Table 2 Correlation between the results of cytological examination and presence/absence of peritoneal dissemination

	P0	P1	Total
Cy0	514	27	541
Cy1	101	124	225
Indeterminate	8	5	13
Undone	196	21	217
	819	177	996

P0 without peritoneal dissemination, *P1* with peritoneal dissemination, *Cy0* cytology-negative, *Cy1* cytology-positive

Table 3 Number of patients per peritoneal dissemination and cytology type of tumors

	Type4	Other Types	Total
P0Cy0	53	432	485
P0Cy1	33	55	88
P1Cy0	9	13	22
P1Cy1	61	45	106
	156	545	701

P0 without peritoneal dissemination, *P1* with peritoneal dissemination, *Cy0* cytology-negative, *Cy1* cytology-positive

701 patients were divided into four groups: (1) peritoneal dissemination-negative and cytology-negative (P0Cy0), (2) peritoneal dissemination-negative and cytology-positive (P0Cy1), (3) peritoneal dissemination-positive and cytology-negative (P1Cy0), and (4) peritoneal dissemination-positive and cytology-positive (P1Cy1). The number of patients in each category is given in Table 3.

Survival

The overall survival curves of the four groups are shown in Fig. 1. The prognosis of the patients with P1 and/or Cy1 was worse than that of the patients with P0Cy0. The prognosis of the P0Cy1 patients was better than that of the P1Cy1 patients ($p = 0.0002$, log-rank). The median survival time of the P0Cy1 patients was 12 months. The 2-year and 5-year survival rates in the P0Cy1 patients were 25.3% (95% confidence interval [CI] = 16.2–34.4%), and 7.8% (95% CI = 2.0–13.5%) (Table 4). Five (5.7%) of the 88 P0Cy1 patients survived for more than 5 years without evidence of recurrent disease.

The 88 P0Cy1 patients consisted of 33 patients with type4 gastric cancer and 55 with other types of gastric cancer. The survival of P0Cy1 patients with type 4 gastric cancer was significantly worse than that of the patients with other types of gastric cancer, as shown in Fig. 2 ($p = 0.0072$, log-rank). The median survival time was 10 months. The 2-year survival rate was 12.1% (95% CI = 0.12–22.1%) (Table 4). None of the patients survived for more than 40 months. Among the 88 P0Cy1 patients, 51 patients received postoperative adjuvant chemotherapy, mainly based on fluorouracil, while 35 did not, although this was not randomized. There was no information about adjuvant therapy for two patients who had moved to other hospitals soon after surgery. There was no significant difference in the survival curves between the P0Cy1 patients who received and did not receive adjuvant chemotherapy ($p = 0.1238$, log-rank) (Fig. 3).

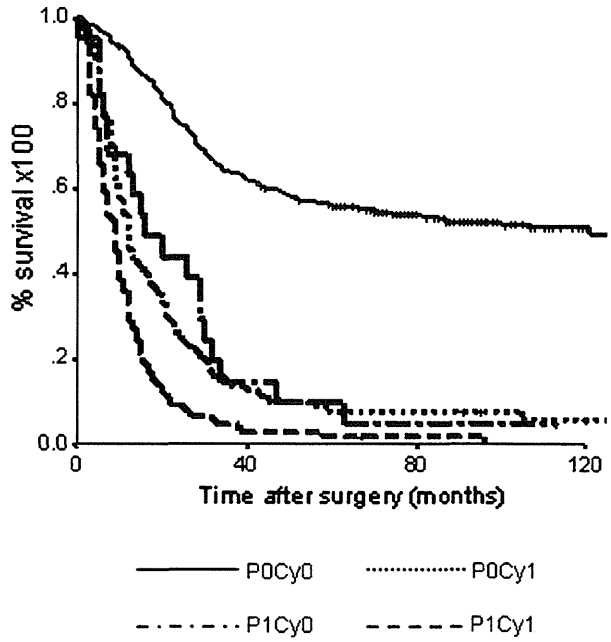

Fig. 1 Overall survival curves of gastric cancer patients (P0Cy0, P0Cy1, P1Cy0, and P1Cy1) are shown. The survival of P0Cy1 patients was poor but better than that of P1Cy1 patients ($p = 0.0002$)

Discussion

Lavage cytology-positive (Cy1) is most commonly encountered among gastric cancer patients with deeply invading tumors that extend outside the gastric wall [9, 15]; therefore, it is thought that the cancer cells escape from the surface of the tumors into the intraperitoneal cavity [16]. This is not clearly supported by some experiments, but Cy1 may reflect systemic spread of the tumor cells via the lymphatic pathway, which can cause retroperitoneal invasion, hydronephrosis, and rectal stenosis [17].

The prognosis of the patients who are found at the time of surgery to show peritoneal dissemination is expectedly very poor. The indication of mass reductive or palliative surgery should be evaluated by clinical trial [18], but it is regarded, by consensus, that gastric cancer patients with

Table 4 Survival rate and median survival time of POCy1 gastric cancer patients per type of tumor

	1 year	2 years	3 years	5 years	MST
POCy1					
All ($n = 88$)	46.0 (35.5–56.5)	25.3 (16.2–34.4)	13.8 (6.5–21.0)	7.8 (2.0–13.5)	12 (9.7–14.3)
Type 4 ($n = 33$)	45.5 (28.5–62.4)	12.1 (0.1–22.1)	0	0	10 (6.8–13.2)
Others ($n = 55$)	51.9 (38.5–65.2)	33.3 (20.8–45.9)	22.2 (11.1–33.3)	12.5 (3.5–21.5)	13 (7.6–18.4)

MST median survival time in months (95% confidence interval)

Values are % (95% confidence interval)

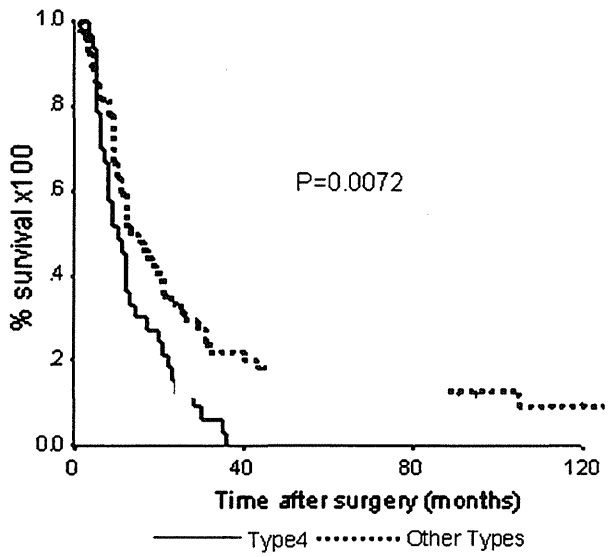

Fig. 2 The survival of POCy1 patients with type 4 advanced gastric cancer was significantly worse than that of patients with other types of advanced gastric cancer ($p = 0.0072$)

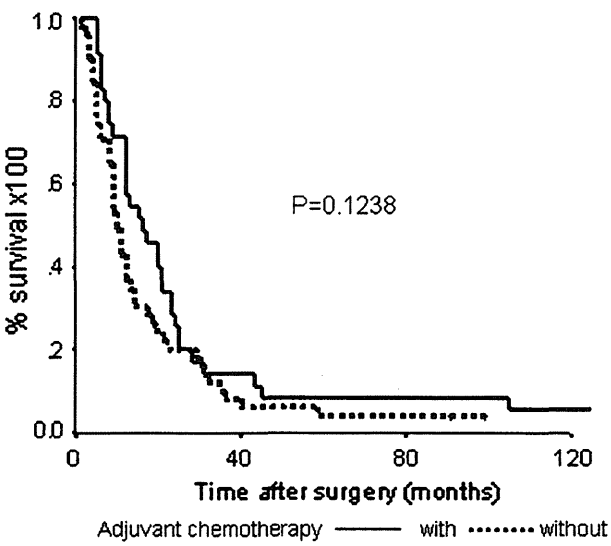

Fig. 3 There was no significant difference in the survival curves between POCy1 patients treated/not treated by adjuvant chemotherapy ($p = 0.1238$)

definite peritoneal dissemination are not suitable candidates for gastrectomy.

Cytological examination of intraperitoneal lavage fluid is performed in many institutions in Japan. In some institutions the result is confirmed intraoperatively, while in others it is confirmed on the following day. Cy1 is now included as one of the factors defining Stage IV in the Japanese classification of gastric carcinoma [19] because the prognosis of these patients with Cy1 is poor. However, the knowledge of a patient being Cy1 alone does not seem to be sufficient to decide on the therapeutic procedure [20]. The current consensus is that gastric cancer patients with intraoperatively confirmed Cy1 undergo standard gastrectomy and postoperative adjuvant chemotherapy [21]. Extended lymph node dissection and resection of other organs have gradually become less frequent in these patients. The efficacy of adjuvant chemotherapy with S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) after curative surgery has been reported [3]; however, no satisfactory postoperative adjuvant chemotherapy regimen for gastric cancer patients with Cy1 has been established. In our study, adjuvant chemotherapy using agents other than S-1 yielded no survival benefit. At our institution, S-1 was given as adjuvant chemotherapy to the patients, mainly after the end of the study period. In a future article we shall report on the efficacy of adjuvant chemotherapy with S-1 in gastric cancer patients with Cy1 compared with that in the subjects of this study as the historical control.

In this study, the 5-year survival rate of gastric cancer patients with POCy1 was 7.8%. This poor result must be interpreted as suggesting that previously used treatment, including surgery alone, was not suitable for these patients [22]. If those patients undergo surgery first, more intensive adjuvant chemotherapy would be needed. Currently, S-1 is given to these patients as adjuvant therapy [21, 23], but is S-1 monotherapy sufficient? A feasibility study of S-1 plus platinum as adjuvant therapy is ongoing (data not published); however, compliance with this therapy may not be favorable due to the unstable postoperative status of the gastric cancer patients. It is quite natural to expect that preoperative chemotherapy might be useful for those patients [24].

In order to carry out preoperative chemotherapy, information on Cy1 must be confirmed by staging laparoscopy [25]. In Japan, staging laparoscopy has been popular, but it may be difficult for it to be routinely performed in every advanced gastric cancer patient at every institution. Definitive evidence on the efficacy of preoperative chemotherapy, such as that from the MAGIC trial [26], is mandatory for encouraging the use of this therapy in Japan.

When only type 4 advanced gastric cancer patients are included in the analysis, the prognosis of those with Cy1 is extremely poor. No patient survived for more than 40 months after surgery in this study. The survival curve of the patients with P0Cy1 was almost the same as that of the patients who were found to have peritoneal dissemination (P1Cy1) at the time of the surgery (data not shown). The indication for gastrectomy for these patients must be discussed [27]. No surgeon performs gastrectomy for linitis plastica with peritoneal dissemination, except for palliating stenosis or bleeding. The former therapeutic strategy of immediate surgery and adjuvant chemotherapy has a less curative power for these patients with such a poor prognosis, and preoperative chemotherapy should be tried. Controlled arm may be the chemotherapy without surgery [28]. Information on Cy1 is necessary for determining the therapeutic strategy in patients with type 4 advanced gastric cancer, therefore, staging laparoscopy must be carried out first.

The patients with peritoneal dissemination are not always cytology-positive. The survival of P1Cy0 patients is better than that of P1Cy1 patients (Fig. 1) ($P = 0.0028$, log-rank). When the analysis is limited to type 4 gastric cancer, the survival of P1Cy0 patients is also better than that of P0Cy1 and P1Cy1patients (not shown), but the sample size (P1Cy0: $n = 9$) is too small for statistical evaluation. The P1Cy0 patients with local disseminated nodules may be the subset that can benefit from intraoperative chemotherapy.

In conclusion, curative treatment has been scarce for gastric cancer patients with Cy1 until now. The prognostic benefit of adjuvant chemotherapy with S-1 has been expected for years, but more intensive adjuvant chemotherapy, preoperative chemotherapy, and intraperitoneal chemotherapy [29] also warrant trials. The prognosis of type 4 gastric cancer patients with Cy1 is especially poor; therefore, it is recommended that such patients be treated at large-volume institutions with new therapeutic strategies developed based on clinical trials.

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ORIGINAL ARTICLE

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

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

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Results A total of 63 enrolled patients have been evaluated. Grade 3/4 toxicities included neutropenia (40%), anorexia (28%), and febrile neutropenia (4%) before protocol amendment ($n = 25$), and neutropenia (37%), anorexia (8%), and febrile neutropenia (3%) after amendment implementation ($n = 38$). Excluding ineligible cases, treatment completion rates were 57% (12/21) before and 81% (30/37) after the protocol amendment.
Conclusions The amended S-1 plus cisplatin is more feasible than the original protocol because of early dose reduction of S-1 prior to cisplatin addition and greater recovery time from surgery prior to cisplatin. This treatment should be considered as a feasible experimental arm for the next postoperative adjuvant phase III trial.

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

Introduction

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

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

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

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

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

Patients and methods

Eligibility criteria

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

Treatment and toxicity assessment

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

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

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

Protocol amendment

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

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

Statistical analysis

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

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

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

Table 1 Patient characteristics

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

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

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

Table 2 Toxicities

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

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

Results

Patient characteristics

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

Toxicity

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

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

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

Compliance

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

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

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

Discussion

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

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

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

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

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

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

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

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Predictive Factors Improving Survival After Gastrectomy in Gastric Cancer Patients with Peritoneal Carcinomatosis

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Abstract
Background The aim of this study was to review prognosis following gastrectomy for gastric cancer patients with synchronous peritoneal carcinomatosis and to identify predictive factors for improving survival after gastrectomy in this setting.
Methods Records of all patients who underwent gastrectomy for gastric cancer with peritoneal dissemination in our center between 1993 and 2004 were reviewed.
Results Data of 101 patients who underwent gastrectomy for gastric cancer with peritoneal dissemination were available. Peritoneal dissemination was classified as P1, metastasis to the adjacent peritoneum in 34 patients; P2, a few scattered metastases to the adjacent peritoneum in 13 patients; and P3, numerous metastases in 54 patients. Nineteen patients sustained 21 adverse events. Overall survival was significantly improved for those in the P1 and P2 groups compared with that for the P3 group (median of 18 months and 15 months vs. 9 months; $P < 0.001$). Seven factors were significant for overall survival: peritoneal carcinomatosis, peritoneal lavage cytology, macroscopic type, resection margin, extent of lymph node dissection, curative potential of gastric resection, and chemotherapy, including perioperative and postrecurrent chemotherapy. In multivariate analysis, two factors were identified as independently associated with poor survival: P3 disease ($P = 0.002$) and absence of chemotherapy ($P = 0.009$). Univariate analysis of gastric cancer patients with P1 or P2 carcinomatosis revealed only tumor differentiation to be significant.
Conclusions Gastric cancer patients with P1/P2 carcinomatosis and well/moderately differentiated tumors are likely to have an improved survival after gastrectomy. We emphasize that patients with good performance status and P1/P2 carcinomatosis should be considered appropriate surgical candidates before embarking on palliative systemic chemotherapy alone.

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Introduction

Gastric cancer disseminates by hematogenous, lymphatic, and direct implants on peritoneal surfaces. Peritoneal dissemination is the most frequent pattern of metastasis and recurrence in patients with gastric cancer [1–3]. Patients (10–20%) investigated for potentially curative resection of gastric cancer will have peritoneal seeding at the time of abdominal examination, and some patients with gastric cancer will present with peritoneal carcinomatosis [4–6].

Traditionally, there was a mutual agreement in the oncology community that those patients with gastric peritoneal dissemination were incurable [7]. Results of published studies have indicated a median survival of about 6 months [8, 9]. Despite improvements in systemic chemotherapy, gastric cancer patients with peritoneal dissemination generally have poor survival, and although palliative systemic chemotherapy has shown encouraging tumor response rates, there has been no improvement in survival [10–12]. Positive effects of palliative gastric cancer resection on survival have been previously demonstrated in patients with peritoneal carcinomatosis [5, 6, 13–17] but surgical strategies for these patients remain controversial.

The aim of this study was to review the prognosis following gastrectomy for gastric cancer patients with synchronous peritoneal carcinomatosis and to identify predictive factors for improving the survival rate after gastrectomy in this setting.

Methods

Patients

Between January 1993 and December 2004, a total of 101 consecutive patients underwent gastrectomy for gastric cancer with peritoneal dissemination at the National Cancer Center Hospital East in Chiba, Japan. The diagnosis of peritoneal dissemination was based on the operative findings and therefore the medical records of these patients were retrospectively reviewed. Clinical, pathological, and treatment-related variables were analyzed. These included age, gender, preoperative symptoms, tumor location, tumor macroscopic type, depth of tumor invasion (T), lymph node metastasis (N), peritoneal lavage cytology (CY), peritoneal dissemination (P), pathological confirmation of peritoneal dissemination, other distant metastasis, histology, lymphatic invasion (ly), venous invasion (v), resection margins, operative procedure, lymph node dissection, curative potential of resection, chemotherapy including perioperative and postrecurrent chemotherapy, and postoperative complications. Patient follow-up lasted until death or until the cutoff date of October 1, 2008. At the cutoff date only one patient was lost to follow-up. The patient had been followed for 10 years after gastrectomy and had completed the follow-up.

Classification of gastric cancer

Histopathological features, except peritoneal metastasis, lymph node dissection, and curative potential of resection, were evaluated according to the second English edition of the Japanese classification of gastric carcinoma published by the Japanese Gastric Cancer Association [18].

Peritoneal carcinomatosis

The second English edition of the Japanese classification of gastric carcinoma published by the Japanese Gastric Cancer Association classified peritoneal metastasis with only three grades: P0, no peritoneal metastasis; P1, peritoneal metastasis; and PX, unknown [18]. We believe that the extent of peritoneal carcinomatosis should influence the survival of gastric cancer patients with synchronous peritoneal carcinomatosis after gastrectomy. Therefore, in this study we classified peritoneal carcinomatosis according to the first edition of the General Rules for Gastric Cancer Study published by the Japanese Research Society for Gastric Cancer as follows: P0, no implants to the peritoneum; P1, cancerous implants to the region directly adjacent to the stomach peritoneum (above the transverse colon), including the greater omentum; P2, several scattered metastases to the distant peritoneum and ovarian metastasis alone; and P3, numerous metastases to the distant peritoneum [19].

Operation

Patients in this study underwent gastrectomy for gastric cancer with peritoneal dissemination. We performed D2 lymphadenectomy as our standard nodal dissection. However, we changed the type of nodal dissection in balance with other factors such as the degree of peritoneal dissemination, peritoneal lavage cytology, and lymph node metastases. D number was evaluated according to the second English edition of the Japanese classification of gastric carcinoma, and the curative potential of resection was evaluated according to this classification as follows: resection A, no residual disease with a high probability of cure (implies resection satisfying all of the following conditions: T1 or T2; N0 treated by D1–3 resection or N1 treated by D2, 3 resection; M0, P0, H0, CY0, and proximal and distal margins >10 mm); resection B, no residual disease but not fulfilling criteria for resection A; and resection C, definite residual disease [18].

Statistical analysis

The clinical characteristics of the different groups were compared using the χ^2 test. Cumulative survival analysis was performed using the Kaplan–Meier method and compared using the log-rank test. The overall survival analysis included all deaths such as in-hospital death or death from unrelated cause. A Cox regression (Cox proportional hazards model) was used for the multivariate analysis. All statistical analyses were performed using the Statistical Package for Social Sciences for Windows (SPSS Japan Inc., Tokyo, Japan). A significant difference was defined as $P < 0.05$.

Results

Descriptive data

Between January 1993 and December 2004, a total of 101 patients underwent gastrectomy for gastric cancer with peritoneal dissemination. The clinicopathological and treatment-related characteristics of the patients are given in

Table 1 Clinicopathological and treatment-related characteristics of the patients

Variables	P1 ($n = 34$)	P2 ($n = 13$)	P3 ($n = 54$)	p
Age (mean ± SD)	58.7 ± 11.1	56.7 ± 11.3	57.4 ± 12.9	NS
Gender (male/female)	22/12	9/4	32/22	NS
Location (U/M/L)	7/9/18	1/4/8	13/24/17	NS
Macroscopic type (non-type 4/type 4)	27/7	7/6	31/23	NS
T (T2/T3/T4)	1/29/4	1/10/2	0/47/7	NS
N (N0-2/N3)	23/11	12/1	41/13	NS
CY (X/0/1)	2/25/7	2/7/4	5/14/35	<0.001
Histology (differentiated/undifferentiated)	7/27	4/9	13/41	NS
Ly (0/1–3)	6/28	3/10	4/50	NS
V (0/1–3)	4/30	0/13	2/52	NS
Resection margin (negative/positive)	31/3	10/3	43/11	NS
Lymph node dissection (≥D2/<D2)	26/8	3/10	8/46	<0.001
Curative potential of gastric resection (B/C)	26/8	1/12	1/53	<0.001
Chemotherapy (including perioperative and postrecurrent) (+/−)	27/7	9/4	36/18	NS

NS not significant

Table 1. Peritoneal dissemination was classified as P1 in 34 patients (34%), P2 in 13 patients (13%), and P3 in 54 patients (53%). Ninety-six patients had peritoneal dissemination alone, whereas 5 patients had liver metastasis (P1, 2 of 34; P2, 0 of 13; P3, 3 of 54). Eighty-seven patients had pathologically confirmed peritoneal dissemination and 14 patients were diagnosed with peritoneal dissemination based on operative findings. The patients without pathological confirmation of peritoneal dissemination in each group were P1, 4 of 34; P2, 1 of 13; and P3, 9 of 54.

No statistical difference was observed in the mean age of the patients in each group. There were more men than women in each group (P1, 22 vs. 12; P2, 9 vs. 4; P3, 32 vs. 22) but the difference in the gender ratio of each group was not significant. The differences in tumor location, macroscopic type, T, N, histology, ly, and v of primary lesions were not significant. Resection margin status and chemotherapy (including perioperative and postrecurrent) were not significant. There were more P3-group patients with a positive CY (P1, 7 of 34; P2, 4 of 13; P3, 35 of 54), and the difference in the CY-positive ratio was significant ($P < 0.001$). Compared with the other groups, more patients in the P1 group required extensive lymphadenectomy ($P < 0.001$) and achieved the curative potential of gastric resection B ($P < 0.001$).

Eighty-two patients (81%) had no postoperative complications. The remaining 19 patients sustained 21 adverse events, including intra-abdominal abscess ($n = 3$), anastomotic leakage ($n = 3$), pancreatic fistula ($n = 7$), anastomotic stenosis ($n = 1$), wound infection ($n = 3$), small bowel obstruction ($n = 1$), cholecystitis ($n = 1$), and pneumonia ($n = 2$). One patient, who underwent gastrectomy and right hemicolectomy simultaneously, suffered from sepsis due to anastomotic leakage after colonojejunostomy and died.

Survival data

Figure 1 shows the overall patient survival after gastrectomy stratified according to the extent of peritoneal dissemination. There was a significant overall improved survival for those in the P1 and P2 groups than in the P3 group (median of 18 months and 15 months vs. 9 months; $P < 0.001$ by log-rank test). The 1-year survival for patients in the P1, P2, and P3 groups was 64.7, 69.2, and 35.2%, respectively. The 5-year survival of each group was 14.7, 15.4, and 0%, respectively. Four patients were alive at the time of follow-up, and there were 13, 7, and 2 patients who survived for 3, 5, and 10 years, respectively.

Univariate analysis of potential prognostic factors for survival

Clinicopathological and treatment-related factors were analyzed for their prognostic significance in these 101 patients. Table 2 gives the univariate analysis of the clinicopathological and treatment-related factors affecting overall survival. Seven factors were found to be significant for overall survival: P ($P < 0.001$), CY ($P = 0.002$), macroscopic type ($P = 0.017$), resection margin ($P = 0.049$), extent of lymph node dissection ($P = 0.018$), curative potential of gastric resection ($P < 0.001$), and chemotherapy, including perioperative and postrecurrent chemotherapy ($P = 0.013$). The following factors were not significant prognostic indicators for overall survival: N ($P = 0.481$), tumor differentiation ($P = 0.056$), other

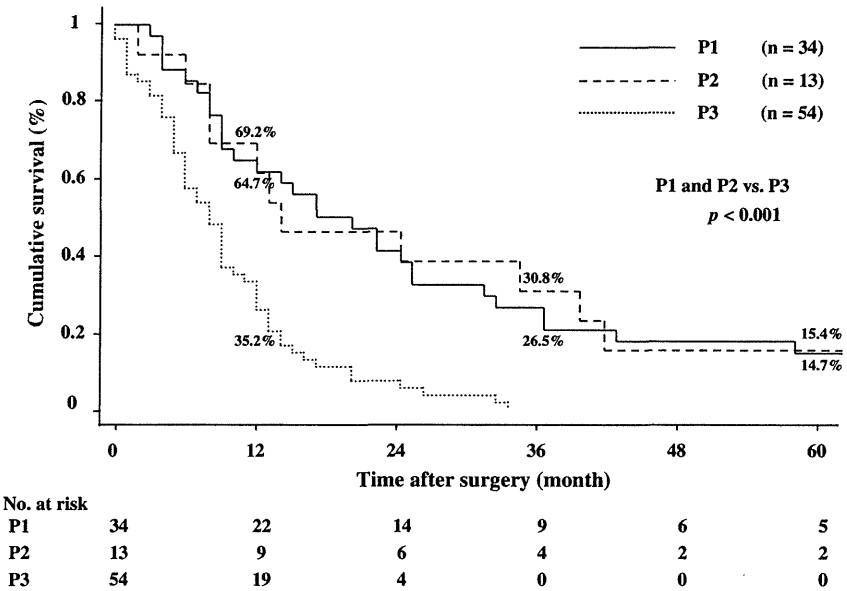

Fig. 1 Overall survival after gastrectomy for gastric cancer patients with peritoneal carcinomatosis. The prognostic significance for the degree of peritoneal dissemination was $P < 0.001$

Table 2 Univariate analysis of the clinicopathological and treatment-related factors affecting overall survival

Variable	Patients (*n*)	Median survival (months)	Survival rate (%)		*P*
			1 year	3 year	
Total	101	11	48.5	12.9	
P					
P1–2	47	18	66.0	27.7	<0.001
P3	54	9	33.3	0.0	
CY					
CY0	46	17	65.2	21.7	0.002
CY1	46	8	30.4	6.5	
Macroscopic type					
Non-type 4	66	13	53.0	18.2	0.017
Type 4	35	10	40.0	2.9	
Resection margin					
Negative	84	13	51.2	15.5	0.049
Positive	17	9	35.3	0.0	
Lymph node dissection					
≥D2	37	15	62.2	21.6	0.018
<D2	64	10	40.6	7.8	
Curative potential of gastric resection					
B	28	18	67.9	32.1	<0.001
C	73	10	41.1	5.5	
Chemotherapy (including perioperative and postrecurrent)					
+	72	13	58.3	13.9	0.013
−	29	7	27.6	10.3	

distant metastases ($P = 0.367$), neoadjuvant chemotherapy ($P = 0.210$), adjuvant chemotherapy ($P = 0.256$), and pathological confirmation of peritoneal dissemination ($P = 0.307$).

Multivariate analysis for survival

In the multivariate analysis of overall survival, two factors were identified to be independently associated with

Table 3 Multivariate analysis of clinicopathologic and treatment-related factors affecting survival

Variable	Hazzard ratio	95% CI	*P*
P (P1 and P2 vs. P3)	2.347	1.372–4.016	0.002
CY (CY0 vs. CY1)	1.378	0.845–2.248	NS
Macroscopic type (non-type 4 vs. type 4)	1.354	0.856–2.141	NS
Resection margin (negative vs. positive)	1.627	0.900–2.941	NS
Lymph node dissection (≥D2 vs. <D2)	1.200	0.728–1.979	NS
Curative potential of gastric resection (B vs. C)	1.169	0.601–2.276	NS
Chemotherapy (including perioperative and postrecurrent) (+ vs. −)	1.858	1.165–2.963	0.009

P peritoneal carcinomatosis; *CY* peritoneal lavage cytology

improved survival: P3 disease (hazard ratio = 2.347; 95% confidence interval = 1.372-4.016; $P = 0.002$), and absence of chemotherapy, including perioperative and postrecurrent chemotherapy (hazard ratio = 1.858; 95% confidence interval = 1.165-2.963; $P = 0.009$) (Table 3).

Potential prognostic factors for survival in the P1/P2 groups

Patients evaluated at P3 stage had no hope for prolonged survival after gastrectomy. Therefore, we analyzed clinicopathological and treatment-related factors for prognostic significance in 47 patients evaluated at P1 or P2 stage. Table 4 gives the univariate analysis of clinicopathological and treatment-related factors of gastric carcinoma patients with P1/P2 carcinomatosis. Gender ($P = 0.498$), preoperative symptoms ($P = 0.188$), tumor location ($P = 0.449$), macroscopic type ($P = 0.173$), T ($P = 0.459$), N ($P = 0.612$), other distant metastases ($P = 0.886$), pathological confirmation of peritoneal carcinomatosis ($P = 0.142$), CY ($P = 0.333$), resection margin ($P = 0.315$), extent of lymph node dissection ($P = 0.883$), operative procedure ($P = 0.830$), curative potential of gastric resection ($P = 0.402$), neoadjuvant chemotherapy ($P = 0.306$), adjuvant chemotherapy ($P = 0.467$), and chemotherapy, including perioperative and postrecurrent chemotherapy ($P = 0.433$), were not significant prognostic indicators for overall survival. Tumor differentiation was the only factor that was found to be significant for overall survival ($P = 0.048$) (Fig. 2).

Discussion

Gastrectomy has been performed in our hospital for gastric cancer patients with either isolated peritoneal carcinomatosis with curative intent or disseminated peritoneal carcinomatosis with palliative intent. Despite several positive reports of palliative resection [5, 6, 13–17] and in the absence of any evidence provided so far on the efficacy of systemic chemotherapy for the selected group of patients, accepting patients with peritoneal dissemination for resection may seem controversial. Indeed, the current opinions on the standard of care for these patients are polarized: chemotherapy with or without resection.

There are several classifications that describe the quantitative prognostic indicators of peritoneal dissemination for gastric cancer [20, 21]. In this study we classified peritoneal dissemination according to the first edition of the General Rules for Gastric Cancer Study [19]. Univariate analysis of clinicopathological and treatment-related factors affecting overall survival of patients with peritoneal dissemination revealed seven significant factors: P, CY, macroscopic type, resection margin, extent of lymph node dissection, curative potential of gastric resection, and chemotherapy, including perioperative and postrecurrent chemotherapy. The results of the multivariate analysis indicated that P and chemotherapy, including perioperative and postrecurrent chemotherapy, were identified as independently associated with improved survival. We observed a postoperative morbidity rate of 19% and mortality rate of 1%, which were comparable with those observed in a previous report on surgery for advanced gastric cancer [14, 22–25]. These survival results and surgical risk for what is regarded as an incurable disease are very encouraging, especially for patients with P1/P2-graded peritoneal dissemination. From a surgeon's perspective, we believe that emphasis should be placed on stringent patient selection to identify the most optimal surgical candidates and to avoid futile aggressive treatment.

Furthermore, the univariate analysis of clinicopathological factors affecting overall survival in gastric cancer patients at P1 or P2 stage carcinomatosis revealed only tumor differentiation to be significant. In this setting, chemotherapy, including perioperative and postrecurrent chemotherapy, was not predictive for improving survival after gastrectomy ($P = 0.433$). In addition, curability and nodal dissection were not significant factors. Therefore, when patients with P1/P2 undergo resection, extent of

Table 4 Univariate analysis of clinicopathological and treatment-related factors of gastric carcinoma patients with P1/P2 carcinomatosis

Variable	Patients (*n*)	Median survival (months)	Survival rate (%)		*p*
			1 year	3 year	
Total	47	18	66.0	27.7	
Macroscopic type					
Non-type 4	35	21	65.7	34.3	0.173
Type 4	12	15	66.7	8.3	
T					
Non-T4	41	23	70.7	29.3	0.459
T4	6	10	33.3	16.7	
N					
<N3	35	18	68.6	28.6	0.612
≥N3	12	15	58.3	25.0	
Other distant metastasis					
−	45	18	64.4	28.9	0.886
+	2	26	100.0	0.0	
Pathological confirmation of peritoneal dissemination					
−	5	32	100.0	40.0	0.142
+	42	15	61.9	26.2	
CY					
CY0	32	25	71.9	31.3	0.197
CY1	11	11	45.5	27.3	
Tumor differentiation					
Well/moderately	11	33	100.0	45.5	0.048
Poorly	36	13	55.6	22.2	
Lymph node dissection					
≥D2	29	18	58.6	27.6	0.883
<D2	18	18	77.8	27.8	
Operative procedure					
Nontotal gastrectomy	19	18	63.2	31.6	0.830
Total gastrectomy	28	18	67.9	25.0	
Curative potential of gastric resection					
B	27	21	66.7	33.3	0.402
C	20	15	65.0	20.0	
Neoadjuvant chemotherapy					
−	44	18	68.2	29.6	0.306
+	3	10	33.3	0.0	
Adjuvant chemotherapy					
−	23	15	60.9	30.4	0.467
+	24	25	70.8	25.0	
Chemotherapy (including perioperative and postrecurrent)					
−	11	13	54.6	27.3	0.433
+	36	23	69.4	27.8	

dissection and curability should not be taken into consideration. Well/moderately differentiated gastric cancer patients with P1 or P2 had a median survival of 25 months, a 3-year survival of 45.5%, and a 5-year survival of 27.3%. These results emphasize that patients in this setting should be considered for better surgical indication.

The median survival time of patients in the P3 group was 9 months. The SPRITS trial by Koizumi et al. [12] showed a median survival time of about 13 months in patients treated with S-1 plus cisplatin for unresectable or recurrent advanced gastric cancer. It is difficult to determine the benefits of tumor reduction surgery in such patients.

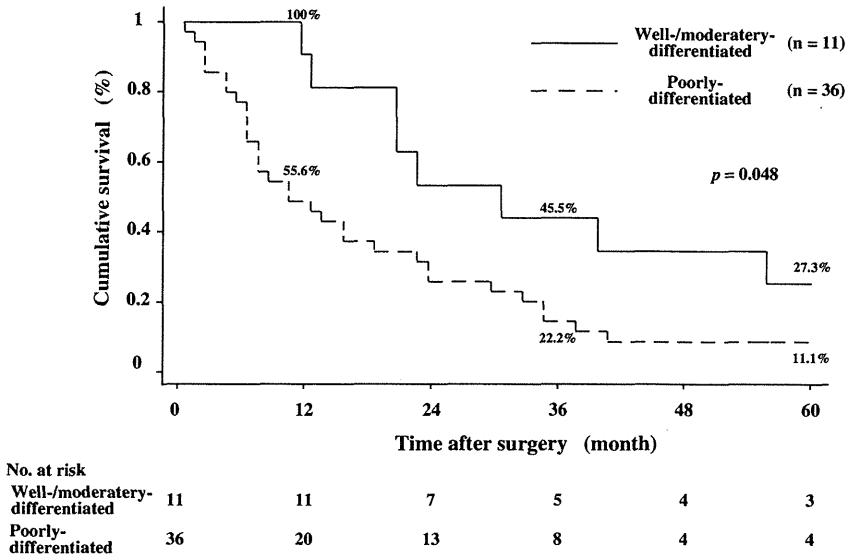

Fig. 2 Overall survival after gastrectomy for gastric cancer patients with peritoneal carcinomatosis (P1 or P2). The prognostic significance for tumor differentiation was $P = 0.048$

It appears that the most important prognostic factors for survival are localization and few peritoneal disseminations. Whether P1/P2 carcinomatosis implies merely the quantity of tumor cells, lower malignancy of the cancer itself, or potency of complete reduction needs further discussion. Indeed, multivariate analysis did not show that curability was not a significant prognostic factor in this study. Nevertheless, these groups of patients should at least be considered appropriate surgical candidates.

The current study had several limitations. This was a retrospective study and therefore the patients might have received a variety of treatments, including palliative or curative resection with or without neoadjuvant and/or adjuvant and palliative chemotherapy. Indeed, the patients with a more advanced degree of peritoneal dissemination had more palliative resection. The chemotherapy regimens were changed a lot. The patients without chemotherapy were in the earlier part of the study, and the patients treated with several regimens were in later period. Among seven patients who lived more than 5 years after surgery, three patients did not undergo postoperative chemotherapy. However, it was difficult to evaluate the effects of chemotherapy in detail.

In conclusion, the present study indicated that gastric cancer patients with P1/P2 carcinomatosis and well/moderately differentiated tumors are likely to have improved survival after gastrectomy. Reduction surgery may have a role in gastric cancer with minimal peritoneal dissemination. We emphasize that patients with good performance status and P1/P2 carcinomatosis should be considered appropriate surgical candidates before embarking on palliative systemic chemotherapy alone.

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腹膜転移を有する胃癌症例に対する治療戦略

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腹膜転移を有する胃癌症例に対する治療戦略

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Strategy of Treatment for Gastric Cancer with Peritoneal Metastasis: Hiromi Tanemura, Hiroo Oshita, Makoto Yamada, Tsuneaki Hatoh, Takahito Adachi and Kouji Matsui (*Dept. of Surgery, Gifu Municipal Hospital*)

Summary

In advanced gastric cancer with peritoneal metastasis, adjuvant chemotherapy after primary tumor resection showed considerably poor prognosis with a median survival time of only 232 days. So, we changed the strategy that we start systemic chemotherapy at the earliest opportunity without resecting the primary tumor for gastric cancer patients who were diagnosed peritoneal metastasis by laparotomy or staging laparoscopy. Eleven cases of gastric cancer with peritoneal metastasis were administered systemic chemotherapy first including S-1+paclitaxel (PTX). The regimen of chemotherapy of two weeks administration of S-1 (80 mg/m^2/day) followed by one week rest and injections of PTX (50 mg/m^2) at day 1 and 8 for 21 days as one course. Five of eleven cases were performed S-1+PTX as the first-line, the other six cases as the second-line. In some cases, this therapy led to transient responses. Ultimately, most of them showed progressive disease. However, two of eleven cases showed a complete response in the peritoneal metastasis and could receive radical operation for gastric cancer. Both patients were still alive without any relapse at the time of this report. The median survival time of eleven cases of gastric cancer with peritoneal metastasis performed the systemic chemotherapy first with this regimen was 464 days. The survival was considerably prolonged (p=0.0500), compared to 232 days in postoperative cases. **Key words**: Gastric cancer, Peritoneal metastasis, S-1, Paclitaxel (*Received May 12, 2009/Accepted Jul. 29, 2009*)

要旨　腹膜転移を有する進行胃癌では術後補助化学療法を行っても，その予後はMSTでわずか232日と不良であった。そこでわれわれは，開腹あるいはstaging laparoscopyにて腹膜転移ありと診断された胃癌に対しては原発巣切除を行わないで，できるだけ早期に全身化学療法を始めることに治療戦略を変更した。11例の腹膜転移を有する胃癌にS-1+paclitaxel (PTX) を含む全身化学療法が優先して行われた。S-1 (80 mg/m^2/day) 2週投与，PTX (50 mg/m^2) はday 1，day 8に投与し1週休薬を1コースとした。11例のうち5例にPTX+S-1をfirst-lineとして，6例はsecond-lineとして行われていた。何例かは一時的な効果を示す症例も認めたものの，ほとんどの症例はprogressive diseaseであった。しかし11例中2例に腹膜転移のcomplete responseが得られ根治的胃切除が可能となった。2例とも現在無再発生存中である。胃癌腹膜転移に対し全身化学療法を優先して行われた11例のMSTは464日であり，手術先行，術後化学療法例のMST 232日に比べ生存期間が延長する（p=0.0500）可能性が示唆された。

はじめに

切除不能進行胃癌・再発胃癌のわが国での標準的治療は，現在のところSPIRITS trial[1]で報告されたようにS-1+CDDPである。しかし，腹膜転移は胃癌再発の40～50%に関与しているとされ[2,3]，胃癌死亡原因の最も重い因子とされている[4]が，腹膜転移に対する治療法に関しては全身療法，局所療法を含めいまだ確立された治療法はない。

最近，種々新しい化学療法剤の開発に伴い，腹膜転移に効果があるとされるS-1[5]とpaclitaxel (PTX)[6]を用い，腹膜転移を有する胃癌症例の予後改善の目的で，腹膜転移を有する初発胃癌に対し胃原発巣切除を行わず，S-1+PTXを含む化学療法を先行して行うことで腹膜転移症例の予後改善が得られるかについて検討した。

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