14］であった．

また手術施行群27例の術式は胃全摘11例，幽門側胃切除術5例，胃空腸吻合術11例，単開腹1例で，化学療法後根治切除症例は16例（根治切除率59.3%）であった．また非根治切除

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表2　患者背景2

		化学療法群 n=59 (%)	手術群 n=27 (%)	P
性	男性	48(81.4)	19(70.4%)	0.62
	女性	11(18.6)	8(29.6)	
年齢	中央値 [Range]	65[34～84]	63 [30～79]	0.74
占拠部位	上部	9(15.3)	6(22.2)	0.12
	中部	30(50.8)	11(40.7)	
	下部	20(33.9)	10(37.0)	
切除不能因子	N	15(25.4)	13(48.1)	0.08
	P	11(18.6)	5(18.5)	
	H	14(23.7)	2(7.4)	
	SI	6(10.2)	7(25.9)	
	M	13(22.0)	0(0)	
化学療法	中央値 [Range]	5 [2～14]	5 [2～8]	0.28
奏効率	CR	0	1	
	PR	18	26	
		30.5%	100%	

表3　患者背景3

		手術根治群 n=16 (%)	手術非根治群 n=11 (%)	P
性	男性	10(62.5)	9(81.8)	0.43
	女性	6(37.5)	2(1.8)	
年齢	中央値 [Range]	63 [38～79]	63 [30～79]	0.87
占拠部位	上部	2(12.5)	0(0)	0.05
	中部	7(43.8)	3(27.3)	
	下部	7(43.8)	8(72.7)	
切除不能因子	N	10(62.5)	3(27.3)	0.05
	P	2(12.5)	4(36.4)	
	H	1(6.3)	2(1.8)	
	SI	3(1.9)	2(1.8)	
	M	0(0)	0(0)	
化学療法	中央値 [Range]	5 [2～5]	5 [2～8]	0.82
奏効率	CR	1	0	
	PR	15	11	
		100%	100%	

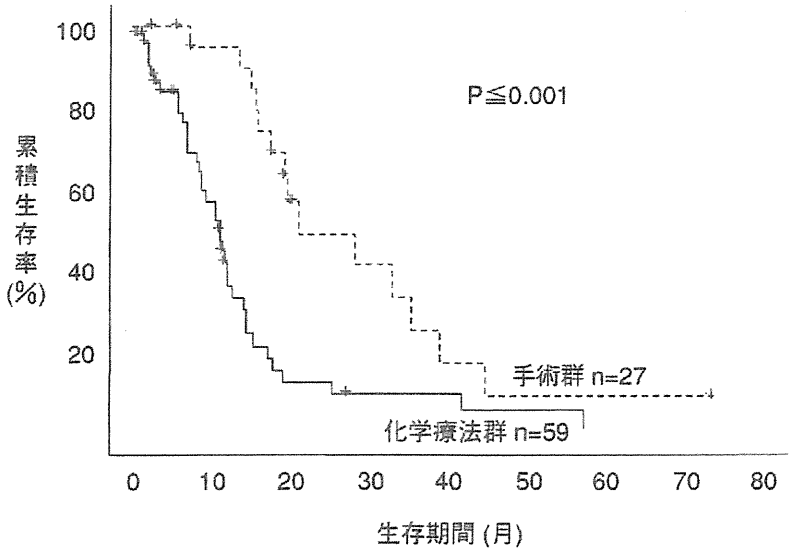

図2　化学療法群 vs 手術群の累積生存率

(11例)となった要因の内訳は，腹膜転移6例，他臓器浸潤3例，肝転移1例，リンパ節転移1例で，切除不能の要因は，腹膜転移が最も多かった(55%)．

化学療法単独群(59例)と，化学療法後手術施行群(27例)，生存率を比較すると，Median Survival Time (MST)は，11.3カ月 vs 21.3カ月と有意に，手術施行群が良好であった(P=0.001)(図2)．手術施行群の根治切除群(16例)と非根治切除群(11例)の生存率を比較すると，MSTは35.6カ月 vs 16.2カ月と有意差に根治切除群が良好であった(P=0.005)(図3)．化学療法単独群(59例)と化学療法後非根治切除群(11例)の生存率の比較を行ったところ，MSTは11.3カ月 vs 16.2カ月(P=0.09)で両群間に有意差は認めなかった(図4)．

3　考　察

当科の根治切除不能 Stage Ⅳ胃癌の化学療法後の手術施行例は化学療法単独群に比べ良好な治療成績であったが，化学療法後手術施行群の

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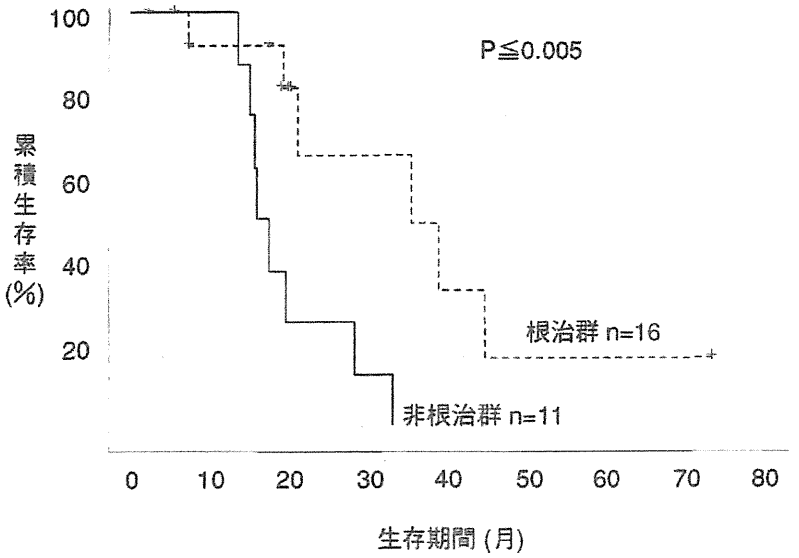

図3　化学療法＋手術根治群 vs 化学療法＋手術非根治群の累積生存率

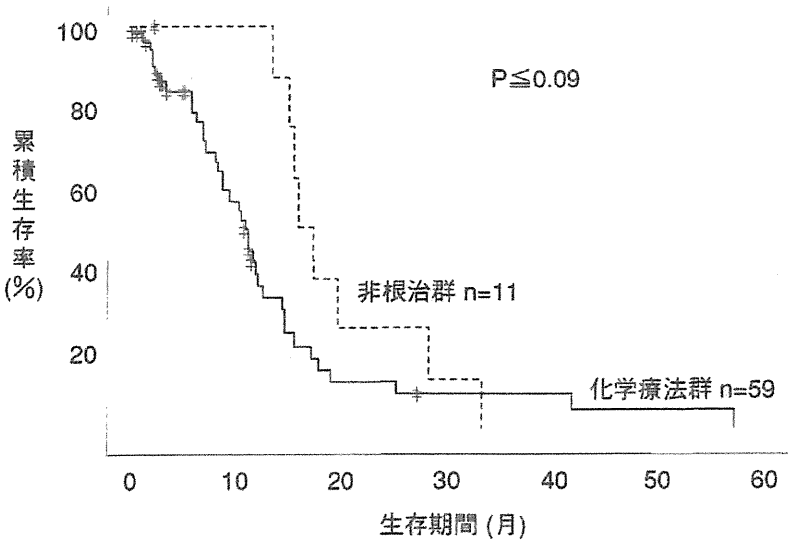

図4　化学療法 vs 化学療法＋手術非根治群の累積生存率

MSTが良好であった要因は，手術施行群中に根治切除が多く含まれるためと考えられた．これは根治切除群と非根治切除群のMSTの比較において根治切除群で有意差があったことと，化学療法群と非根治切除群のMSTで有意差を認めなかった結果より，姑息的手術や減量手術といった非根治切除術には予後改善の影響力がないことが推測され，切除不能進行胃癌においては，化学療法後の根治切除が，長期予後を得る条件であることが示唆された．

岡部らは根治切除不能胃癌で手術先行群（134例），化学療法先行手術施行群（55例）の比較検討をしているが，いずれも治癒切除例が非治癒切除例より生存曲線において有意に良好であると報告している[3]．

本検証では非根治切除の要因として腹膜転移が多かったため，術前検査としてP因子やCY因子の存在の有無の検索目的に，術前審査腹腔鏡検査を施行し，非根治切除因子の有無を明らかにした上で手術適応を決定する必要があると考えた．

今回の化学療法のregimenはS-1/CDDPのみであった．これはJCOG9912試験とSPIRITS trialの結果により，5-FUに対するS-1の非劣性と，S-1/CDDP併用療法がS-1単独療法の全生

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存において勝ることが示されたことに基づいており，そのため現状わが国における切除不能再発胃癌の化学療法の第一選択はS-1/CDDPとなっていることによる[4,5]．しかし腎不全でS-1やCDDPが使用不可能な場合もあり，さらに現在ToGA trial等の結果が示すように，分子標的治療薬を含め，他の有効なregimenが出現する可能性があるため，今後他のregimenでの解析が必要であると考えられた[6]．

まとめ

切除不能stage Ⅳ進行胃癌に対する化学療法後の手術治療は，根治手術が求められると考えられた．非根治切除の最大の原因が腹膜転移であったことから，これらの手術治療の決定には術前審査腹腔鏡検査の必要性が考えられた．

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ANTICANCER RESEARCH *31*: 1019-1022 (2011)

A Case of Complete Response to S-1 plus CDDP in Early-Stage Mucosal Esophageal Cancer

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Abstract. *We report a case of early-stage mucosal esophageal cancer, showing a complete response to S-1 and cis-diamminedichloplatinum (CDDP). The patient was a 67-year-old man with synchronous double primary early-stage mucosal esophageal and advanced gastric cancer. We planned neoadjuvant chemotherapy with S-1 and CDDP for the advanced gastric cancer and endoscopic mucosal resection for the early-stage esophageal cancer. After the first course of chemotherapy, the endoscopy revealed that the esophageal cancer had become a normal mucosal lesion, and the biopsy was negative for cancer. We diagnosed a complete response to S-1 and CDDP in early-stage esophageal cancer. After two courses of chemotherapy, distal gastrectomy was performed. The patient is still alive with no sign of recurrence at 16 months after the disappearance of the original tumor. These results suggest that chemotherapy with S-1 plus CDDP may be effective in early-stage esophageal cancer.*

The standard treatment for early-stage esophageal cancer is esophagectomy (1, 2). Despite advances in endoscopic therapy, the prognosis of early-stage mucosal esophageal cancer is still poor (3, 4). Several prospective trials have demonstrated that neoadjuvant chemotherapy, in conjunction with surgical intervention, confers a survival benefit for locally advanced esophageal cancer (5, 6). Tumor response to chemotherapy in early-stage esophageal cancer, however, remains to be elucidated. Complete remission of early-stage esophageal cancer with preoperative chemotherapy is rare. One such case is reported here.

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Key Words: Early-stage esophageal cancer, S-1 plus CDDP, complete response.

Case Report

The patient was a 67-year-old man who had previously consulted his home doctor with atrial fibrillation. In January 2009, the patient was referred to the Department of Digestive Surgery, Nihon University School of Medicine, Itabashi Hospital, with esophageal and gastric tumors which were identified during a follow-up examination. Upper gastrointestinal endoscopy revealed a mid-esophageal type IIc tumor measuring 2.0 cm×1.5 cm (Figure 1a) and a type 2 tumor in the lower stomach, measuring 3.5 cm×3.5 cm (Figure 2). Biopsy specimens revealed that the esophageal tumor was a well differentiated squamous cell carcinoma and the stomach tumor was a poorly differentiated adenocarcinoma. We diagnosed synchronous double primary early-stage mucosal esophageal and advanced gastric cancer. Computed tomography, revealed multiple lymph node metastases around the stomach (Figure 3). Neoadjuvant chemotherapy with S-1 (Taiho Pharmaceutical, Tokyo, Japan) and cis-diamminedichloroplatinum (CDDP) was carried out for the advanced gastric cancer and endscopic mucosal resection was planned for the early-stage esophageal cancer. S-1 was administered orally, at a dose of 80 mg/m^2 per day, for 21 days. Infusional CDDP was administered at a dose of 90 mg/m^2 for 90 minutes on day 8. The patient developed grade 3 diarrhoea during the first course, which resolved spontaneously after the discontinuation of chemotherapy. After the first course of chemotherapy, endoscopy was performed with the aim of carrying out endoscopic mucosal resection. However, the endoscopy revealed that the esophageal cancer had become a normal mucosal lesion (Figure 1b), and the biopsy was negative for cancer. We diagnosed a complete response to S-1 and CDDP in early-stage esophageal cancer. Due to grade 3 diarrhea in the first course, a second course of chemotherapy was carried out with an 80% dose reduction, followed by distal gastrectomy. Over the next 6 months, periodic upper gastrointestinal endoscopy was carried out to detect any further possible esophageal lesions. Currently, the patient remains on an outpatient chemotherapy consisting of S-1 at a dose of 80 mg/m^2 per day for 14 consecutive days followed by a 14-day, drug-free interval. A periodically performed upper gastrointestinal endoscopy, executed in December 2009, revealed no new tumor lesions. The patient was still alive at publication, with no sign of recurrence at 16 months after disappearance of the original tumor.

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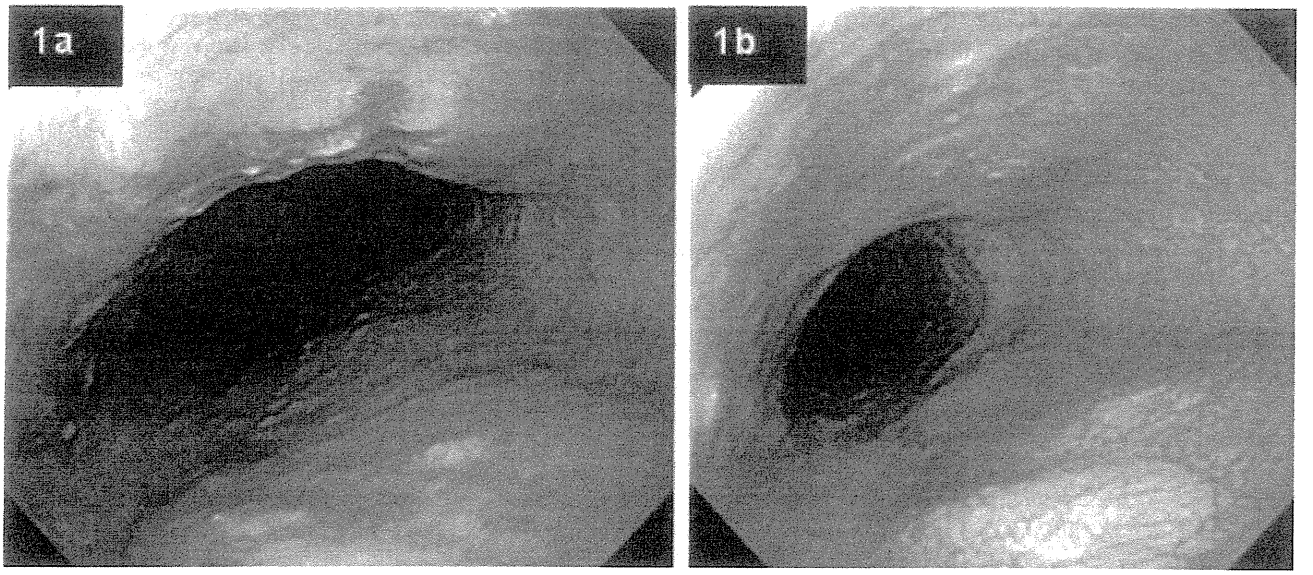

Figure 1. *a. In May 2009, upper gastrointestinal endoscopy disclosed mid-esophageal type IIc tumor measuring 2.0 cm × 1.5 cm. b. In August 2009, after first course of S-1 plus CDDP, upper gastrointestinal endoscopy revealed complete disappearance of tumor, and no further lesions were identified.*

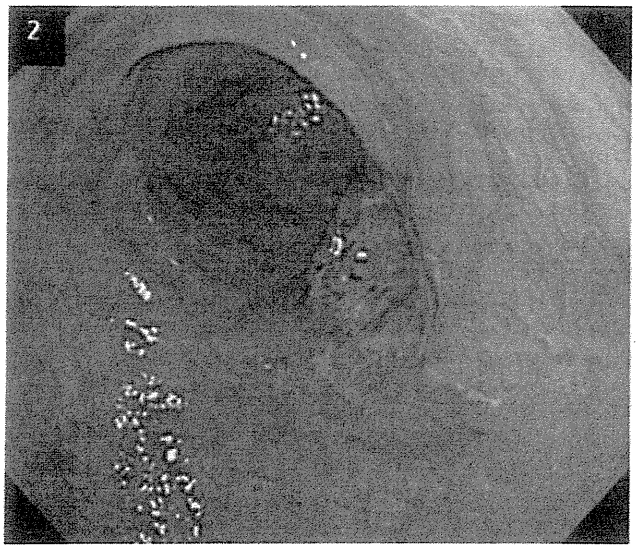

Figure 2. *In May 2009, upper gastrointestinal endoscopy disclosed Bormann type II tumor in stomach measuring 3.5 cm × 3.5 cm.*

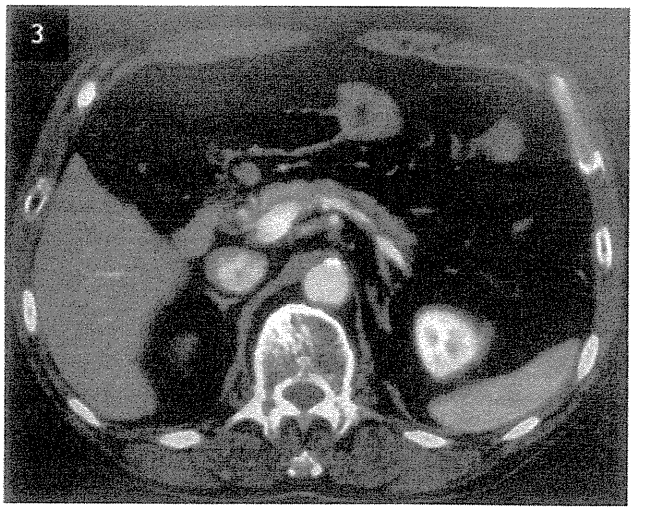

Figure 3. *Computed tomography revealed multiple lymph node metastases around stomach.*

Discussion

Reports of a complete response to chemotherapy in early-stage esophageal cancer are very rare. Several prospective trials have reported that complete response to chemotherapy in advanced esophageal cancer is 2.0-5.6% (5-9). However, this extremely low complete response rate may be due to the fact that the standard treatment in such cases is surgical or endoscopic mucosal resection.

Our results suggest that chemotherapy may be effective against early-stage esophageal cancer. Recently, the effect of docetaxel and CDDP plus 5-fluorouracil (DCF) in gastroesophageal cancer was reported. The overall survival time was 9.2 months. However, grade 3 or 4 treatment-related adverse events occurred in 69% of patients on DCF (5, 6). This suggests that DCF may be unsuitable for early-stage esophageal cancer due to the high rate of adverse side effects.