Three patients died within 30 days after the final dose of the study drug. All 3 of the deaths were attributed to disease progression, and there were no treatment-related deaths.

Efficacy

It was possible to assess all 40 eligible patients who received the RD for response. Thirty-four patients had died by the completion of the follow-up period. There were no complete responses, but a partial response was achieved in seven patients (18, 95% confidence interval, 7.3–32.8%). Stable disease was noted in 19 patients (48%) and progressive disease in 14 patients (35%). Tumor responses to second-line FGS therapy are classified according to the tumor responses to first-line gemcitabine in Table 5. Three of 10 patients whose best response was progression disease in first-line chemotherapy achieved partial response in FGS therapy. The median progression-free survival time was 2.8 months. The median overall survival time after the start of second-line therapy was 7.0 months (range 1.3–18.9+), and the 1-year survival rate was 18% (Fig. 1). The median overall survival time after the start of first-line therapy was 13.9 months (range 5.2–31.4).

Table 5 Objective tumor response

Response (2nd line)	*n* (%)	Response (1st line)		
		PR	SD	PD
PR	7 (18)	1	3	3
SD	19 (48)	3	12	4
PD	14 (35)	2	9	3
Total	40 (100)	6	24	10

Response rate: 18% (95% CI: 7.3–32.8)

RECIST criteria

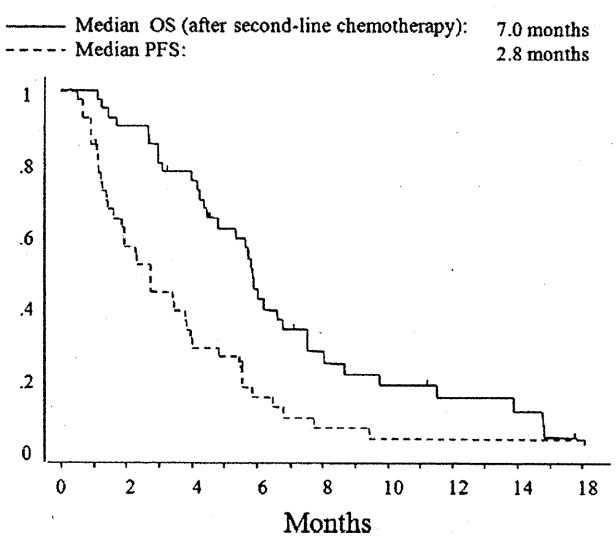

Fig. 1 Survival curves. Survival ($n = 40$). Progression-free survival (*dashed line*) and overall survival time (*solid line*) curves of patients with gemcitabine-refractory pancreatic cancer receiving systemic chemotherapy with FGS

Discussion

In the last decade, several clinical trials (mainly phase II) have been conducted in patients with advanced pancreatic cancer after failure of first-line gemcitabine or a gemcitabine-based combination regimen. The results of a randomized trial ($n = 168$) comparing fluorouracil and folinic acid versus oxaliplatin, fluorouracil and folinic acid (OFF) indicated that OFF improved progression-free survival and overall survival as a second-line chemotherapy. The median progression-free survival time and median survival time of OFF were 3 and 6 months, respectively [22]. In the present study, FGS yielded a median progression-free survival time of 2.8 months and a median overall survival time of 7.0 months, similar to the data mentioned above. Furthermore, the response rate of 18% in the present study was above the pre-established boundary (objective response in five or more of the 40 patients) required for the regimen to be considered effective. However, the gap between the median overall survival time and the median progression-free survival time in the present study was relatively large. Although the reason for this gap is unknown, a bias arising from the selection of patients with a good general condition or with a small tumor burden may explain these findings.

Whether gemcitabine as an FDR infusion is active even after progression during treatment with the standard 30-min administration of gemcitabine was the critical clinical question examined in this study. Differentiating between the relative roles of gemcitabine and S-1 in overcoming tumor resistance is difficult. The efficacy and survival data obtained in the present study seem to be better than those of previous studies for oral fluoropyrimidine monotherapy as a salvage chemotherapy for advanced pancreatic carcinoma (Table 6) [1, 2, 17, 28, 29]. However, since all the data were obtained in single-arm studies, a randomized study is needed to make these suggestions reliable. Furthermore, whether the combined regimen in the present study is superior to other regimens, such as the OFF regimen, remains an essential clinical question.

Safety and convenience as well as antitumor efficacy are critically important issues with regard to second-line chemotherapy. One patient experienced an acute myocardial infarction. Although she had other risk factors, such as a smoking habit and hyperlipidemia, a relation between gemcitabine and the acute myocardial infarction cannot be ruled out because gemcitabine had been administered on the day of the infarction. The toxicity profile of FGS

Table 6 Comparison between the current study and previous studies of oral fluoropyrimidine monotherapy as salvage chemotherapy for advanced pancreatic carcinoma

Study	References	Phase	Regimen	*n*	PR + CR (%)	Median PFS (months)	Median OS (months)
Morizane et al.	[12]	II	S-1	40	15	2.0	4.5
Abbruzzese et al.	[29]	II	S-1	45	0	1.4	3.1
Sudo et al.	[31]	II	S-1	21	9.5	4.1	6.3
Todaka et al.	[32]	Retrospective	S-1	52	4	2.1	5.8
Boeck et al.	[30]	II	Capecitabine	39	0	2.3	7.6
Morizane et al.	Current study	II	FGS	40	18	2.8	7.0

therapy in the other patients was acceptable, and the most common grade 1–4 adverse reactions were anorexia (68%), leukocytopenia (60%) and neutropenia (60%), although most episodes were tolerable and reversible. The safety profile in this study suggests that FGS can be safely administered to pancreatic cancer patients even in a second-line setting, at least in select populations. The biweekly schedule allows enough time to recover from myelosuppression and non-hematological toxicities before the following cycle, enabling patients to receive treatment as scheduled. Actually, the relative dose intensities of gemcitabine and S-1 in our study were high (90.8 and 90.1%, respectively). Furthermore, because of the biweekly schedule, patients do not need to come to the hospital for treatment as often compared with the first-line standard schedule of gemcitabine therapy. Our new treatment schedule may therefore improve the patients' quality of life during anticancer treatment.

We concluded that combination therapy consisting of gemcitabine as a fixed dose rate infusion and S-1 (FGS) provided a promising antitumor activity and tolerable toxicity in patients with gemcitabine-refractory metastatic pancreatic cancer. A larger randomized controlled trial is needed to confirm the clinical benefits of FGS following gemcitabine failure.

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Multicenter Phase II Study of Gemcitabine and S-1 Combination Therapy (GS Therapy) in Patients With Metastatic Pancreatic Cancer†

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Objective: The aim of this multicenter Phase II study was to assess the efficacy and toxicity of gemcitabine and S-1 combination therapy for metastatic pancreatic cancer.
Methods: Chemotherapy-naïve patients with histologically or cytologically proven metastatic pancreatic adenocarcinoma were eligible for this study. Gemcitabine was administered at a dose of 1000 mg/m^2 over 30 min on days 1 and 8, and oral S-1 at a dose of 40 mg/m^2 twice daily from days 1 to 14, repeated every 3 weeks.
Results: A total of 55 patients were included and the efficacy and toxicity were analyzed in 54 patients who received at least one dose of gemcitabine and S-1 combination therapy. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44.4% (95% confidence interval: 30.9–58.6%). The median progression-free survival was 5.9 months (95% confidence interval: 4.1–6.9 months) and the median overall survival was 10.1 months (95% confidence interval: 8.5–10.8 months) with a 1-year survival rate of 33.0%. The major Grade 3–4 toxicities were neutropenia (80%), leucopenia (59%), thrombocytopenia (22%), anorexia (17%) and rash (7%). Hematological toxicity was mostly transient and there was only one episode of febrile neutropenia ≥Grade 3.
Conclusions: Gemcitabine and S-1 combination therapy produced a high response rate with good survival in patients with metastatic pancreatic cancer. A randomized Phase III study to confirm the efficacy of gemcitabine and S-1 combination therapy is ongoing.

Key words: pancreatic cancer – Phase II – chemotherapy – gemcitabine – S-1

†Part of the content of this report was presented at the ASCO 2007 meeting in the poster presentation (abstract 4550).

INTRODUCTION

Pancreatic cancer is a highly malignant disease and the fifth most common cause of cancer death in Japan. Approximately 80% of patients are ineligible for surgery at diagnosis and more than half of patients have metastatic disease.

Gemcitabine has been the standard chemotherapeutic agent for metastatic pancreatic cancer on the basis of a Phase III study showing clinical and survival benefits over 5-fluorouracil (5-FU) (1). However, the efficacy of gemcitabine monotherapy for advanced pancreatic cancer is limited; most clinical trials have shown response rates of around 10% with a median overall survival of 6–7 months (2–5). Therefore, numerous studies have attempted to increase the efficacy of chemotherapy, but almost all the regimens evaluated in Phase III studies have failed to show survival benefits over gemcitabine. To date, only two randomized trials, gemcitabine plus erlotinib and combination therapy of 5-FU/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) have shown significant prolongation of overall survival (6,7). However, the reported difference in median survival between the gemcitabine plus erlotinib group and the gemcitabine-only group was small (6.24 versus 5.91 months). The results of the FOLFIRINOX trial are more impressive than those of gemcitabine plus erlotinib because FOLFIRINOX led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group. However, the FOLFIRINOX regimen was quite toxic (e.g. 5.4% of patients had Grade 3 or 4 febrile neutropenia), and a survival benefit was shown only among a highly select population with a good performance status, an age of 75 years or younger and normal or nearly normal bilirubin levels (8).

S-1, an oral fluoropyrimidine derivative, is now widely used for a variety of malignancies such as gastric cancer (9,10). In Phase II studies of S-1 for metastatic pancreatic cancer, response rates of 21.1–37.5% and median overall survival of 5.6–9.2 months were reported (11,12). Preclinical studies have demonstrated a synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells (13). On the basis of these findings, we decided to investigate combination therapy with gemcitabine and S-1 therapy (GS therapy) for pancreatic cancer. We initially conducted a Phase I study of GS therapy in patients with advanced pancreatic cancer (14). In that study, gemcitabine was administered as a 30-min intravenous infusion on days 1 and 8 along with oral S-1 twice daily from day 1 through day 14, concluding that a gemcitabine dose of 1000 mg/m^2 and an S-1 dose of 40 mg/m^2 twice daily was recommended in future studies. Since GS therapy showed promising activity, with a 33% response rate and a median survival of 7.6 months, the present multicenter Phase II study was conducted in patients with metastatic pancreatic cancer to evaluate the efficacy and toxicity profile of GS therapy.

PATIENTS AND METHODS

Patient Selection

Patients were included if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma of the pancreas; at least one measurable metastatic lesion; no history of prior chemotherapy or radiotherapy for pancreatic cancer; age 20–74 years; Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ functions (leucocyte count, 4000–12 000/mm^3; neutrophil count, $\geq$2000/mm^3; platelet count, $\geq$100 000/mm^3; hemoglobin level, $\geq$9.0 g/dl; serum creatinine level, $\leq$1.5 mg/dl; serum AST and ALT levels, $\leq$150 U/l and serum total bilirubin level, $\leq$2.0 mg/dl or $\leq$3.0 mg/dl if biliary drainage was present).

The exclusion criteria were as follows: symptomatic pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; central nervous system metastasis; active concomitant malignancy; severe mental disorder; serious complications such as active gastrointestinal ulcer or severe diabetes mellitus and pregnancy or lactation. The study was approved by the institutional review board of each participating center, and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research (the Ministry of Health, Labour and Welfare, Japan). Written informed consent was obtained from all patients. This study is registered in the UMIN Clinical Trials Registry with the identifier C000000173.

Treatment

This study was an open-label, multicenter, single-arm Phase II study. The dose schedule of gemcitabine and S-1 was planned based on the results of the previous Phase I study (14): gemcitabine at a dose of 1000 mg/m^2 was administered as a 30-min intravenous infusion weekly for 2 weeks followed by 1 week of rest. Oral S-1 was administered at a dose of 40 mg/m^2 twice daily (80 mg/day for body surface area (BSA) $<$1.25 m^2, 100 mg/day for 1.25 $\leq$ BSA $<$ 1.50 m^2 and 120 mg/day for BSA $\geq$1.50 m^2) from days 1 to 14 followed by a 1 week rest period. The treatment was repeated every 3 weeks until disease progression, unacceptable toxicity or patient refusal.

Prophylactic administration of antiemetic agents such as dexamethasone and/or a 5-HT3 receptor antagonist was allowed at the investigator's discretion. If patients showed a leucocyte count of $<$2000/mm^3 or $>$12 000/mm^3, or a platelet count of $<$70 000/mm^3 during the cycle, administration of both gemcitabine and S-1 was suspended. If patients showed a leucocyte count of $<$3000/mm^3 or $>$12 000/mm^3, platelet count of $<$100 000/mm^3, total bilirubin $>$3.0 mg/dl, AST and ALT levels $>$150 U/l, or a creatinine level $>$1.5 mg/dl, initiation of the next cycle was postponed until recovery. When patients experienced (i) Grade 4 leucopenia or neutropenia, (ii) febrile

neutropenia or infection with Grade 3 leucopenia or neutropenia, (iii) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia requiring transfusion or (iv) ≥Grade 3 non-hematological toxicity excluding anorexia, nausea, vomiting, constipation, fatigue and hyperglycemia, the dose of gemcitabine was reduced to 800 mg/m^2 and the dose of S-1 was reduced by 20 mg/day in the subsequent cycle. The protocol treatment was discontinued if the patients required more than two dose reductions or if the subsequent cycle could not be initiated within 28 days after the final day of the anti-cancer drug administration in the previous cycle.

Evaluation

All the eligible patients who received at least one dose of GS therapy were included in the response and toxicity evaluations. Physical examination, complete blood cell counts and biochemistry tests were assessed at least on days 1 and 8 in each cycle during chemotherapy. Tumor marker carbohydrate antigen (CA) 19-9 was measured every 4–6 weeks. Objective tumor response was evaluated every 4–6 weeks by computed tomography or magnetic resonance imaging according to the Response Evaluation Criteria In Solid Tumors version 1.0. For the purpose of confirmation of objective response, an interval of at least 4 weeks was required for complete response (CR), partial response (PR) and stable disease (SD) in this study. The response duration was defined as the interval from the first documentation of response (PR or CR) to the first documentation of tumor progression. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Progression-free survival (PFS) was calculated from the date of the initiation of treatment until documented disease progression or death due to any cause (whichever occurred first); overall survival was calculated from the date of treatment initiation to the date of death or censored at the last follow-up. An external review committee confirmed objective responses and adverse events.

Statistical analysis

The primary endpoint was the response rate (CR and PR) of GS therapy. Forty-nine patients were required based on the assumption of an expected response rate of 25% and the threshold rate of 10%, with α-error of 2.5% (one-sided) and β-error of 20%. In consideration of ineligible patients or those who dropped out, it was planned that 55 patients would be included in this study. We calculated the response rate with 95% confidence interval (CI) in the patients who met eligibility criteria and received at least one GS therapy. The progression-free and overall survival periods were estimated by the Kaplan–Meier method.

RESULTS

Patients

Fifty-five patients were enrolled from 10 institutions between October 2004 and July 2005. Of these 55 patients, one patient was excluded from analysis because he left the study before administration of GS therapy due to an allergic skin reaction caused by insulin. All of the remaining 54 patients received at least one dose of GS therapy and were included in the evaluation of response and toxicity. Patient characteristics of the 54 patients are listed in Table 1. All patients had metastatic disease and no patient received any prior therapies except surgery for pancreatic cancer. Six patients underwent percutaneous transhepatic or endoscopic biliary drainage for obstructive jaundice prior to the study enrollment.

Treatments

The final data were fixed on 31 March 2007. A total of 425 therapy cycles were administered to the 54 patients,

Table 1. Patient characteristics ($n = 54$)

Characteristics		Number of patients (%)
Median age, years (range)	62 (32–74)	
Sex		
Women		24 (44)
Men		30 (56)
ECOG performance status		
0		38 (70)
1		16 (30)
Body surface area		
Median (range), m^2	1.59 (1.18–1.83)	
History of surgical resection		9 (17)
Metastatic disease		54 (100)
Sites of metastasis		
Liver		50 (93)
Distant lymph nodes		11 (20)
Peritoneum		3 (6)
Lung		2 (4)
Other		2 (4)
Histology		
Adenocarcinoma		53 (98)
Adenosquamous carcinoma		1 (2)
Differentiation		
Well		2 (4)
Moderate		28 (52)
Poor		13 (24)
Unknown		11 (20)

ECOG, Eastern Cooperative Oncology Group.

Table 2. Efficacy results

		Number of patients (%)
Tumor response ($n = 54$)		
Complete response		0 (0)
Partial response		24 (44.4)
Stable disease		26 (48.1)
Progressive disease		2 (3.7)
Cannot be evaluated		2 (3.7)
Response rate (95% CI), %	44.4 (30.9–58.6)	
Tumor control rate (95% CI), %	92.6	
CA 19-9 response ($n = 41$)		
Decreased (≥50%)		35 (85.4)
Decreased (<50%)		3 (7.3)
Increased		3 (7.3)
Progression-free survival ($n = 54$)		
Median (95% CI), months	5.9 (4.1–6.9)	
Overall survival ($n = 54$)		
Median (95% CI), months	10.1 (8.5–10.8)	
1-year survival rate, %	33	

CA 19-9, carbohydrate antigen 19-9.

with a median of 7 cycles each (range, 1–24). GS therapy could generally be administered on an outpatient basis. The gemcitabine on day 8 was administered in 367 (86.4%) of 425 cycles. Dose reduction was required in 30 patients (55.6%), mainly due to leucopenia, neutropenia, rash or gastrointestinal toxicities. At the time of analysis, protocol treatment was discontinued in 52 patients because of disease progression ($n = 30$) or adverse events ($n = 22$). The reasons for discontinuation due to adverse events were the second episode of Grade 4 neutropenia after one dose reduction (11), prolonged myelosuppression (3), anorexia or nausea (4), rash (2), cerebral infarction (1) and cholangitis (1). After discontinuation of GS therapy, 30 patients received gemcitabine-based chemotherapy, 6 patients received other anticancer drugs including irinotecan and the remaining 18 patients received only supportive care.

Efficacy

The efficacy results are shown in Table 2. Of the 54 patients, 2 patients could not be assessed for response since they withdrew their consent due to toxicity before the first response evaluation. Although no CR was observed, a PR was achieved in 24 of 54 patients, resulting in an overall response rate of 44.4% (95% CI: 30.9–58.6%). The median response duration was 5.3 months (range, 2.4–15.6 months). SD was noted in 26 patients (48.1%) and progressive disease (PD) in 2 patients (3.7%). The serum CA 19-9 level was reduced to less than half from baseline values in 35 (85.4%) of the 41 patients whose pretreatment levels were >100 U/ml. The median PFS was 5.9 months (95% CI: 4.1–6.9 months) with a median overall survival of 10.1 months (95% CI: 8.5–10.8 months) and a 1-year survival rate of 33.0% (Fig. 1).

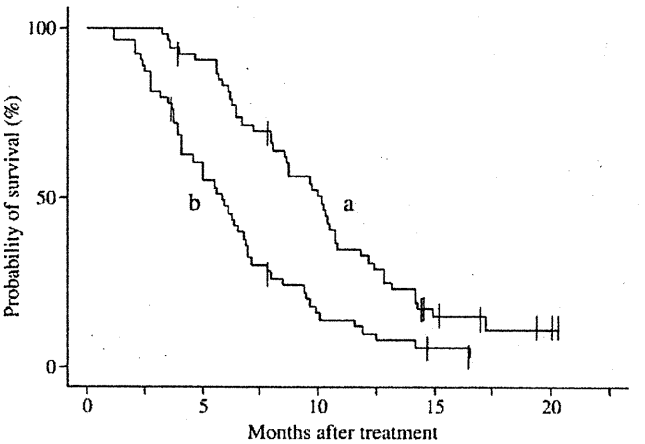

Figure 1. Overall survival curve (a) and progression-free survival (b) for 54 patients.

Toxicity

The major toxicities observed in the 54 patients are listed in Table 3. The most common toxicity was myelosuppression. Grade 3–4 neutropenia and thrombocytopenia occurred in 80 and 22% of the patients, respectively. The neutrophil and platelet count nadirs typically were observed on day 15. Although most of these hematologic toxicities were transient and recovered without serious events, one patient developed Grade 3 febrile neutropenia. No other unexpected severe toxicities were observed during the study and there were no treatment-related deaths. Although gastrointestinal toxicities and skin rash were frequently observed, most of these were manageable with appropriate medical treatment. There were no cumulative toxicities.

DISCUSSION

The major toxicity of GS therapy is myelosuppression, especially neutropenia. Although the incidences of Grade 3–4 neutropenia and thrombocytopenia observed in the current study were high (Table 3), most of these episodes were transient. There was only one episode of neutropenic fever without treatment-related death. Therefore, most patients could be treated on an outpatient basis without receiving granulocyte colony-stimulating factor or a blood transfusion. Although anorexia, nausea, fatigue, rash, pigmentation and aminotransferase elevation were also observed frequently in our study, most of these non-hematological toxicities were manageable with appropriate treatments. Therefore, it is considered that GS therapy in this study is tolerable for patients with metastatic pancreatic cancer.

Table 3. Adverse events ($n = 54$)

	Grade				Grades 1–4	Grades 3–4
	1	2	3	4	%	%
Hematological toxicity						
Leucocytes	3	19	31	1	100	59
Neutrophils	2	9	24	19	100	80
Hemoglobin	11	29	8	0	89	15
Platelets	15	23	12	0	83	22
Non-hematological toxicity						
Bilirubin	15	9	3	0	50	6
AST	23	6	2	0	57	4
ALT	20	11	4	0	65	7
Creatinine	7	0	0	0	13	0
Nausea	19	11	3	—	61	6
Vomiting	11	5	1	0	32	2
Anorexia	18	11	9	0	70	17
Stomatitis	20	10	1	0	57	2
Diarrhea	12	5	0	0	32	0
Constipation	2	0	1	0	6	2
Ileus	—	0	1	0	2	2
Colitis	—	0	1	0	2	2
Fatigue	22	14	3	0	72	6
Fever	15	5	0	0	37	0
Alopecia	13	2	—	—	28	0
Rash	13	17	4	0	63	7
Pigmentation changes	27	7	—	—	63	0
Hand-foot skin reaction	3	0	0	0	6	0
Infection without neutropenia	2	2	2	0	11	4
Febrile neutropenia	—	—	1	0	2	2
CNS cerebrovascular ischemia	—	—	1	1	4	4

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

To date, several Phase II studies testing the gemcitabine plus S-1 combination as first-line therapy for advanced pancreatic cancer have been published (Table 4) (15–18). One study was conducted in Japan and the remaining studies were in Korea. Although various schedules of gemcitabine and S-1 administration were used, the regimens adopted in all studies including this study were similar: gemcitabine at a dose of 1000–1250 mg administered on days 1 and 8 or 8 and 15 and S-1 at a dose of 60–80 mg/m^2/day on days 1–14 of a 21-day cycle. The incidences and severity of toxicities reported in these trials, especially hematological toxicities, have varied widely among the studies. Interestingly, hematological toxicities were more frequently observed in the two Japanese studies, including this study, than the Korean studies. It is well known that the toxicity profile of S-1 differs between Asians and Caucasians (19); Goh and coworkers (20) carried out a study to compare S-1 pharmacokinetics and CYP2A6 activity among Asian and Caucasian patients, and reported that Asian patients had lower 5-FU exposure and lower CYP2A6 activity compared with Caucasian patients. However, the reasons for the discrepancies between the Japanese and Korean studies remain unclear.

In this trial, GS therapy produced a promising efficacy with a response rate of 44.4%. The efficacy of GS therapy reported in the recent studies as well as this study has been consistent (Table 4), with response rates of 27.3–38%, median time to tumor progression of 4.6–5.43 months and median overall survival of 7.89–12.5 months. Recently, the results of a randomized Phase II study comparing GS therapy with gemcitabine alone were reported (21). In that study, 106 patients were randomly assigned at a 1:1 ratio to either the GS group or the gemcitabine-alone group. Patients assigned to GS therapy received gemcitabine at a dose of 1000 mg/m^2 on days 1 and 15 and S-1 at a dose of 40 mg/m^2 twice daily on days 1–14, every 4 weeks. The objective response rate was 18.9% in the GS group and 9.4% in the gemcitabine group. Patients in the GS group demonstrated significantly longer PFS than those in the gemcitabine group [median PFS, 5.4 versus 3.6 months; hazard ratio = 0.64 (95% CI: 0.42–0.97); $P = 0.036$], while overall survival did not differ significantly between the two groups [median

Table 4. Phase II studies of GS therapy for advanced pancreatic cancer

Author	Gemcitabine (mg/m^2)	S-1 (mg/m^2/day)	Cycle (day)	No. of patients	Metastatic disease (%)	RR (%)	Median TTP/PFS (months)	Median OS (months)	Grade 3/4 neutropenia (%)	Grade 3/4 thrombocytopenia (%)
Nakamura *et al.* (15)	1000 (days 8, 15)	60 (days 1–14)	21	33	100	48	5.4	12.5	55	15
Lee *et al.* (16)	1250 (days 1, 8)	80 (days 1–14)	21	32	90.6	44	4.92	7.89	28.1	15.6
Kim *et al.* (17)	1000 (days 8, 15)	60 (days 1–14)	21	22	86.3	27.3	4.6	8.5	18.2	4.5
Oh *et al.* (18)	1000 (days 1, 8)	80 (days 1–14)	21	38	84	29	5.43	8.4	39.5	2.6
Current study	1000 (days 1, 8)	80 (days 1–14)	21	55	100	44.4	5.9	10.1	80	22

RR, response rate; TTP, time to progression; PFS, progression-free survival; OS, overall survival.

overall survival, 14.1 versus 8.7 months; hazard ratio = 0.69 (95% CI: 0.43–1.08); $P = 0.105$].

Since it is speculated that combination chemotherapy with S-1 and gemcitabine might be superior to monotherapy with gemcitabine from the results of the recent trials, a Phase III trial was planned to confirm the efficacy of GS therapy (ClinicalTrials.gov, NCT00498225). The Phase III study known as 'GEST' is a randomized controlled study involving three arms: gemcitabine monotherapy as a control arm, S-1 monotherapy and GS therapy. The trial was designed to evaluate overall survival as the primary endpoint, non-inferiority of S-1 to gemcitabine and superiority of GS therapy over gemcitabine. The enrollment of 750 patients was planned and has already been completed and the final analysis of the results will be reported in the near future.

In conclusion, the current Phase II study demonstrated encouraging antitumor activity following GS therapy with good overall survival in patients with metastatic pancreatic cancer. The clinical benefits of GS therapy are now investigated in the GEST trial.

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Conflict of interest statement

None declared.

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Appendix

In addition to the authors listed in the author field, following are the authors who contributed equally to this study.

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Construction and Validation of a Prognostic Index for Patients With Metastatic Pancreatic Adenocarcinoma

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Objectives: To identify prognostic factors in patients with metastatic pancreatic adenocarcinoma.

Methods: The relationship between patient characteristics and outcome was examined by multivariate regression analyses of data from 409 consecutive patients with metastatic pancreatic adenocarcinoma who had been treated with a gemcitabine-containing regimen, and we stratified the patients into 3 risk groups according to the number of prognostic factors they had for a poor outcome. A validation data set obtained from 145 patients who had been treated with agents other than gemcitabine was analyzed. The prognostic index was applied the each of the patients.

Results: The multivariate regression analyses revealed that the presence of pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value significantly contributed to a shorter survival time. The patients were stratified into 3 groups according to their number of risk factors, and their outcomes of the 3 groups were significantly different. When the prognostic index was applied to the validation data set, the respective outcomes of the 3 groups were found to be significantly differed from each other.

Conclusions: Pain, peritoneal dissemination, liver metastasis, and an elevated serum C-reactive protein value are important prognostic factors for patients with metastatic pancreatic adenocarcinoma.

Key Words: pancreatic cancer, prognostic factor, validation, chemotherapy, multivariate analyses, prognostic index

(*Pancreas* 2011;40: 415–421)

Despite the major advances in cancer management that have been achieved in recent years, pancreatic adenocarcinoma (PC) remains a challenge to clinicians because of the difficulty of early diagnosis. Most PC patients have locally advanced or metastatic disease by the time the diagnosis is made. Even when resection is performed, the recurrence rate is extremely high, and nonsurgical treatments after recurrence have largely been ineffective.[1,2] Although gemcitabine (GEM) has been demonstrated to provide a modest clinical benefit and therefore become the standard chemotherapy for advanced PC,[3,4] the median survival time of patients with advanced disease remains only around 6 months. Many clinical trials of treatments with combinations GEM and other agents have been conducted to improve treatment efficacy in patients with advanced PC, and one of them, a combination of GEM and erlotinib, has resulted in longer survival than treatment with single-agent GEM.[5] However, because the difference in median overall survival between the 2 regimens was only 0.3 months and the incidence of adverse events with GEM plus erlotinib tended to be higher, this combination has been considered a treatment option for patients in good general condition, not an alternative to GEM monotherapy. Because various treatment options according to the patient's general condition and prognosis are expected to be developed in the future, if the survival time of patients with metastatic PC could be predicted before the start of the treatment, those with an extremely poor prognosis could be offered supportive care alone or more conservative treatment, such as GEM monotherapy and spared the adverse effects of combination chemotherapy. A validated prognostic index would identify subgroups of patients for specific treatments and predict survival, and identification of prognostic factors would be helpful in designing clinical trials of systemic chemotherapy and analyzing their results. Furthermore, clinical trials of various new treatments will be conducted in the future, and because some of the candidate drug combinations for new treatment regimens may contain GEM and others may not, establishment of an accurate prognostic index that can be applied to various treatment regimens is needed. Although many possible prognostic factors, such as performance status,[6–8] the serum carbohydrate antigen (CA 19-9) level,[9–14] and the serum C-reactive protein (CRP) level[11,13,15,16] have been identified in advanced PC, most were identified in small numbers of patients, and the results were not validated, possibly making the analyses underpowered and unreliable.

The purposes of this study were (1) to identify the most helpful, readily available prognostic factors for predicting the survival time of metastatic PC patients and (2) to construct and validate a practical and universal prognostic index for metastatic PC patients.

MATERIALS AND METHODS

Cases Used as the Basis for Construction of the Prognostic Index (Construction Set)

Data from 409 consecutive patients with metastatic PC who had received GEM-containing systemic chemotherapy at the National Cancer Center Hospital, Tokyo, Japan, between March 2001 and January 2007 were reviewed to construct the prognostic index. None of the patients had been treated for their cancer before chemotherapy, except that some of them had undergone by pancreatectomy. All patients had distant metastasis based on diagnostic imaging findings obtained by various modalities, including chest radiography, ultrasonography, and computed tomography. The diagnosis of adenocarcinoma was confirmed pathologically in every case by examination of the surgical specimen or a fine-needle aspiration biopsy specimen. Whenever possible, peritoneal or pleural fluid cytodiagnosis was performed in patients with an intraperitoneal or intrapleural fluid collection. Percutaneous transhepatic or endoscopic retrograde biliary drainage was performed in all patients who had

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TABLE 1. Patient Characteristics

			Construction Set		Validation Set	*P*
Age		Median (range)	64 (21–81)		59.5 (39–75)	0.0005*
Sex	Male	n (%)	241 (59)		98 (68)	0.10†
	Female	n (%)	168 (41)		47 (32)	
Performance status	0–1	n (%)	395 (97)		138 (95)	0.40†
	2–3	n (%)	14 (3)		7 (5)	
Prior pancreatectomy	(+)	n (%)	66 (16)		16 (11)	0.24†
Abdominal and/or back pain‡	(+)	n (%)	138 (34)		62 (43)	0.074†
Diabetes mellitus	(+)	n (%)	171 (42)		46 (31)	0.037†
Location of primary tumor	Uncus and head	n (%)	191 (47)		48 (33)	0.01†
	Body or tail	n (%)	217 (53)		94 (65)	
Liver metastasis	(+)	n (%)	297 (73)		111 (77)	0.39†
Lymph node metastasis	(+)	n (%)	124 (30)		49 (34)	0.44†
Lung metastasis	(+)	n (%)	68 (17)		22 (15)	0.76†
Peritoneal dissemination	(+)	n (%)	88 (22)		37 (26)	0.40†
Pleural metastasis	(+)	n (%)	28 (7)		4 (3)	0.10†
Bone metastasis	(+)	n (%)	8 (2)		2 (1)	0.92†
Leukocytes count, /mL	(3900–6300)§	Median (range)	6100 (2100–35,500)		6800 (3400–18,000)	0.015*
Hemoglobin level, g/dL	(11.3–14.9)§	Median (range)	12.3 (6.7–16.1)		12.2 (8.6–15.9)	0.50*
Platelets count, /mL	(12.5–37.5)§	Median (range)	22.3 (9.2–57.4)		22.5 (9.5–47.1)	0.55*
Albumin level, g/dL	(3.7–5.2)§	Median (range)	3.7 (2.2–4.9)		3.7 (2.2–4.7)	0.50*
Total bilirubin level, mg/dL	(0.3–1.2)§	Median (range)	0.7 (0.2–3.1)		0.7 (0.3–3.2)	0.92*
AST level, IU/L	(13–33)§	Median (range)	27 (10–196)		26 (10–204)	0.46*
ALT level, IU/L	(6–27)§	Median (range)	29 (5–465)		28 (7–366)	0.90*
LDH level, IU/L	(119–229)§	Median (range)	188 (19–2311)		162 (15–2192)	0.001*
CRP level, mg/dL	(−0.1)§	Median (range)	0.6 (0.0–20.6)		0.8 (0–17.8)	0.15*
CEA level, ng/mL	(−5.0)§	Median (range)	6 (0.6–2090)		6.9 (0.4–9990)	0.55*
CA19-9 level, U/mL	(−37)§	Median (range)	1857 (1–1620,000)		3022 (1–1,857,600)	0.088*
Treatment		n (%)	GEM alone 302 (74)	Irinotecan	16 (11)	
		n (%)	GEM + S-1 41 (10)	Docetaxel	6 (4)	
		n (%)	GEM + 5-FU 27 (7)	S-1	29 (20)	
		n (%)	GEM + CDDP 39 (10)	UFT	22 (15)	
		n (%)		5-FU + CDDP	31 (21)	
		n (%)		MTX + 5-FU	41 (28)	

*Mann-Whitney *U* test.

†χ^2 test.

‡Abdominal and/or back pain: treated with opioid.

§Reference range.

CDDP indicates cisplatin; FU, fluorouracil; MTX, methotrexate.

obstructive jaundice before chemotherapy. All patients provided written informed consent before the start of treatment.

Factors Analyzed

The following 24 variables were selected for analysis in this study based on the results of previous investigations[12,13,15,17–23] and/or our own clinical experience: (1) age, sex, prior pancreatectomy, Eastern Cooperative Oncology Group performance status, abdominal and/or back pain treated with an opioid, diabetes mellitus, leukocyte count, hemoglobin level, platelet count, and serum level of albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total bilirubin, CRP, as host-related variables, and (2) location of the primary tumor, liver metastasis, lymph node metastasis, lung metastasis, peritoneal dissemination, pleural metastasis, bone metastasis, serum level of carbohydrate antigen 19-9 (CA19-9), and CEA, as tumor-related variables. All data were obtained immediately before the start of systemic chemotherapy. Nodules more than 1 cm in diameter and/or a conspicuous volume of effusion in the abdominal or thoracic cavity observed by ultrasonography or computed tomography and cytologically proven malignant effusions were considered evidence of peritoneal dissemination or pleural metastasis in this study.

Cases Used as a Basis for Validation of the Prognostic Index (Validation Set)

A data set from 145 patients who participated in clinical trials of anticancer agents other than GEM at the National Cancer Center Hospital between August 1991 and January 2004 was used to validate the prognostic index. The treatment regimens were docetaxel,[24] irinotecan,[25] S-1,[26] UFT,[27] 5-fluorouracil + cisplatin,[28] and methotrexate + 5-fluorouracil.[29]

TABLE 2. Univariate Analysis

Categorical Variables			Continuous Variables		
	Median Survival Time, d	*P*		Coefficient (β)	*P*
Sex					
Male	209		Age, yr	−0.005	0.3542
Female	188	0.3543	Leukocytes count, /mL	7.59	<0.0001
Performance status					
0–1	207		Hemoglobin level, g/dL	−1.59	<0.0001
2–3	102	0.138	Platelets count, /mL	0.021	0.001
Prior pancreatectomy					
+	298		Albumin, g/dL	−0.867	<0.0001
−	191	<0.0001	Total bilirubin level, mg/dL	−0.088	0.3902
Abdominal and/or back pain*					
+	144		AST level, IU/l	0.008	<0.0001
−	238	<0.0001	ALT level, IU/L	0.003	0.0095
Diabetes mellitus					
+	201		LDH level, U/L	0.003	<0.0001
−	198	0.9802	CRP level, mg/dL	0.129	<0.0001
Location of primary tumor					
Uncus or head	200		CEA level, ng/mL	0.001	<0.0001
Body or tail	204	0.9885	CA19-9 level, U/mL	1.296	0.0004
Liver metastasis					
+	186				
−	243	<0.0001			
Lymph node metastasis					
+	167				
−	219	0.0584			
Lung metastasis					
+	224				
−	196	0.5835			
Peritoneal dissemination					
+	156				
−	219	0.0063			
Pleural metastasis					
+	198				
−	200	0.5435			
Bone metastasis					
+	113				
−	204	0.0336			

*Abdominal and/or back pain: treated with an opioid.

Statistical Analysis

Survival rates were calculated by the method of Kaplan and Meier.[30] All deaths regardless of cause were considered events. The stratified log-rank test was used to compare survival curves, and censored data were taken into account.[31]

Univariate Analysis

A univariate analysis was conducted to select candidate factors to adopt in the multivariable analysis. For categorical data, factors were divided into 2 categories, and the log-rank test was applied. Because dichotomizing continuous variable data, such as the serum biochemical and hematological data, by using arbitrary cutoff points might have resulted in major biases, we used the Cox proportional hazards model, which enables selection of candidate factors without dichotomization.[32,33] Differences with a $P < 0.01$ were considered significant.

Multivariate Analysis

The variables identified as having prognostic significance in the univariate analyses were included in the subsequent multivariate analysis. To construct a simple and practical prognostic index for routine clinical use, all factors were divided into 2 categories. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cutoff value to maximize both the sensitivity and the specificity of continuous variables. Each ROC curve was constructed as a predictor of death at 6.6 months, which was the median survival time of the cases in the construction set. The Cox proportional hazards model was used to identify the variables that made the most significant contribution to survival. Differences with a $P < 0.01$ were considered significant. All P values were 2 sided. All analyses were performed by using Dr SPSS statistical software (SPSS Inc, Chicago, Ill).

The numbers of risk factors present were used to construct the prognostic index. Patients were stratified into 3 risk groups on the basis of the number of risk factors present.

RESULTS

Patient Characteristics

There were 241 men and 168 women in the construction set. Their median age was 64 years (range, 21–81 years), and the performance status of 395 patients was 0 to 1. Liver metastasis had been diagnosed in 297 patients, and peritoneal dissemination had been diagnosed in 88 patients (Table 1). The treatment regimens were GEM alone in 302 patients, GEM + cisplatin, 39, GEM + 5-flurorouracil, 27, and GEM + S-1, 41.

Survival

As of the date of the survival analysis, 404 patients had died, and the median survival time and 1-year survival rate were 6.6 months and 22%, respectively.

Univariate Analysis

The following 14 of the 24 pretreatment variables evaluated were identified as significantly associated with shorter survival time (Table 2): absence of prior pancreatectomy ($P < 0.0001$), presence of abdominal and/or back pain treated with an opioid ($P < 0.0001$), presence of liver metastasis ($P < 0.0001$), presence of peritoneal dissemination ($P = 0.0063$), elevated leukocyte count ($P < 0.0001$), elevated platelet count ($P = 0.001$), elevated serum AST level ($P < 0.0001$), elevated serum ALT level ($P < 0.0095$), elevated serum LDH level ($P < 0.0001$), elevated serum CRP level ($P < 0.0001$), elevated serum CA19-9 level ($P = 0.0004$), elevated serum CEA level ($P < 0.0001$), low hemoglobin level ($P < 0.0001$), and low serum albumin level ($P < 0.0001$).

Multivariate Analysis

The 14 variables found to be of prognostic significance in the univariate analysis were included in the subsequent multivariate Cox regression model. Receiver operating characteristic curve analysis was used to determine the cutoff point for continuous variables. Finally, to simplify the prognostic index, some cutoff values were approximated, thus: leukocyte count, from 7200/mL to 7000/mL; hemoglobin level, from 11.9 to 12 g/dL; platelet count, from $27.8 \times 10^4/\mu L$ to $28 \times 10^4/\mu L$; serum CRP level, from 0.9 to 1.0 mg/dL; serum CA19-9 level, from 3414 to 3000 U/mL; and serum CEA level, from 6.7 to 7 ng/mL. Originally simple values, such as serum albumin level (3.7 g/dL), serum AST level (22 IU/L), serum ALT level (28 IU/L), and serum LDH level (190U/L) were not approximated. Only 4 of the previously mentioned factors, presence of abdominal and/or back pain treated with an opioid ($P < 0.0001$), presence of liver

TABLE 3. Multivariate Analysis

		Coefficient (β)	Hazards Ratio	99%CI	P
Prior pancreatectomy	−	0.297	1.346	0.906–2.000	0.530
Abdominal and/or back pain*	+	0.526	1.692	1.262–2.271	<0.0001
Liver metastasis	+	0.353	1.423	1.015–1.995	0.0071
Peritoneal dissemination	+	0.563	1.756	1.238–2.492	<0.0001
Leukocyte count	>7000 (/μL)	0.058	1.060	0.775–1.449	0.6313
Hemoglobin level	<12 (g/dL)	0.244	1.277	0.949–1.717	0.0337
Platelet count	>28 ($\times 10^4/\mu L$)	0.269	1.309	0.954–1.796	0.0285
Albumin level	<3.7 (g/dL)	0.124	1.132	0.841–1.523	0.2826
AST level	>22 (IU/L)	0.078	1.081	0.731–1.599	0.6089
ALT level	>28 (IU/L)	0.212	1.236	0.858–1.781	0.1352
LDH level	>190 (U/L)	0.259	1.295	0.951–1.764	0.0309
CRP level	>1 (mg/dL)	0.432	1.540	1.117–2.124	0.0005
CEA level	>7 (U/mL)	0.205	1.227	0.924–1.631	0.0634
CA19-9 level	>3000 (ng/mL)	0.101	1.106	0.825–1.482	0.3762

CI indicates confidence interval.

*Abdominal and/or back pain: treated with an opioid.

TABLE 4. Prognostic Index of Patients With Metastatic PC Receiving Systemic Chemotherapy

Risk Factors	
• Abdominal and/or back pain treated with an opioid	Present
• Liver metastasis	Present
• Peritoneal dissemination	Present
• Serum CRP level	>1 (mg/dL)
Risk groups	
No. risk factors	
0	Low risk
1–2	Intermediate risk
3–4	High risk

metastasis ($P = 0.008$), presence of peritoneal dissemination ($P < 0.0001$), and elevation of the serum CRP level to greater than 1.0 mg/dL ($P < 0.0007$), were identified as independent prognostic factors (Table 3).

Risk Groups Based on the Regression Model

To be able to apply the indicated prognostic factors to clinical routine use, patients were stratified into 3 risk groups according to their number of the negative prognostic factors (Table 4): a low-risk group of 47 patients with 0 risk factors, an intermediate-risk group of 276 patients with 1 to 2 risk factors, and a high-risk group of 86 patients with 3 to 4 risk factors. The survival curves of these groups are shown in Figure 1. There were significant differences between survival time in the 3 groups (median survival time: low-risk group, 11.0 months; intermediate-risk group, 7.3 months; and high-risk group, 3.2 months; $P = 0.0001$ for the difference between the low- and intermediate-risk groups and $P < 0.0001$ for the difference between the intermediate- and high-risk groups).

Validation of the Prognostic Index

The prognostic index was applied to each of the 145 cases used for validation. The patient's characteristics were similar to those of the cases in the construction set (Table 1), but the proportion of patients with diabetes mellitus and the proportion of patients whose primary tumor was in the uncus or the head were lower in the validation set. In addition, median age was younger, the median leukocyte count was higher, and the LDH value was lower in the validation set than those in the construction set. Of the 145 patients in the validation set, 141 had died. The median survival time of the 145 patients was 4.8 months, and their 1-year survival rate was 12%. We calculated the prognostic index of the 145 patients and then stratified them into 3 risk groups as described previously and compared the distribution of survival times among the 3 risk groups. Figure 2 shows a comparison of the survival curves of the 3 risk groups. There were significant differences in survival time among the 3 groups (median survival time: low-risk group, 8.6 months; intermediate-risk group, 5.2 months; and high-risk group, 2.3 months; $P = 0.03$ for the difference between the low- and intermediate-risk groups and $P < 0.0001$ for the difference between the intermediate- and high-risk groups).

DISCUSSION

In this study, we attempted to identify prognostic factors in patients with metastatic PC who had received systemic chemotherapy, and 14 of the 24 potential prognostic factors assessed were identified as significant predictors of survival by the univariate analysis. However, only 4 factors, abdominal and/or back pain treated with an opioid, peritoneal dissemination, liver metastasis, and elevated serum CRP level, were found to have independent prognostic value by the multivariate analysis.

Abdominal and/or back pain is one of the most common symptoms of PC patients. Previous studies have shown correlations between pancreatic tumor size, invasion of the anterior pancreatic capsule, and lymph node metastasis and the pain intensity of patients with operable tumors.[23,34] Several studies have also shown a significant impact of preoperative pain has on the outcome after resection.[34–36] However, the pain of patients with unresectable, more advanced PC may be attributable to invasion of the retroperitoneum or extrapancreatic nerve plexus

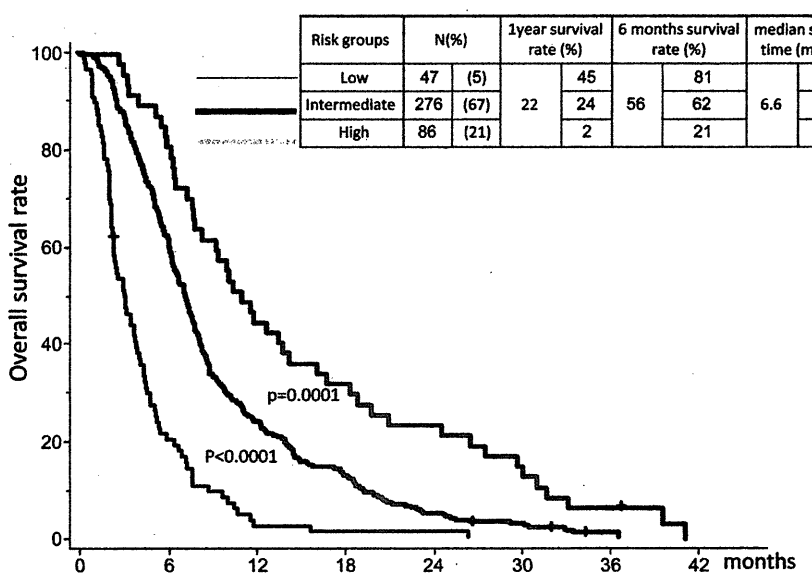
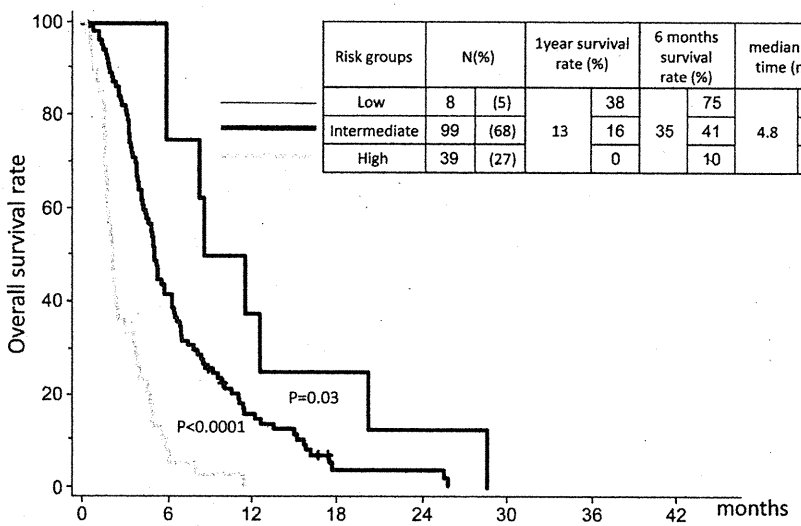


FIGURE 1. Comparison of the survival curves of patients who have received GEM-containing systemic chemotherapy and stratified into 3 risk groups according to the prognostic index. There was a significant difference in survival between the low- and intermediate-risk groups ($P = 0.0001$) and between the intermediate- and high-risk groups ($P < 0.0001$). P values were calculated by the log-rank test.



Risk groups	N(%)		1year survival rate (%)		6 months survival rate (%)		median survival time (months)	
Low	8	(5)	13	38	35	75	4.8	8.6
Intermediate	99	(68)		16		41		5.2
High	39	(27)		0		10		2.3

FIGURE 2. Comparison of the survival curves of patients used for validation stratified into 3 risk groups according to the prognostic index. There was a significant difference in survival between the low- and intermediate-risk groups ($P = 0.03$) and between the intermediate- and high-risk groups ($P < 0.0001$). P values were calculated by the log-rank test.

because such advanced tumors sometimes destroy nerves more extensively than resectable tumors.

Peritoneal dissemination[37,38] and liver metastasis[39–41] have long been considered to tend to result in a fatal clinical course. Patients with peritoneal dissemination exhibit the clinical manifestations of bowel obstruction, ascites, and abdominal pain. Such complications often cause malnutrition and general deterioration. Patients with liver metastasis often have jaundice or lapse into a hepatic coma. Moreover, the dose and the schedule of chemotherapy sometimes have to be modified for patients with peritoneal dissemination or liver dysfunction because the adverse effects of chemotherapy are more severe in such patients. A previous study found that peritoneal dissemination predicts limited the effectiveness of chemotherapy in advanced PC.[42]

An elevated CRP level[13,16] has been demonstrated to be of prognostic significance in patients with PC and a variety of other gastrointestinal neoplasms.[43–45] Proinflammatory cytokines, including interleukin 6, are key signals in promoting hepatic CRP production, and there is evidence that they play a role in the genesis of cancer-associated cachexia,[46–48] which shortens the survival time of patients with metastatic PC.

Although previous studies have shown that performance status is one of the most important prognostic factors in patients with advanced PC,[13,49,50] it was not identified as a significant predictor of survival in this study. One of the main reasons for not having identified it as a significant predictor may be that proportion of patients with a performance status of 2 to 3 was extremely small in this study, only 3%.

Many models for clinical outcome prediction have been described in the medical literature, but most never find their way into clinical practice. One reason for their failure to be adopted in clinical practice may be that they have not been validated by external data and therefore lack universality and credibility. To our knowledge, this is the first report of not only construction but also validation of a practical prognostic index for patients with metastatic PC.

Some of the factors assessed in this study were continuous variables, and continuous variables are often converted into categorical variables by grouping the values into 2 or more categories. However, there is also the risk of major bias when the choice of the cutoff value is data driven, and the use of different cutoff points across multiple studies hinders direct comparisons. Dichotomizing continuous variables, on the other hand, is a reasonable method of constructing simple and practical tools for routine clinical use. To achieve a balance between convenience and credibility, we applied the Cox regression model to continuous variables in the univariate analysis to select candidates for the multivariable analysis. We then identified objective cutoff values by ROC curve analysis for the candidates, divided continuous variables into 2 categories, and applied the multivariate analysis.

Because we used a data set of patients treated with a GEM-containing regimen to construct the prognostic index and a data set of patients treated with anticancer agents other than GEM to validate it, this prognostic index may be helpful in designing clinical trials of systemic chemotherapy even if the investigational regimen does not contain GEM.

In conclusion, the presence of abdominal and/or back pain treated with an opioid, peritoneal dissemination, liver metastasis, and serum CRP elevation to 1.0 mg/dL or greater were identified as significant prognostic factors in patients with metastatic PC who had received systemic chemotherapy. Accurate prediction of survival may be achieved by applying a prognostic index incorporating these 4 factors. This index facilitates stratification of patients with metastatic PC into 3 risk groups. Our index is expected to be useful for selecting treatment strategies; patients with an extremely poor prognosis could be offered supportive care alone or more conservative treatment. Furthermore, it is also expected to be useful for designing future clinical trials for patients with metastatic PC.

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ORIGINAL ARTICLE

Convergence Process of Volumetric Liver Regeneration After Living-Donor Hepatectomy

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Abstract
Background We investigated the long-term profiles of liver regeneration after living-donor hepatectomy.
Methods Thirty-three donors participated in the study. Preoperative and postoperative liver volume was calculated using computed tomography. Volume assessment was repeated at 1 week, 2 weeks, 1 month, 3 months, 6 months, 12 months, and 4 years postoperatively.
Results Donors were divided into the right (n=23; residual liver volume, 42%) and left (n=10; residual liver volume, 63%) groups according to the operative procedures. The restoration ratio to the preoperative liver volume (right vs. left groups) were 51%, 57%, 64%, 74%, 77%, 81%, and 88% vs. 69%, 72%, 76%, 79%, 83%, 84%, and 91% at 1 week, 2 weeks, 1 month, 3 months, 6 months, 12 months, and 4 years, respectively; the interindividual variation in the restoration ratio to the preoperative liver volume became narrower with time.
Conclusion Liver resection in humans resulted in rapid regeneration during the first 3 months, followed by a more moderate rate of regeneration thereafter, in proportion to the amount of liver mass resected. The volume of the regenerating liver appeared to converge towards the individual preoperative volume with time. However, the liver volume was not restored to the preoperative volume at 4 years after the resection.

Keywords CT volumetry · Donor hepatectomy · Liver regeneration · Total liver volume

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Abbreviations

ALB	Albumin
LDLT	Living-donor liver transplantation
TLV	Total liver volume
CT	Computed tomography
ICG	Indocyanine green
BMI	Body mass index
TB	Total bilirubin
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
PT-INR	Prothrombin time international normalized ratio
ICG R15	ICG retention rate at 15 min

Introduction

Although the knowledge that the liver can regenerate after being deprived of its mass dates back to the ancient Greek myth of Prometheus, a scientific description of

this process cannot be traced back prior to that by Higgins and Anderson in 1931. They reported that the weight of the residual liver after two thirds partial hepatectomy in rats increased to approximately 45% and 70% of the original liver weight by 24 and 72 h after the operation (early phase).[1] The rate of liver regeneration became slower during the subsequent late phase, but eventually, the original preoperative weight was reached by approximately 2 weeks after the operation.[1,2] Subsequently, the process of liver regeneration has been studied extensively. Although most studies were conducted using the rodent model of partial hepatectomy, the phenomenon of liver regeneration following the loss of liver mass is seen in all vertebrate organisms, from fish to humans, and that it is also triggered when the livers from small individuals, e.g., dogs, are transplanted into larger recipients of the same species.[3,4]

This regenerative phenomenon of the liver serves as the biological basis of living-donor liver transplantation (LDLT) in adults[5] as a safe and valid treatment option for end-stage liver diseases in the era of donor shortage;[6] it has been demonstrated that both a partial liver graft implanted into a large recipient and a paired residual donor liver show regenerative activity. In addition, the practice of LDLT provides a unique research opportunity, since the livers of living donors are supposed to follow a pattern of regeneration almost identical to the natural regenerative process of a normal liver, in contrast to the regenerative process in recipients influenced by multiple factors or that after hepatectomy in patients with a diseased liver.[7–9]

To date, several reports have investigated the liver regeneration process after donor hepatectomy.[10–18] The findings of these previous reports have been conflicting; while some reported almost complete liver regeneration within 2 weeks,[11] others documented that the donor livers did not return to their preoperative volume even by 6–12 months after the hepatectomy.[12–16,18] In addition, because most previous studies were conducted in donors undergoing right hemiliver resection, the regeneration responses to different extents of liver mass deprivation have not yet been precisely assessed. Moreover, the liver volumetric follow-up was carried out for no longer than 6–12 months in most previous studies. Thus, the long-term chronological profiles of volumetric regeneration of the donor liver remain largely unclear.

The question remains to be addressed whether each LDLT donor is able to finally achieve the full restoration of his/her original liver volume after the graft donation. Therefore, in the present study, we conducted an assessment of the pattern of liver regeneration in donors for LDLT serially until 4 years after the operation. The aim of the present study was to clarify, in detail, the chronological profiles of normal liver regeneration after different extents of major hepatic resection, paying particular attention to the long-term outcomes, and to investigate the clinical factors influencing the regenerative process.

Patients and Methods

Donors

Our criteria for potential living donors were as follows: healthy individuals between 20 and 65 year of age; ABO blood type, identical or compatible; no significant medical history; no underlying liver disease, including a history of viral hepatitis; candidates within three degrees of consanguinity or a spouse.[19,20] Deviation from these criteria, if any, was discussed on a case-by-case basis by both the transplant team and the institutional ethics board. Total liver volume (TLV), as well as the segmental liver volume, which corresponds to the scheduled graft volume of the donor, was estimated by contrast-enhanced computed tomography (CT).[21] The type of the graft is determined by balancing the safety of the donor and the adequacy of the graft volume, as previously described.[22] The indocyanine green (ICG) retention test is then performed to rule out the presence of liver disease and/or injury unidentified by the conventional liver function test. Liver biopsy is performed when a fatty liver is suspected, especially in donor candidates whose body mass index (BMI) exceeds 25.0. If the ratio of steatosis exceeds 10%, the candidate is requested to reduce his/her weight to improve the steatotic condition.

According to these criteria, we conducted 63 LDLTs between May 2001 and September 2002. Among these selected donors, 30 refused participation, and consequently, 33 were enrolled in the present study after providing written informed consent. The background characteristics of these 33 donors are shown in Table 1. The study protocol was approved by the local ethics committee of the Graduate School of Medicine, University of Tokyo and was conducted in accordance with the Declaration of Helsinki. The same donors had also participated in our previous study conducted to investigate the relationship between volumetric and functional liver regeneration over the short-term after donor hepatectomy; therefore, the liver volumetric data at 7 and 14 postoperative days overlap with those in the previous report.[23]

Donor Hepatectomy

The surgical techniques for various types of donor operation have been described in detail previously.[22,24–27]

Table 1 Donor characteristics

	All donors (n=33)	Right group (n=23)	Left group (n=10)	P value
Sex (male/female)	22:11	15:8	7:3	NS
Age	34.0 (18–61)	32.0 (18–61)	41.5 (19–59)	NS
BMI	20.9 (16.7–29.0)	19.8 (16.7–26.6)	25.0 (17.8–29.0)	<0.01
ICG R15 (%)	5.8 (2.8–12.0)	5.6 (3.0–10.2)	8.0 (2.8–12.0)	NS
Congestive area (present/absent)	12:21	2:21	10:0	<0.0001
Operation time (min)	514 (355–700)	514 (355–685)	515 (430–700)	NS
Blood loss (g)	500 (169–1,125)	470 (169–1,125)	530 (285–1,080)	NS
Peak TB (mg/dl)	1.9 (1.1–4.2)	2.0 (1.5–4.2)	1.6 (1.1–3.2)	0.02
Peak AST (IU/L)	191 (108–856)	177 (108–398)	235 (149–856)	0.006
Peak ALT (IU/L)	210 (97–623)	171 (97–429)	290.5 (125–623)	0.01
Peak PT-INR	1.59 (1.21–2.52)	1.67 (1.21–2.52)	1.42 (1.27–2.10)	NS
Complication (yes/no)	18 (55%):15 (45%)	15 (65%):8 (35%)	3 (30%):7 (70%)	NS

Values are expressed as median (range)

BMI body mass index, *ICG R15* indocyanine green retention rate at 15 min

P indicates the results of comparisons between Right and Left groups

Of the 33 donors in the present series, a right hemiliver graft with (n=2) or without (n=21) the middle hepatic vein was obtained from 23 donors, a left hemiliver graft with the middle and left hepatic veins and with the caudate lobe was obtained from 6 cases, and a right lateral sector graft with the right hepatic vein was obtained from 4 cases, respectively. We previously reported that the overall donor liver regeneration at 3 months after LDLT was not retarded in spite of the impaired regeneration in congested parts since the regeneration of the other noncongested parts showed compensatory augmentation.[28,29] Taking this into account, we classified the donors undergoing right hemiliver resection with and without the middle hepatic vein together into the right group (corresponding to resection of approximately two thirds of the TLV), while amalgamating donors of a left hemiliver graft and a right lateral sector graft was classified as the left group (corresponding to resection of about one third of the TLV).

Pringle's maneuver was applied during donor hepatectomy.[30] After the operations, the hepatic function was assessed by blood tests for the serum total bilirubin (TB), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) and the plasma prothrombin time international normalized ratio (PT-INR). All postoperative complications were recorded.[19]

Assessment of the Liver Volumetric Change

The residual liver volume just after the operation, i.e., the liver volume at zero time-point, was calculated by subtracting the graft weight from the preoperative TLV, assuming that the liver has the same density as water. Subsequent liver regeneration was assessed by CT conducted at 1 week, 2 weeks, 1 month, 3 months, 6 months, 12 months, and 4 years after the operation. Serial abdominal transverse CT scans taken at 0.5-cm intervals were used. The boundary of each liver slice was traced manually by one of the authors (T.A.), and the encircled areas were calculated using Photoshop® software. The degree of liver regeneration at the respective time-points was then expressed as a percentage of the liver volume to the preoperative TLV and was designated as "restoration ratio to the preoperative TLV." In addition, the rate of change in the restoration ratio to the preoperative TLV from the previous time-point was calculated and was expressed as the percent change per month.

Assessment of Biochemical Parameters After Donor Hepatectomy

Biochemical parameters were assessed preoperatively and at 3 and 12 months after the hepatectomy. The parameters assessed were AST, ALT, TB, ALB, and PT-INR.

Statistics

The chronological changes in the donor liver volume in the right and left groups, as well as the rate of change in the restoration ratio to the preoperative TLV, were analyzed by two-way analysis of variance with repeated measures, followed by Bonferroni–Holm corrected post hoc t tests.[31] Multiple comparisons of postoperative values of the biochemical parameters with those measured before surgery were conducted using the Bonferroni correction. The significance of the correlation of the potential clinical factors with the regeneration process was analyzed using

the multiple regression models. The stepwise method with a P value of ≤ 0.15 for the variable elimination was used to select the variables.[32]

Results

Donor Characteristics in the Right and Left Groups

The characteristics of the donors in the right and left groups were compared and are shown in Table 1. The BMI was significantly higher in the left group compared with that in the right group ($P<0.01$). The ratio of the residual liver volume relative to the preoperative TLV just after the donor hepatectomy was 42.3±5.5% (range, 28.8–49.6%) in the right group vs. 63.4±3.5% (range, 57.5–66.4%) in the left group ($P<0.01$).

Time Course of Liver Regeneration After Donor Hepatectomy

The regeneration of the donor liver (restoration ratio to the preoperative TLV) in the right and left groups is shown in Fig. 1a, b. Volumetric data for the regenerating livers were available for 25 donors (17 in the right group and 8 in the left group) at 1 year after surgery and for 13 donors (8 in the right group and 5 in the left group) at 4 years after surgery. The rate of liver regeneration was rapid during the first 3 months (early phase; Fig. 1b). The restoration ratio to the preoperative TLV in the right group was 51.5±4.8%, 57.4±5.7%, 63.5±7.6%, and 73.6±7.8% at 1 week, 2 weeks, 1 month, and 3 months, respectively, and that in the left group at the corresponding time-points was 69.0±6.1%, 71.9±5.1%, 75.7±5.9%, and 79.3±5.3%, respectively. Therefore, the liver regained approximately one third and one half of the resected liver mass by 1 and 3 months postoperatively, respectively, irrespective of the extent of the liver resection. Thereafter, after 3 months, the rate of liver regeneration decreased (late phase). The restoration ratio to the preoperative TLV in the right group was 76.9±6.7%, 80.9±6.7%, and 88.2±5.7% at 6 months, 12 months, and 4 years, respectively, and that in the left group at the corresponding time-points was 83.3±7.0%, 84.5±6.7%, and 91.1±5.7%, respectively.

Meanwhile, the rate of change in the restoration ratio to the preoperative TLV from the previous time-point in the right group was 36.4±3.6%/month, 23.8±18.3%/month, 12.8±10.3%/month, 5.2±2.7%/month, 1.1±1.1%/month, 0.6±0.6%/month, and 0.2±0.1%/month at 1 week, 2 weeks, 1 month, 3 months, 6 months, 12 months, and 4 years, respectively, while that in the left group at the corresponding time-points was 22.4±20.1%/month, 11.6±8.8%/month, 7.6±9.5%/month, 2.4±2.7%/month, 1.4±1.1%/month, 0.2±0.2%/month, and 0.1±0.2%/month, respectively.

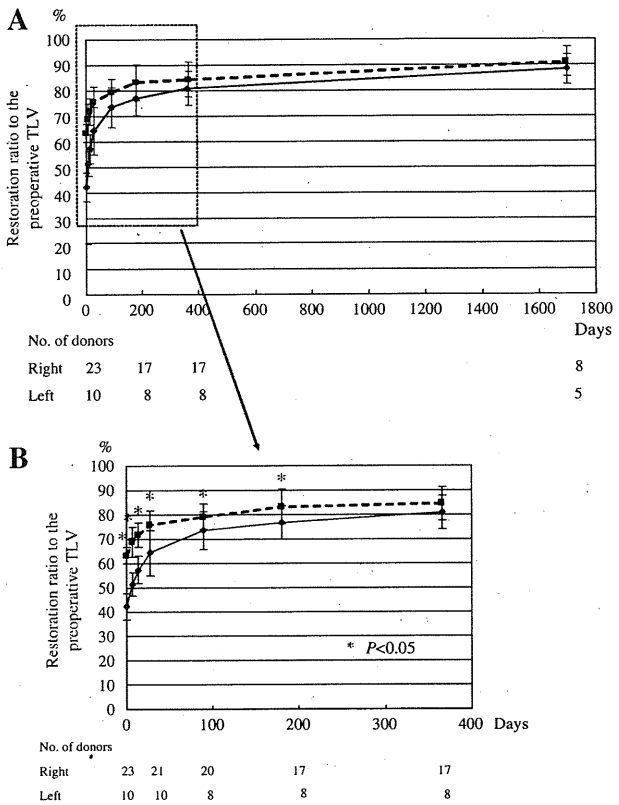

Fig. 1 Chronological profiles of liver regeneration in the right (*solid line*) and left (*dotted line*) groups as assessed by estimation of the restoration ratio to the preoperative TLV. **a** Degree of regeneration by the end of 4 years postoperatively. Restoration ratio at each time-point, when compared with that at the previous time-point, showed statistical significance throughout the study period until 4 years, e.g., $P=0.0004$ for 12 months vs. 4 years. **b** Magnified view of the regenerating liver at the end of 12 months postoperatively. Comparison of the restoration ratio in the right and left groups revealed significant differences at 1 week, 2 weeks, 1 month, 3 months, and 6 months after the operation (*$P<0.05$); however, the difference was not significant at 12 months and 4 years post surgery. *TLV* total liver volume

Comparison of the restoration ratio to the preoperative TLV at each time-point with that at the previous time-point showed statistical significance throughout the study period until 4 years (Fig. 1a). Nevertheless, only 1 out of the 25 donors at 1 year and 1 out of the 13 donors at 4 years who underwent postoperative volumetric examination showed full (more than 95%) restoration to the preoperative TLV, and both of these donors belonged to the left group.

Comparison of the restoration ratio to the preoperative TLV between the right and left groups revealed significant intergroup differences at 1 week, 2 weeks, 1 month, 3 months, and 6 months after the operation; however, the difference was not significant at 12 months and 4 years post surgery. On the other hand, the rate of change in the