23 patients, and progressive disease in 4 patients. The reason for the discontinuation of mFOLFOX6 therapy was disease progression in 20 patients, hypersensitivity reactions in 12 patients, and peripheral neurotoxicity in 10 patients. Calcium/magnesium therapy was given before and after oxaliplatin therapy in a total of 21 (50%) patients. Of these, 17 patients received calcium/magnesium therapy in the clinical trial [25], and 4 received it in clinical practice.

mFOLFOX6 therapy

Oxaliplatin 85 mg/m^2 and levofolinate calcium 200 mg/m^2 were given concomitantly by drip infusion over 2 h, followed by rapid intravenous infusion of 5-fluorouracil (FU) at 400 mg/m^2. Thereafter, 5-fluorouracil was given at 2400 mg/m^2 as a continuous drip infusion over 46 h. The above procedure represented one cycle of treatment, and the treatment cycles were repeated every 2 weeks. The drugs were administered into the central vein via a subcutaneous indwelling port. Patients were hospitalized for the initial treatment, whereas the subsequent cycles were given in an outpatient chemotherapy clinic. Treatment was discontinued when evidence of disease progression (progressive disease, PD) was noted according to the Response Evaluation Criteria in Solid Tumors ver. 1.0 (RECIST) [26], or when there were intolerable adverse events. When an adverse event(s) of grade 3 or greater severity according to NCI-CTCAE ver. 3.0 occurred, the mFOLFOX6 therapy was suspended until the severity of the reaction improved to grade 2 or lower severity, and when mFOLFOX6 therapy was resumed, the dose of oxaliplatin was reduced to 70–80% of the initial dose level. 5-FU/LV therapy not combined oxaliplatin therapy was not adopted in any of the patients of this series. When calcium/magnesium was given to the patients, calcium gluconate hydrate 10 mL and 0.5 M magnesium sulfate 10 mL were dissolved together in 5% dextrose solution 100 mL, and given by intravenous drip infusion before and after the administration of oxaliplatin. FOLFIRI therapy was begun after a drug-free period of 4 weeks following the end of mFOLFOX6 therapy. FOLFIRI therapy was given a median 12 times (range 6–33).

Evaluation of neurotoxicity

On every visit of the patients to the clinic for chemotherapy, the patient's history was obtained by a nurse, pharmacist or physician in-charge at the outpatient chemotherapy clinic to determine the severity and duration of neurotoxicity according to both the NCI-CTCAE ver. 3.0 and DEB-NTC scales. The data were recorded prospectively in the medical charts, and later analyzed retrospectively.

Statistical analysis

The statistical software StatFlex ver. 6.0 (Artec, Osaka, Japan) was used for the statistical analysis. The κ statistic [27] was obtained to determine the rates of concordance of the neurotoxicity grades determined by the two sets of criteria. More specifically, the concordance was rated as follows: poor, $\kappa \leq 0.0$; slight, $0.0 < \kappa \leq 0.2$; fair, $0.2 < \kappa \leq 0.4$; moderate, $0.4 < \kappa \leq 0.6$; substantial, $0.6 < \kappa \leq 0.8$; almost perfect, $0.8 < \kappa \leq 1.0$. Curves of cumulative incidence and cumulative improvement of peripheral neurotoxicity were drawn by the Kaplan–Meier method, and the log-rank test was used for comparison of the curves. The results were regarded as statistically significant at $P < 0.05$.

Results

The median duration of mFOLFOX6 therapy was 181 days (range 91–422 days). Grade 0–2 peripheral neurotoxicity was recorded a total of 472 times during this period. The rate of concordance of grade 0–2 peripheral neurotoxicity as evaluated by the two sets of criteria was 48.8%, with $\kappa = 0.26$ (95% confidence interval 0.21–0.32) (Table 3). The median observation period after discontinuation of oxaliplatin, i.e., the median duration of FOLFIRI therapy, was 244 days (range 84–728 days). During this period, evaluation of neurotoxicity was carried out a total of 573 times. The rate of concordance of grade 0 to grade 2 peripheral neurotoxicity as evaluated by the two sets of criteria was again low, at 47.3%, with $\kappa = 0.18$ (95% confidence interval 0.13–0.22) (Table 4).

Figure 1a, b shows the cumulative incidence rates of grades 1 and 2 peripheral neurotoxicity during mFOLFOX6 therapy. According to both NCI-CTCAE ver. 3.0 and DEB-NTC, neurotoxicity of grade 1 or greater severity occurred in 41 of the 42 patients. There was a tendency for grade 1 neurotoxicity to be detected at a lower total dose of oxaliplatin when the evaluation was based on DEB-NTC

Table 3 Concordance rate of the peripheral neurotoxicity grade evaluated by NCI-CTCAE and DEB-NTC scales during mFOLFOX6 therapy

	DEB-NTC			
	Grade	0	1	2
NCI-CTCAE	0	103	73	24
	1	15	71	124
	2	3	8	61

Concordance rate 48.8%, κ 0.26 (95% confidence interval 0.21–0.32), $P < 0.001$

Table 4 Concordance rate of the peripheral neurotoxicity grade evaluated by NCI-CTCAE and DEB-NTC scales during FOLFIRI therapy

	DEB-NTC			
	Grade	0	1	2
NCI-CTCAE	0	23	24	49
	1	1	57	204
	2	0	10	178

Concordance rate 47.3%, κ 0.18 (95% confidence interval 0.21–0.32), $P < 0.001$

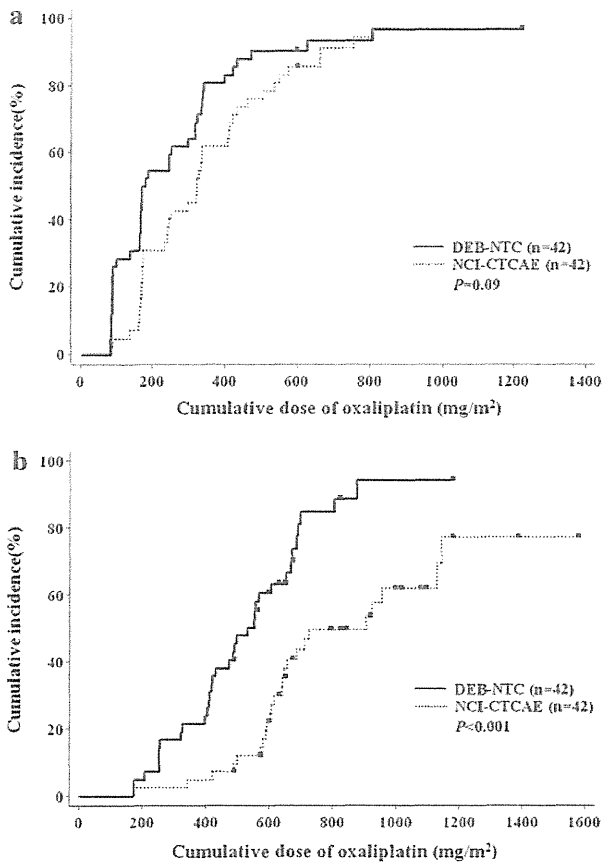

Fig. 1 a Cumulative incidence of grade 1, b cumulative incidence of grade 2 during mFOLFOX6 therapy

than when it was based on NCI-CTCAE ver. 3.0 ($P = 0.09$) (Fig. 1a). The total dose of oxaliplatin at which the incidence of grade 2 neurotoxicity reached 50% was 480 mg/m^2 when the evaluation was based on DEB-NTC and 627 mg/m^2 when the evaluation was based on NCI-CTCAE ver. 3.0; the total dose of oxaliplatin until the occurrence of grade 2 neurotoxicity was significantly lower when the evaluation was based on DEB-NTC ($P < 0.001$) (Fig. 1b). The cumulative dose between the occurrence of grade 1 neurotoxicity and increase in its severity to grade 2 was about 300 mg/m^2 according to evaluation by both DEB-NTC and NCI-CTCAE ver. 3.0. Grade 3 neurotoxicity (according to both NCI-CTCAE and DEB-NTC) occurred in 7 patients (16.7%).

Figure 2a–d shows the cumulative improvement of peripheral neurotoxicity during FOLFIRI therapy. Grade 3 peripheral neurotoxicity was found in 7 patients according to NCI-CTCAE ver. 3.0, and improved to grade 2 in 6 of these patients during the observation period. There was no difference in the improvement curves between the two sets of criteria ($P = 0.35$) (Fig. 2a). When the evaluation was based on NCI-CTCAE ver 3.0, improvement from grade 2 to grade 1 was found in 50% of the patients by 200 days after discontinuation of oxaliplatin, whereas when it was based on DEB-NTC, the rate of improvement within the observation period remained at 5% ($P < 0.001$) (Fig. 2b). In regard to the improvement from grade 2 to grade 0, the cumulative improvement reached a plateau at 40% during the observation period when the evaluation was based on NCI-CTCAE ver. 3.0, whereas when the evaluation was based on DEB-NTC, the cumulative improvement was determined to be only 5% ($P < 0.05$) (Fig. 2c). There was no significant difference in the curve of cumulative improvement from grade 1 to grade 0 between the two sets of criteria ($P = 0.19$) (Fig. 2d). However, a cumulative improvement of 45% was obtained during the observation period when the evaluation was based on NCI-CTCAE ver. 3.0, whereas the corresponding rate obtained was only 20% when the evaluation was based on the DEB-NTC scale.

Discussion

The present study revealed a discrepancy between the NCI-CTCAE ver. 3.0 and DEB-NTC scales in the evaluation of peripheral neurotoxicity associated with oxaliplatin-based chemotherapy for metastatic colorectal cancer. Specifically, it appears that grade 1 or grade 2 peripheral neurotoxicity after the start of mFOLFOX6 therapy can be detected earlier when the evaluation was based on DEB-NTC than when it was based on NCI-CTCAE ver. 3.0. With respect to evaluation of improvement in the peripheral neurotoxicity after discontinuation of oxaliplatin, grade 1 or grade 2 neurotoxicity persisted for longer when the evaluation was based on the DEB-NTC scale. In particular, it is noteworthy that scarcely any improvement of neuropathy was found during the observation period after discontinuation of oxaliplatin (84–728 days, median 240 days) in patients with grade 2 symptoms, i.e., those who had peripheral neuropathy persisting for at least 14 days. There was no close relationship between the grade of paresthesia and the duration of peripheral neurotoxicity.

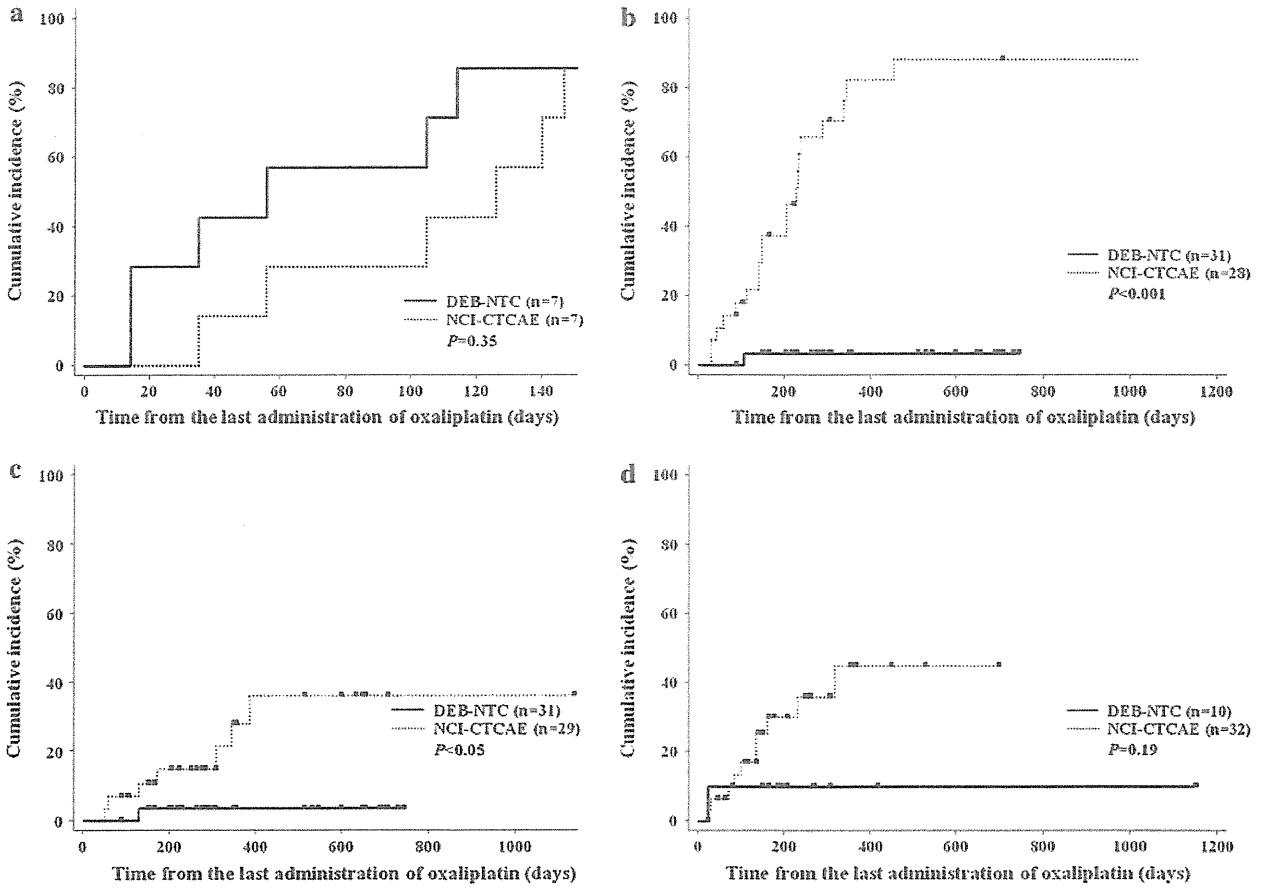

Fig. 2 **a** Cumulative improvement from grade 3 to grade 2, **b** cumulative improvement from grade 2 to grade 1, **c** cumulative improvement from grade 2 to grade 0, **d** cumulative improvement from grade 1 to grade 0 during FOLFIRI therapy

Therefore, we speculated that this discrepancy between the evaluations by NCI-CTCAE ver. 3.0 and DEB-NTC arose from the criteria used for toxicity up to grade 2, because the former criteria place stress on the grade of paresthesia, whereas the latter attach more importance to the duration of peripheral neurotoxicity.

How to apply these findings to practical oxaliplatin-based chemotherapy is an important issue. A key point in oxaliplatin-based chemotherapy is to prevent the appearance of grade 3 peripheral neuropathy. In patients with paraesthesias associated with pain or functional impairment persisting until the next cycle, oxaliplatin should be permanently discontinued [28]. Therefore, it is crucial to predict the development of grade 3 neuropathy as early as possible. The present study revealed that peripheral neuropathy persisting for at least 14 days, i.e., grade 2 neuropathy, was detected earlier, at an oxaliplatin dose 150 mg/m^2 lower, when the evaluation was based on DEB-NTC than when it was based on NCI-CTCAE ver. 3.0. Therefore, it is important to ask the patient carefully about the duration of neuropathy. When DEB-NTC is used for the evaluation of neuropathy in daily clinical practice, continuation of treatment should be considered as long as there is no interference with the patient's daily activities. However, there may be criticism that if a physician decides to discontinue or restart the chemotherapy according to the DEB-NTC scale, the total dose of oxaliplatin, which may affect the survival period, would be lower than that with the use of the NCI-CTCAE scale. We cannot address this issue exactly, but it deserves further investigation in future clinical trials or accumulated cases in clinical practice.

The usefulness of FOLFOX4 [2] and FLOX [4] as adjuvant chemotherapy for colon cancer has been reported. However, a follow-up study of the MOSAIC trial [3] showed that peripheral neuropathy was persistent in 15.4% of the surviving patients who were followed up for at least 4 years after adjuvant chemotherapy with FOLFOX4. In the MOSAIC study, peripheral neuropathy was evaluated by NCI-CTCAE ver. 1.0. It would be interesting to speculate on what results might have been obtained if the evaluation had been based on DEB-NTC, since even more delayed improvement of neuropathy tends to be obtained

when the evaluation is based on DEB-NTC than when it is based on NCI-CTCAE. If clinical trials aimed at reducing peripheral neuropathy in patients receiving oxaliplatin-based chemotherapy in the adjuvant setting are planned in the future, the use of DEB-NTC together with NCI-CTCAE is recommended for the evaluation of neuropathy. Although it would be ideal for specific scales to be designed for the evaluation of acute and chronic peripheral neuropathy, no such scales are available at present.

Some oxaliplatin-specific scales other than DEB-NTC have been proposed. In the NSABP C-07 study, Stephanie et al. [4] evaluated pain during oxaliplatin therapy by means of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Oxaliplatin-Specific Neurotoxicity Scale (NTX-12) and NCI-Sanofi grade. A questionnaire evaluation of the quality of life (QOL) of patients was also carried out in the N04C7 study [29]. In addition, de Gramont et al. [2] evaluated peripheral neurotoxicity as a factor affecting the patient's QOL using QOL scores. A patient-oriented survey technique based on the Patient Neurotoxicity Questionnaire (PNQ): oxaliplatin has also been reported. From this point of view, evaluation of the duration of peripheral neuropathy, a subjective variable that can only be described by the patients themselves, by DEB-NTC might be able to contribute to QOL improvement of the patients given oxaliplatin-based chemotherapy.

When evaluating the grade of peripheral neurotoxicity in patients examined in previous clinical trials or treated in clinical practice, attention should be paid to which set of criteria was used: NCI-CTCAE ver. 3.0 or other oxaliplatin-specific scales. At present, NCI-CTCAE is used commonly in many medical institutions for the evaluation of adverse events during anticancer drug treatment. When the grade was different between these scales, we preferred the evaluation using the NCI-CTCAE scale because NCI-CTCAE is believed to be a global standard. However, it would appear that the addition of DEB-NTC to NCI-CTCAE for the evaluation of adverse events in patients receiving oxaliplatin may contribute to the formulation of better treatment plans from the aspects of reduction, discontinuation, or even resumption of oxaliplatin therapy in the future.

In order to maintain comparability among the results of different trials, neurotoxicity should be always graded according to the NCI-CTCAE scale, and use of any oxaliplatin-specific scales should be regarded as supplemental. However, all physician-based assessment tools used to grade subjective toxicity phenomena, such as neurotoxicity, have shown dramatic disagreements between physician-reported and patient-reported severity of symptoms [30].

In the future, patient-based assessment of neurotoxicity could provide more reliable and more accurate information about the incidence and severity of oxaliplatin-induced neurotoxicity.

Conflict of interest No author has any conflict of interest.

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ORIGINAL ARTICLE

Combination chemotherapy with S-1 plus cisplatin for gastric cancer that recurs after adjuvant chemotherapy with S-1: multi-institutional retrospective analysis

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Abstract
Background It is unclear whether S-1 plus cisplatin is effective for patients with recurrent gastric cancer after adjuvant S-1 chemotherapy.
Methods We retrospectively evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant S-1 chemotherapy.
Results In the 52 patients evaluated, the median duration of adjuvant S-1 chemotherapy was 8.1 months, and the median recurrence-free interval (RFI) since the last administration of adjuvant S-1 was 6.4 months. Among the 36 patients with measurable lesions, 7 achieved a complete or partial response, and 13 were evaluated as having stable

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disease, for an overall response rate of 19.4% and a disease control rate of 55.6%. For all patients, the median progression-free survival (PFS) was 4.8 months, and the median overall survival (OS) was 12.2 months. Compared with patients with an RFI of <6 months ($n = 25$), patients with an RFI of ≥6 months ($n = 27$) had a significantly higher response rate (5.0 vs. 37.5%, respectively), longer PFS (2.3 vs. 6.2 months, respectively), and longer overall survival (7.3 vs. 16.6 months, respectively). According to a multivariate Cox model including performance status (PS) and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS and OS. *Conclusions* S-1 plus cisplatin is effective for patients with gastric cancer that recurs after adjuvant S-1 chemotherapy, especially for those with an RFI of ≥6 months.

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

Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8% of total malignancy cases) and the second leading cause of cancer death (737,419 deaths, 9.7% of total) [1]. The prognosis of patients with advanced or recurrent gastric cancer remains poor; chemotherapy confers only a minimal survival advantage, with a median survival of approximately 1 year. The most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine [5-fluorouracil (5-FU) or oral fluoropyrimidine] plus a platinum agent with or without docetaxel or anthracyclines [2–6].

S-1 is an oral anticancer drug composed of the 5-FU prodrug tegafur and two 5-FU modulators; it has achieved high response rates in patients with gastric cancer in phase II studies [7, 8]. In the Japan Clinical Oncology Group (JCOG) 9912 trial, which compared S-1, cisplatin plus irinotecan, and 5-FU, S-1 demonstrated non-inferiority compared to 5-FU [9]. In another phase III trial that compared S-1 alone to S-1 plus cisplatin (SPIRITS trial), S-1 plus cisplatin showed a significantly higher response rate (54 vs. 31%), longer progression-free survival (PFS; 6.0 vs. 4.0 months), and longer overall survival (OS; 13 vs. 11 months) [4]. Also, in a large, non-Japanese, phase III trial (the First-Line Advanced Gastric Cancer Study; FLAGS trial), S-1 plus cisplatin was associated with fewer toxic effects and demonstrated non-inferiority compared with 5-FU plus cisplatin by exploratory analysis [6]. Therefore, S-1 plus cisplatin is now considered to be one of the standard regimens for metastatic or recurrent gastric cancer.

In addition, the ACTS-GC trial has demonstrated that S-1 is also effective as adjuvant chemotherapy for Japanese patients who have undergone curative gastrectomy for locally advanced gastric cancer [10]. However, approximately 30% of patients still develop recurrence after curative resection followed by adjuvant S-1 [10]. As few patients who received adjuvant chemotherapy were included in the phase III trials described above [4, 7, 9], it is unclear whether patients who develop recurrence after adjuvant S-1 could achieve efficacy with S-1 plus cisplatin similar to that achieved in patients without adjuvant chemotherapy. To address this issue, we conducted the following multi-institutional retrospective analysis.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy of first-line chemotherapy with S-1 plus cisplatin for recurrence in patients with gastric cancer who had undergone curative gastrectomy followed by adjuvant S-1 chemotherapy. Patients with histopathologically proven recurrent gastric adenocarcinoma after gastrectomy and lymph node dissection with no residual tumor were eligible for analysis. Additional eligibility criteria were: (1) previous adjuvant S-1 chemotherapy at a planned standard dose and schedule (80 mg/m^2 for 28 consecutive days followed by a 14-day rest; 42-day cycles to be repeated for 1 year); (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) adequate bone marrow, hepatic, and renal function to be treated with S-1 plus cisplatin; (4) evaluable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1); and (5) treated with a standard regimen of S-1 plus cisplatin (S-1 80 mg/m^2 for 21 consecutive days followed by a 14-day rest; cisplatin 60 mg/m^2 intravenous infusion on day 8; 35-day cycles to be repeated) [4]. Written informed consent for treatment was obtained from each patient prior to treatment initiation. The Institutional Review Board of each participating center approved the study.

Evaluation of treatment and statistical analysis

The tumor response was assessed objectively according to RECIST ver. 1.1, and the best overall response was recorded as the antitumor effect for that patient. The disease control rate (DCR) represented the percentage of patients with a complete response (CR), partial response (PR), or stable disease (SD). PFS was measured from the date of initiation of S-1 plus cisplatin to the date of progressive disease or death from any cause. Time to treatment failure

(TTF) was measured from the date of initiation of S-1 plus cisplatin to the date of last administration of S-1. OS was estimated from the date of initiation of S-1 plus cisplatin to the date of death or last follow-up visit, using the Kaplan–Meier method. The interval from the last administration of adjuvant S-1 to recurrence was defined as the recurrence-free interval (RFI).

The Cox proportional hazards model was used to estimate the impact of the RFI on TTF, PFS, and OS, with adjustment for other factors that were shown to be significant with a univariate log-rank test. *P* values for testing differences between proportions and response rates were calculated with χ^2 tests for homogeneity or for trend, or with Fisher's exact test. Results were considered to be statistically significant when the *P* value was <0.05. All reported *P* values are two-sided. In particular, we compared the response rate, DCR, time to progression (TTP), PFS, and OS between patients with RFIs of ≥6 and <6 months, because several clinical trials in the first-line setting set this interval of ≥6 months as an inclusion criterion [5, 9, 11].

Results

Patient characteristics

A total of 406 patients with recurrent gastric cancer after adjuvant S-1 chemotherapy had received chemotherapy at 18 institutions until October 2010. Among them, 57 patients (14.0%) had received S-1 plus cisplatin as first-line chemotherapy for recurrence. After the exclusion of 5 patients (1 patient with a non-evaluable lesion and 4 patients with insufficient data), 52 patients were included in the final

Table 1 Patient characteristics

Characteristic	All ($n = 52$)	RFI <6 months ($n = 25$)	RFI ≥6 months ($n = 27$)	*P* value
Age, years				
Median (range)	61 (32–77)	59 (32–77)	62 (32–77)	
Gender, *n* (%)				
Male	30 (58)	15 (60)	15 (56)	0.75
Female	22 (42)	10 (40)	12 (44)	
ECOG PS at recurrence, *n* (%)				
0	32 (62)	11 (44)	21 (78)	*0.012*
1	20 (38)	14 (56)	6 (22)	
Histological type[a], *n* (%)				
wel or mod	27 (52)	10 (40)	17 (63)	0.1
por or sig	24 (46)	15 (60)	9 (33)	
Other	1 (2)	–	1 (4)	
Pathological stage[a], *n* (%)				
Stage I or II	8 (15)	4 (16)	4 (15)	0.57
Stage IIIA	17 (33)	6 (24)	11 (41)	
Stage IIIB	15 (29)	8 (32)	7 (26)	
Stage IV	12 (23)	7 (28)	5 (19)	
Site of recurrence, *n* (%)				
Peritoneum	21 (40)	7 (28)	14 (52)	0.08
Lymph node	25 (48)	13 (52)	12 (44)	0.59
Liver	14 (27)	10 (40)	4 (15)	*0.041*
Lung	4 (8)	3 (12)	1 (4)	0.262
Bone	6 (12)	1 (4)	5 (19)	0.102
Local	2 (4)	1 (4)	1 (4)	0.96
Number of recurrence sites, *n* (%)				
1	38 (73)	18 (72)	20 (74)	0.87
2 or more	14 (27)	7 (28)	7 (26)	

P values shown in italics indicate significant differences

RFI Recurrence-free interval, *PS* performance status, *ECOG* Eastern Cooperative Oncology Group, *wel* well-differentiated adenocarcinoma, *mod* moderately differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring-cell-like carcinoma

[a] According to the Japanese classification

analysis (Table 1). The median duration of adjuvant S-1 chemotherapy was 8.1 months (range 0.7–37.4 months), and the median RFI since the last administration of adjuvant S-1 was 6.4 months (range 0–81.3 months). Thirty of the 52 patients (57.7%) completed the planned duration of adjuvant S-1 therapy. In contrast, 14 patients discontinued S-1 due to disease recurrence, and 8 patients stopped therapy due to toxicity or patient refusal. Other than PS and liver metastasis, characteristics did not differ significantly between patients with an RFI of ≥6 months ($n = 27$) and those with an RFI of <6 months ($n = 25$) (Table 1).

Treatment results and efficacy

The median TTF was 4.1 months (95% confidence interval [CI] 2.5–5.1 months), with a median duration of follow-up of 32 months. Forty-four patients discontinued S-1 plus cisplatin due to disease progression ($n = 40$, 90.9%) or toxicity ($n = 4$, 9.1%). Of the 36 patients with measurable lesions, 7 achieved a CR ($n = 3$) or a PR ($n = 4$), and 13 were evaluated as having SD, for an overall response rate of 19.4% (95% CI 7.0–37.0%) and a DCR of 55.6% (95% CI 38.1–72.1%). The median PFS was 4.8 months (95% CI 3.9–6.2 months), and the median OS of all patients was 12.2 months (95% CI 10.2–16.6 months) (Fig. 1). Of the 44 patients who had discontinued S-1 plus cisplatin, 31 (70.4%) received second-line or third-line chemotherapy, including taxanes ($n = 25$) or irinotecan ($n = 17$).

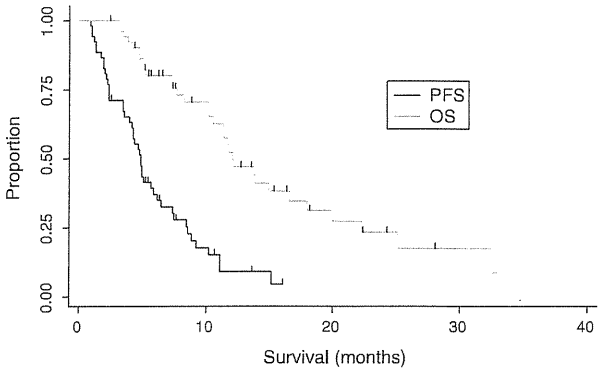

Fig. 1 Progression-free survival (*PFS*) and overall survival (*OS*) in all patients. The median PFS was 4.8 months (95% confidence interval [CI] 3.9–6.2 months), and the median OS was 12.2 months (95% CI 10.2–16.6 months). *PFS* progression-free survival, *OS* overall survival

Significance of the RFI

The response rate was significantly better in patients with an RFI of ≥6 months (37.5%; 95% CI 14–61%) than that in patients with an RFI of <6 months (5.0%; 95% CI 0–15%, $P = 0.014$, Table 2). In addition, compared with patients with an RFI of <6 months, patients with an RFI of ≥6 months had a significantly longer TTF (2.5 vs. 5.1 months, respectively, $P = 0.025$), longer PFS (2.3 vs. 6.2 months, respectively, $P < 0.001$, Fig. 2), and longer OS (7.3 vs. 16.6 months, respectively, $P = 0.003$, Fig. 2). According to a multivariate Cox model including PS and reason for discontinuation of adjuvant S-1, an RFI of 6 months was still significantly associated with PFS (hazard ratio [HR] 0.35, 95% CI 0.16–0.77, $P = 0.009$) and OS (HR 0.21, 95% CI 0.08–0.54, $P = 0.001$), although the association with TTF was not significant (HR 0.55, 95% CI 0.27–1.12, $P = 0.1$). When we divided the patients into two groups based on an RFI of 12 months, no significant difference between the groups was found in response rate, TTP, PFS, or OS.

Discussion

In the ACTS-GC study, adjuvant S-1 chemotherapy significantly improved the survival of patients who had undergone curative gastrectomy for locally advanced gastric cancer [10]. On the other hand, several small studies have suggested that patients with recurrence after adjuvant S-1 were refractory to S-1-containing regimens or had a worse prognosis compared with that of patients without adjuvant chemotherapy [12–14]. Although these reports never precluded the use of adjuvant S-1 chemotherapy, they raised the issue of how to treat recurrent disease after adjuvant S-1.

In the present retrospective study, we evaluated the efficacy of S-1 plus cisplatin in patients whose gastric cancer recurred after adjuvant chemotherapy with S-1. The response rate of 19.4% and PFS of 4.8 months were

Table 2 Objective response rates in patients with measurable lesions

	n	CR	PR	SD	PD	NE	ORR (%)	95% CI (%)
All	36	3	4	13	14	2	18.8	7–32
RFI <6 months	20	0	1	6	13	0	5.0	0–15
RFI ≥6 months	16	3	3	7	1	2	37.5	14–61

CR Complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval

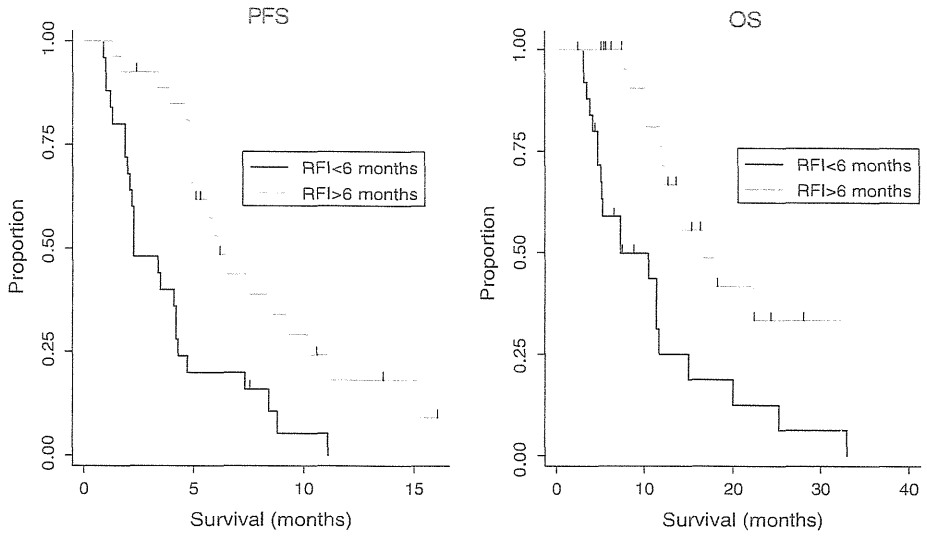

Fig. 2 Progression-free survival (*PFS*) and overall survival (*OS*) according to the length of the recurrence-free interval (*RFI*). Patients with an RFI of ≥6 months had a significantly longer median PFS (6.2 vs. 2.3 months, $P < 0.001$) and OS (16.6 vs. 7.3 months, $P = 0.003$) than patients with an RFI of <6 months. *RFI* recurrence-free interval, PFS progression-free survival, OS overall survival

relatively worse compared with those in the SPIRITS study [4]. However, our results also suggested that patients with an RFI of ≥6 months who received S-1 plus cisplatin had a significantly better response rate, longer PFS, and longer OS compared to patients with an RFI of <6 months. The efficacy of S-1 plus cisplatin for patients with an RFI of ≥6 months in this study was almost compatible with that of patients in the SPIRITS trial in terms of PFS and OS, although these results should be interpreted cautiously due to the heterogeneity of the characteristics of the patients in the two studies. Although no prospective study has evaluated any chemotherapy specifically for patients who have failed adjuvant S-1, Kang and colleagues [15] conducted a phase II study of capecitabine plus cisplatin for 32 patients with gastric cancer that recurred after adjuvant chemotherapy with doxifluridine or 5-FU-containing regimens. They reported a response rate of 28% and a median TTP of 5.8 months, and concluded that capecitabine plus cisplatin was effective as first-line treatment in patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant chemotherapy. In their report, the response rates (21 vs. 39%, $P = 0.427$), TTF (8.3 vs. 5.4 months, $P = 0.072$), and OS (14.1 vs. 9.3 months, $P = 0.075$) tended to be better in patients with an RFI of >6 months ($n = 13$) than in patients with an RFI of ≤6 months ($n = 19$), although the differences did not reach statistical significance [15]. These results were also consistent with those of previous studies in patients with other types of cancer, which suggested the importance of the RFI or treatment-free interval as a predictive marker of responsiveness to similar types of chemotherapy after recurrence [16–18]. Additionally, in the present study, the RFI cut-off value of 6 months was better than that of 12 months for predicting better outcomes and this finding may support the use of the conventional exclusion criteria in clinical trials in the first-line setting, which excluded patients who experienced disease recurrence within 6 months after the last adjuvant chemotherapy [5, 9, 11]. Therefore, selected patients with an RFI of ≥6 months with sufficient organ function may be adequately treated as chemo-naïve patients with standard chemotherapies such as S-1 plus cisplatin.

In contrast to the results for patients with an RFI of ≥6 months, the response rate in patients with an RFI of <6 months in the present study seemed to be worse than that of commonly used second-line chemotherapy regimens such as irinotecan and taxane combinations, which have a reported response rate of approximately 20% for patients with gastric cancer who received prior chemotherapy with fluoropyrimidines alone [18–23]. Based on these results, it may be suggested that the evaluation of chemotherapy regimens other than S-1 plus cisplatin might be warranted for the initial treatment of gastric cancer recurrence after adjuvant S-1. The response rate of 5.0% in our subset of patients with an RFI of <6 months was also lower than that reported previously by Kang et al. for capecitabine plus cisplatin after adjuvant chemotherapy (21%) [15]. The exact reasons for this difference are unknown. One possible reason is that Kang and colleagues did not use the same fluoropyrimidine (capecitabine after doxifluridine or 5-FU), and this choice might have contributed to a higher response in regard to early recurrence, although rechallenge with different types of fluoropyrimidine after the failure of another drug is still controversial in several types of cancer [24–28]. Second, the planned dose intensity of cisplatin as another key drug for gastric cancer was higher in their capecitabine plus cisplatin regimen (60 mg/m^2 every 3 weeks) [15] than that in the S-1 plus cisplatin regimen (60 mg/m^2 every 5 weeks). The efficacy of capecitabine plus cisplatin compared with other

chemotherapy (irinotecan, taxane or irinotecan plus cisplatin) for recurrence after adjuvant S-1 should be evaluated in future clinical trials.

It is important to note the limitations of the present study. First, it was retrospective, and treatment after recurrence was selected by each physician individually. Considering the low proportion of patients who received S-1 plus cisplatin after recurrence (14.0%), the selected population may have been biased toward patients with good performance status (PS) and low tumor burden. Second, toxicity was not evaluated in this study, although the proportion of patients who discontinued S-1 plus cisplatin due to toxicity was low. Third, human epidermal growth factor receptor 2 (HER2) status was not evaluated. Trastuzumab, a humanized monoclonal antibody against HER2, has recently been shown to improve the prognosis of HER2-positive advanced gastric cancer [29], and the HER2 status of all gastric cancer types should be evaluated, even in this setting of recurrent disease. Fourth, the moderate sample size in a single-country study is another limitation; therefore, it would be better to validate the significance of the RFI after adjuvant failure on the PFS in other cohorts as well.

In conclusion, this is the first report to have evaluated the efficacy of chemotherapy with S-1 plus cisplatin in patients with gastric cancer that recurred after adjuvant chemotherapy with S-1. S-1 plus cisplatin was effective in such patients, especially in those with an RFI of $\geq$6 months. Further well-defined, prospective trials in this important patient population are required to identify optimal treatment regimens.

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Conflict of interest None of the authors have financial or personal conflicts of interest to disclose.

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特集 外科医が行う胃癌化学療法

S-1+CDDPによる胃癌Neoadjuvant chemotherapyの治療意義
—1コース施行群と2コース以上施行群の比較—

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Significance of Neoadjuvant Chemotherapy with S-1+CDDP for Gastric Cancer—Comparison between 1 Course Treatment Group and More than 2 Courses Treatment Group—: Takiguchi N[*1], Nagata M[*1], Nabeya Y[*1], Ikeda A[*1], Kainuma O[*1], Hayata H[*1], Cho A[*1], Ohta T[*1], Park S[*1], Iwase T[*1], Yanagihashi H[*1], Arimitsu H[*1] and Yamamoto H[*1] ([*1]Department of Gastroenterological Surgery, Chiba Cancer Center)

Purpose: Gastric cancer with wide serosal invasion or bulky lymph node involvements have been treated by neoadjuvant chemotherapy with S-1+CDDP (SP). We estimated the significance of neoadjuvant chemotherapy for advanced gastric cancer and compared 1 cycle SP (A group) with more than 2 cycles SP (B group) from the clinicopathological point of view. **Methods:** Sixty seven gastric cancer patients with resection after SP neoadjuvant chemotherapy were examined. Gastric cancer with widespread serosal invasion or bulky node involvements were treated SP neoadjuvant chemotherapy (one cycle is treated for 5 weeks. S-1; 80 mg/m^2×21 days+CDDP; 30 mg/m^2×2 days (day1, day8) with 14 days rest). They were composed of 52 cases in 1 cycle (A), and 15 cases in more than 2 cycles (B). **Results:** 1) No serious adverse effects were found in both groups. 2) As the histologic response, the ratio of more than Grlb was 50% in A and 66% in B. 3) Peritoneal lavage cytology positive ratio of gastric cancer with sT3-4 and P0 was 8.8% in A and 0% in B. 4) According to final Stage, the cumulative 4 years survival rate was 88.9% in fStage I-II, and 81.3% in fStage III. **Conclusions:** It is suggested that the 2 cycles SP neoadjuvant chemotherapy for gastric cancer with wide serosal invasion or bulky node involvements is approvable.

Key words: Gastric cancer, Neoadjuvant chemotherapy, S-1+CDDP
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はじめに

新規抗癌剤の開発，なかでもS-1の開発により胃癌化学療法は大きく変化した．治癒切除後の進行胃癌の術後補助化学療法は，ACTS-GCの臨床試験結果により，fStageII，IIIにおける術後補助化学療法の意義が証明された[1]．その結果，S-1が適応薬剤としてガイドラインにも記載され，標準療法となっている．一方，そのSubgroup解析では，fStageIIIの予後は決して満足できるものではない．その原因は，治癒切除された

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としても，肉眼的に確認されない微小な転移が遺残していることにある．そのような症例に対して，術前化学療法を行うことが，予後向上に寄与することが期待されている．

われわれは，漿膜浸潤および高度リンパ節転移性胃癌に対しS-1＋CDDP（SP）療法による胃癌術前化学療法を外来化学療法として施行してきた．今回，1コース群と2コース以上群に分けて組織学的治療効果を中心に臨床病理学的に分析を行ない，進行胃癌に対する術前化学療法の意義を考察した．

1 対象と方法

術前の画像診断で，広範囲なcT3以上またはcN2以上と診断された胃癌に対し，術前化学療法の治療適応としてきた．術前検査としての審査腹腔鏡は実臨床の現場では施行していない．2004年10月より2010年3月までの症例を対象に，modified S-1＋CDDP療法（TS-1; 80 mg/m²×21 days（day1-21）＋CDDP; 30 mg/m²×2 days（day1, day8））を1コース施行（A）群52例と2コース以上施行（B）群15例を比較した．

本化学療法では，CDDP 30 mg/m²の投与であり，制吐剤としてカイトリル3 mg，デカドロン8 mg プリンペラン10 mgを点滴投与とし，CDDPを含めて総補液量は約1,700 mlとなるが，400 ml/hrでの点滴投与により約4.5時間の外来化学療法として治療を行なっている．なお，本論文における進行度表記は手術治療および術前治療の判定を明確にするため，第13版胃癌取扱い規約を使用した．

2 結　果

1) 両群間の患者背景

表1に両群間の患者背景を示す．2008年4月を境としてA群は主に前期，B群は主に後期に集積されている．性，年齢に差はなく，切除標本での最大腫瘍径も，平均約80 mmで腫瘍径の大きな症例が多く両群間に差はなかった．肉眼型ではType 3, Type 4が多くを占めていた．cStageⅢ，Ⅳが大半を占めていたが，両群間に差は認めなかった．cT, cN, H, P，については両群に差はない．

表1

	A群	B群	P value
性別（男性：女性）	31：21	8：7	0.891
年齢（歳）	61.6±10.9	65.3±9.0	0.217
腫瘍長径（mm）	80.8±42.5	79.8±58.7	0.723
肉眼型 Type 1	0	0	2
Type 2	5　35	5	0.091
Type 3	9	5	
Type 4	3	3	
Type 5			
cStage Ⅱ：Ⅲ：Ⅳ	3：32：17	3：6：6	0.152
H1	3	1	0.647
P1	4	1	1
T-2：3：4	2：45：5	2：12：1	0.382
N 0：1：2：3	1：15：28	2：4：6：3	0.262

2) 術前化学療法の治療完遂率と有害事象

コースが完遂できない症例は10例（15%）で，A群は7例（13.5%）で，B群は3例（20%）であったが，両群間に差はなかった．その原因は，A群では好中球減少；1例，発疹；2例，食欲不振2例，嘔吐2例であった．B群では，好中球減少；1例，発熱；1例，発疹；1例であった（表2）．

しかしながら実際のGrade3以上の副作用が出現した症例は，A群で食欲不振1.9%，好中球減少3.8%，血小板減少1.9%，発熱1.9%であった．B群では，好中球減少6.7%，皮膚反応6.7%，発熱6.7%であった．いずれの群においても，腎障害の出現はなかった（表3）．

3) 術前化学療法による主病巣の組織学的効果

化学療法による主病巣の組織学的効果判定は，Grade 1a以下がA群26例（50%），B群6例（33.3%），Grade 1bがA群14例（26.9%），B群2例（13.3%），Grade 2がA群11例（21.2%），B群6例（40%），Grade 3がA群1例（1.9%），B群2例（13.3%）であった．すなわち，Grade 1b以上の組織学的効果はA群26例

表2

	A群	B群	P value
非完遂	7/52(13.5)	3/15(20.0)	0.681
理由	好中球減少；1	好中球減少；1	
	発疹　；2	発熱　；1	
	食欲不振　；2	発疹　；1	
	嘔吐　；2		

コースが完遂できない症例は10例（15%）で群間差はなかった．

表3

	A群（52例）		B群（15例）	
	Gr 1, 2	3, 4	Gr 1, 2	3, 4
口内炎	1	0	0	0
嘔気/嘔吐	3	0	2	0
食欲不振	2	1(1.9)	2	0
白血球減少，好中球減少	2	2(3.8)	0	1(6.7)
血小板減少	1	1(1.9)	0	0
肝機能障害	0	0	0	0
発疹	3	0	0	1(6.7)
腎機能障害	0	0	0	0
発熱	0	1(1.9)	2	1(6.7)
血栓症	0	0	1	0

（ ）%

(50%)，B群10例（66%）であった（表4）．

4）術前化学療法による深達度改善

治療対象者の大半が広範な漿膜浸潤陽性胃癌であるので，組織学的深達度を確認することで術前化学療法による深達度の改善効果を推測することができる．術前未治療症例でのsT3症例のpT3正診率は71.9%であるのに対し，A群は48.5%，B群は25%となっており，pSSについてもその比率は，術前未治療群；24.0%，A群；45.5%，B群50%，pMP以浅の比率が，術前未治療群；2.6%，A群；6.1%，B群25%となっており，術前化学療法と未治療群との間には深達度分布に有意な差（p=0.0016）があることが示された．以上の結果は，組織学的深達度の改善を示唆している（表5）．

表4

	A群	B群
Gr 0, 1a	26(50)	5(33.3)
Gr 1b	14(26.9)	2(13.3)
Gr 2	11(21.2)	6(40.0)
Gr 3	1(1.9)	2(13.3)
Total	52	15

（ ）%

Grade 1b以上の組織学的効果はA群26例（50%），B群10例（67%）であった．

表5

	−MP	SS	SE	SI	Total
Control	5	47	141(71.9)	3(1.5)	196
A群	2	15	16(48.5)	0	33
B群	2	4	2(25)	0	8

Neoadjuvant: Control　p=0.0016　（ ）%
A：B　p=0.2013

5）術前化学療法による洗浄細胞診陽性率低下への寄与

sT3, T4かつP0でのDouglas窩の洗浄細胞診陽性率を示す（表6）．Cy1比率は，未治療群；22.9%に対し，A群；8.8%，B群；0%であった．術前化学療法の有無で有意差を認めた（p=0.020）．以上から，術前化学療法による洗浄細胞診陽性率低下への寄与も示唆される．

6）術前化学療法のリンパ節転移への効果

cNの判定の正診率は限界があり，組織学的リンパ節転移率の評価は困難であるが，リンパ節の縮小，消失により切除率の向上も考えられる．A群およびB群のリンパ節転移率の現状を示すと，pN0がA群；11.5%，B群；40%であり，pN2はA群；51.9%，B群；20%で深達度の同様にB群の転移率が低かった（表7）．多数例の症例を集積してこの傾向が明確になれば，リンパ節転移率の低下として証明しうると思われる．

7）生存曲線

術前化学療法症例の生存曲線を示す（図1，2）．B群は，術後観察期間が短いため死亡例は出ていないが，A群においても，4年生存率65.6%

表6

	Cy 0	Cy 1	Total
Control	162	48(22.9)	210
A群	31	3(8.8)	34
B群	9	0	9
Neoadjuvant : Control	p=0.020		( ) %
A : B	p=0.851		

表7

	pN0	pN1	pN2	pN3-
A群 [52]	6(11.5)	11	27	8
B群 [15]	6(40)	5	3	1

組織学的リンパ節転移率は82.1%

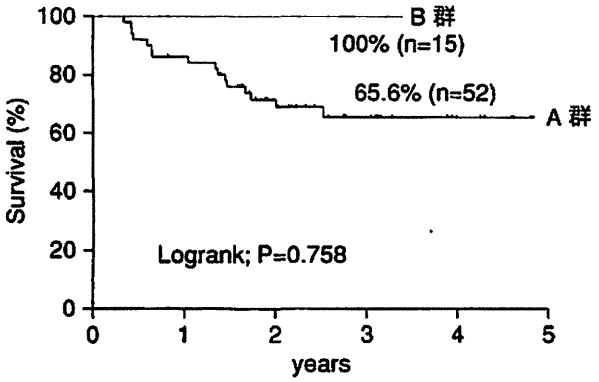

図1

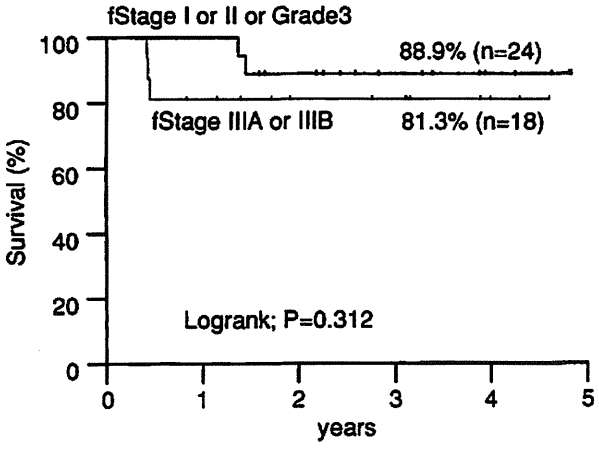

図2

の成績が出ており，さらに，fStageⅡまでの症例は，4年生存率88.9%，fStageⅢ症例でも81.3%の4年生存率であり，術前化学療法による生存率向上の可能性が示された．

3 考　察

StageⅡ～Ⅲ進行胃癌に対するD2根治切除後の補助化学療法は，ACTS-GC[1]の結果から，S-1の1年間投与が標準治療となったが，そのSubgroup解析では，fStageⅢの予後は決して満足できるものではない．また，日本胃癌学会の全国統計においてもfStageⅢは5年生存率41.5%である[2]．術前化学療法はcStageⅢa～Ⅲbに対する，あるいは肉眼的根治切除が可能なcStageⅣ胃癌に対する治療として期待されている[3,4]．

術前化学療法の意義は，

1. 術後補助化学療法より高い薬物濃度を維持できる．
2. 腫瘍のdown stagingは，切除率向上につながる．
3. 微小転移の制御．
4. 術後化学療法に対する感受性試験としての位置づけ．
5. 集学的治療としての位置づけ．

とされている．

実際の臨床試験としては，大型3型，4型胃癌に対する術前補助化学療法としてS-1＋CDDPを用いたJCOG0210があるが，治療完遂割合（術前化学療法完遂しかつ根治度A/Bの切除；CYを除く）が70%であった[5]．

われわれの行っているmodified S-1＋CDDP療法（TS-1; 80 mg/m^2×21 days＋CDDP; 30 mg/m^2×2 days（day1, day8））は，Total doseは同一条件として，外来化学療法として実臨床で施行している．術前治療コースは，初期は1コース施行としていたが，現在は2コースを基本としている．今回はその両群の比較を中心に，術前化学療法の意義を検討した．治療コースが完遂できない症例は10例（15%）で，A群は7例（13.5%）で，B群は3例（20%）であったが，食思不振，嘔吐など，胃癌そのものの病状と関係する症例も混在した．そのほかには好中球減少や発疹が原因であった．腎機能障害の出現はなく，外来化学療法として安全に施行された．

化学療法による治療効果は，主病巣の組織学的効果で判定することが基本となるが，その結果は，Grade 1b以上の組織学的効果はA群26例（50%），B群10例（66%）であった．術前化学療法によるpathological CRはA群1.3%，B群13.3%であった．

化学療法によるdown staging効果は，stageⅡ以上の胃癌を対象とし，術前後の化学療法＋手術を手術単独と比較したRCTであるMAGIC trialによって証明されている[6]．すなわち術前化学療法群が，手術単独群に比して病理学的T3以上の割合が62%から48%（p＝0.009），N2以上の割合が29%から16%（p＝0.01）と有意な低下を示した．著者らは，2003年にFP療法による漿膜浸潤胃癌対象の術前化学療法でも，手術単独群に比して病理学的T3以上の割合の減少と洗浄細胞診陽性率の低下の可能性を報告している[7]．今回のmodified S-1＋CDDP術前化学療法からは，術前未治療症例でのsT3症例のpT3正診率は71.9%であるのに対し，A群は48.5%，B群は25%となっており，治療群とくにB群でより浅い深達度比率が増加しており，2コースの術前化学療法意義が示されている．その効果は，洗浄細胞診陽性率でも明確に示されており，実臨床の現場では術前審査腹腔鏡を省略した現状の症例選択が許容されると考えている．リンパ節転移率は，漿膜浸潤胃癌であれば，おおむね80%程度である．リンパ節の術前画像正診率は決して高くないため，cNとpNの関係をみることは困難である．したがって，リンパ節転移率の低下があるかどうか，あるいはリンパ節個数の面から検討する必要があると思われる．A群のリンパ節転移率では，リンパ節のdown stagingはほとんどないと判定されるが，B群ではその可能性に期待したい．B群の症例集積が少ないので，今後の症例集積により判定することが必要と思われる．

生存期間に関しては，4型胃癌を対象にS-1術前補助化学療法2コース後胃切除を行うJCOG0002試験では，病理学的奏効率27.3%で2年生存率59%であった[8]．われわれのデータでは，B群においても，4年生存率65.6%で，fStageⅠ～Ⅱで4年生存率88.9%，fStageⅢで81.3%の4年生存率で，術前化学療法による生存率向上の可能性が示唆された．

臨床試験として治療する場合は，そのプロトコールにしたがって治療しているが，本データは当院における実臨床データであるものの，決して他の臨床試験報告に成績が劣るものではなく，B群の治療集積を行なっている．

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ORIGINAL ARTICLE

Identification of patients likely to benefit from metastasectomy in stage IV colorectal cancer

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Abstract
Purpose The aim of the present study was to determine selection criteria for patients with stage IV colorectal cancer (CRC) who were likely to show survival benefits of metastasectomy.
Methods Clinicopathological data of 119 patients with stage IV CRC who underwent primary CRC resection were retrospectively reviewed. The prognostic factors were analyzed according to the disease resectability status, and patients likely to show survival benefits of metastasectomy were identified.
Results Metastasectomy was performed in 63 patients. Among these patients, R0 resection was reported in 55 patients, who comprised the curable group. The other 64 patients comprised the noncurable group. For the noncurable group, postoperative chemotherapy was identified as the only significant prognostic factor. In the curable group, T stage, histological type, elevated serum carcinoembryonic antigen (CEA) level and the presence of extra hepatic disease were identified as independent prognostic factors. Patients within the curable group were further classified into a low-risk group (zero to two prognostic factors) and a high-risk group (three or more prognostic factors). The overall survival (OS) of the high risk patients in the curable group was as poor as that of the patients in the noncurable group.
Conclusions Stage IV CRC patients consisted of heterogeneous populations who had different prognostic factors, stratified by the disease resectability status. No prognostic benefit of metastasectomy was observed in high-risk patients undergoing curative metastasectomy. These results suggested that patients showing survival benefits of metastasectomy can be identified by considering the prognostic factors in patients undergoing curative metastasectomy.

Keywords Colorectal cancer · Stage IV · Metastasectomy · Selection criteria · Resectability status

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer and the fourth leading cause of cancer death worldwide [1]. Although the early stage disease of some patients is potentially curable, the detection of distant metastases at the time of presentation is common [2]. Although recent advances in chemotherapeutic regimens, including molecular targeted agents, have led to improved survival in patients with metastatic CRC, patients with stage IV disease have a very poor prognosis, with a 5-year survival of only 10–20 % [3].

Complete surgical resection of both primary CRC and its metastases remains the only potential curative therapy for stage IV CRC patients [2]. An increasing body of data suggests that patients who undergo curative resection of isolated metastases show survival benefits regardless of the metastatic site such as liver [4–6], lung [7–9], peritoneal [10, 11], ovarian metastases [12, 13] and extra regional lymph nodes [14, 15]. Although complete surgical resection of these metastases contributes to long-term survival in selected patients, some patients have early recurrence and very poor prognosis.

To identify the patients with poor prognosis after hepatic or pulmonary resection of metastatic CRC, investigators have proposed several different prognostic scoring systems

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[5, 8, 16, 17]. However, the factors contributing to the identification of patients likely to benefit from resection of metastatic disease have not been defined [18]. The actual indication of metastasectomy depends on the decision of surgeons or oncologists in each institution. The establishment of selection criteria for metastasectomy in patients with stage IV CRC is necessary.

Stage IV CRC encompasses a heterogeneous patient population in which both palliative and curative treatment strategies may be used [19]. The different treatment strategies are determined by the disease resectability status, and wide variation in the outcome has been shown [20]. In the present study, prognostic factors were compared between patients who underwent curative resection and those who did not to determine which patients are likely to benefit from metastasectomy among patients with stage IV CRC. The aim of this study is to establish selection criteria for metastasectomy in patients with stage IV CRC, based on the disease resectability status.

Patients and methods

We identified 131 patients with stage IV CRC disease from a prospective database from January 1992 to December 2008 at the Department of Surgery of Hiroshima University. Among these 131 patients, 119 patients underwent primary CRC resection (90.8 %), regardless of the resection of metastatic disease. These 119 patients were retrospectively analyzed based on the availability of detailed information about tumor-related factors.

Surgical treatment considered resection of the primary CRC when possible, with the exception of patients in poor condition. Determination of treatment strategy did not depend on the presence of tumor-related complications such as small bowel obstruction, bleeding or pain. In all cases with resectable synchronous metastases, simultaneous resection of both the primary and metastatic tumor was performed, regardless of the location of primary tumors and the extent of metastasis. Exceptionally, staged metastasectomy after resection of the primary tumor was performed in patients with lung metastasis or showing complications such as small bowel obstruction. For primary tumor resection, all patients underwent standard resection of colon and rectum with regional lymphadenectomy according to the Japanese general rules for clinical and pathological studies on cancer of the colon, rectum and anus, 7th edition (JGR) [21]. The indications for metastasectomy were the ability of the patient to tolerate the required surgical procedure and surgically controllable disease including primary lesion. For resection of liver metastases, radical operation was possible along with the preservation of at least 30 % of normal parenchyma. These criteria were independent of the number and size of liver tumors. The indications for pulmonary resection were the preservation of adequate postresection respiratory function. Potentially resectable bilateral or multiple lesions were not excluded from the selection criteria [7]. The resection of ovarian, peritoneal and extra regional lymph nodes was performed, if these metastases were isolated and could be completely removed. Curative resection (R0) was defined as microscopically free tumor margins.

Individual demographic and clinicopathological data were collected including age, sex, tumor location, tumor stage (T stage), nodal stage (N stage), tumor histology, presence of lymphovascular invasion, preoperative serum carcinoembryonic antigen (CEA) level, the presence of extra hepatic disease, the extent of hepatic lesions, the presence of lung metastasis, the presence of peritoneal dissemination, the presence of postoperative complications, application of postoperative therapy and survival rate. T stage, N stage and tumor histology were pathologically determined from resected specimens. All patients were staged according to the American Joint Commission for Cancer Staging (AJCC/TNM the sixth edition) system [22]. Survival data were updated until March 2011. Survival was computed from the date of the primary tumor resection. All postoperative complications were reviewed for at least 30 days following surgery. The complications were graded according to the method described by Dindo et al. [23]. Complications with a grade above III were categorized as morbid. Postoperative mortality was defined as any death that occurred within 30 days of surgery.

Statistical analysis

Survival curves were plotted by the Kaplan–Meier method, and univariate analyses of factors thought to influence overall survival (OS) were estimated using the logrank test. The Cox proportional hazard model was used for multivariate analyses. To achieve an optimal cutoff value of serum CEA levels, receiver operating characteristic (ROC) curve analysis for survival was performed to obtain the area under the ROC curve (AUC), and optimal cutoff values were defined as the point on a ROC curve nearest to the point where both sensitivity and specificity were one. In all analyses, statistical significance was set at a p value of less than 0.05. All statistical analyses were performed using JMP 8 software (version 8.02, SAS Institute Inc., Cary, NC, USA).

Results

Clinicopathological features

The clinicopathological features of the 119 patients are summarized in Table 1. Seventy-five male and 44 female

Table 1 Patients' characteristics

	n=119
Male/female	75/44
Age (mean)	61.8 (range, 23–85)
Median follow up time (month)	23.8 (range, 1.0–141.4)
Tumor location	
Colon/rectum	70/49
Number of metastatic organs	
One organ/more than 2 organs	94/25
Metastatic organs	
Liver	88
Lung	9
Extra regional lymph node	22
Peritoneal dissemination	26
Ovary	2
Metastasectomy	63 (52.9 %)
Curative/noncurative	55/8

patients were included in this study, with a median age of 61.8 years (range, 23–85 years). The median follow-up period was 23.8 months (range, 1.0–141.4 months). The distribution of tumor location included 70 colon and 49 rectal cancers. Ninety-four patients had metastatic disease in only one organ, and the other 25 patients had metastasis to more than two organs. The distribution of metastases was 88 in the liver, nine in the lung, 22 in extra regional lymph nodes, 26 with peritoneal dissemination and two in the ovary (including overlapped cases).

Metastasectomy was performed in 63 patients (52.9 %). Synchronous resection of primary and metastatic tumors was performed in 59 patients, and staged resection was performed in four patients. Among these 63 cases, histological tumor-free margin was seen in 55 patients (R0), and histological positive tumor margin was seen in the other eight patients (R1, 2). In the 55 patients with curative resection, the metastatic organ distribution was liver in 47 cases, peritoneal dissemination in four cases, lungs in two cases, extra regional lymph nodes in two cases and ovaries in two cases (including overlapped cases). In cases with liver surgery (n=47), ten cases had more than three subsegments of the liver resected. Postoperative complications were reported in six cases (10.2 %) for patients with only primary CRC resection (n=59) and ten cases (16.7 %) for patients with both primary and metastatic CRC resection (n=60), respectively. There were no reports of mortality in either of the groups.

Overall survival (OS) and classification based on the disease resectability status

The 5-year OS was 24.9 % for all patients combined. The 5-year OS for patients who underwent curative resection (R0), those who underwent noncurative resection (R1, 2) and those who did not undergo metastasectomy were 45.9 %, 12.5 % and 6.7 %, respectively (Fig. 1). The OS of patients who underwent curative resection for both primary and metastatic diseases was significantly better than that of the other two groups (p<0.001, Fig. 1). On the other hand, the OS of patients who could not undergo curative resection of primary or metastatic disease was as poor as that of the patients who did not undergo resection of metastases (p= 0.257, Fig. 1). Therefore, we stratified patients with stage IV CRC into two subgroups according to the disease resectability status: the patients who underwent curative resection for both primary and metastatic diseases (R0) were classified as the 'curable group' (n=55), and the patients who did not undergo curative resection for primary or metastatic diseases (R1, 2) and those who did not undergo resection of the metastatic disease were classified as the 'noncurable group' (n=64). The prognostic factors for both curable and noncurable patient groups were analyzed separately.

Postoperative chemotherapy

Among the patients in the noncurable group (n=64), 52 patients (82.8 %) received postoperative chemotherapy after primary tumor resection. The first-line postoperative therapy regimens were as follows: peroral drug regimen, such as S-1 (n=11) and tegafur-uracil (n=7), 5-FU/leucovorin (n=14), irinotecan-based regimen (n=7), transarterial chemotherapy (n=8) and oxaliplatin-based regimen (n=5).

For patients in the curable group (n=55), postoperative chemotherapy after metastasectomy was administered to 52 patients (94.5 %). The first-line postoperative therapy regimens were as follows: peroral drug regimen, such as S-1 (n=9), tegafur-uracil (n=8), tegafur-uracil/oral leucovorin (n=6) and capecitabine (n=1), transarterial chemotherapy (n=20), 5-FU/leucovorin (n=5) and oxaliplatin-based

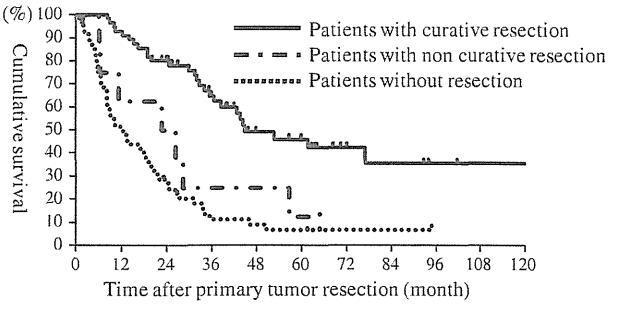

Fig. 1 Overall survival (OS) in patients with stage IV CRC classified by resectability status of the diseases. The OS of patients with curative resection was significantly better than that of the other two groups (p< 0.001). On the other hand, the OS of patients with noncurative resection was as poor as that of the patients without resection of metastases (p=0.257)