Table 4. Adverse events

Grade	Group IP (n = 44)					Group SP (n = 32)				
	1	2	3	4	3<(%)	1	2	3	4	3<(%)
Leukopenia	1	9	13	3	36	7	9	4	2	19
Neutropenia	1	4	4	11	34	3	2	6	3	28
Hemoglobin	3	5	9	8	39	2	13	4	6	31
Thrombocytopenia	8	5	0	0	0	6	5	2	2	13
Nausea	4	18	1	0	2	11	2	2	0	6
Anorexia	6	17	3	2	11	11	7	3	1	9
Diarrhea	9	4	2	0	5	4	2	1	0	3
Fatigue	12	7	3	0	7	9	6	1	0	3
Neuropathy	0	3	1	0	2	3	1	0	0	0
Creatinine	9	10	0	0	0	12	2	0	0	0
Febrile neutropenia	0	0	2	0	5	0	0	2	0	6

DISCUSSION

Until the release of the results of the JCOG9912 and SPIRITS trials at the annual meeting of the American Society of Clinical Oncology in 2007, there was no standard chemotherapy for advanced gastric cancer in Japan. In this study, patients were treated between September 2002 and July 2006, at that time, the treatment for each patient was decided by the patient's choice or randomization after explaining about the JCOG9912 (randomization of 5-FU alone, CPT-11 plus CDDP or S-1 alone) trial. If a patient refused to participate in the JCOG9912 trial, we explained another treatment option including S-1 plus CDDP therapy.

Table 5. Second-line chemotherapy

Second-line chemotherapy	IP (n = 44)	SP (n = 32)
	86%(38/44)	90%(26/32)
5-FU based regimen		
S-1	21	—
S-1+CDDP	1	—
MF	2	—
Taxane		
Paclitaxel (weekly)	9	7
Paclitaxel	1	—
Docetaxel	—	1
CPT-11-based regimen		
CPT-11+MMC	—	10
FOLFIRI	—	3
CPT-11 alone	—	3
Others	4	1

5-FU, 5-fluorouracil; MF, methotrexate plus 5-FU; MMC, mitomycin C.

Therefore, the medical oncologists had no specific selection criteria for both regimens, and they might have had little impact on the patient's treatment decision.

In the previous studies, it was reported that the RR, MST and PFS of IP therapy were 38–58%, 9–12.3 and 3.7–6 months (3,5,6) and 51–74%, 10.9–13 and 4.8–6 months for SP therapy (4,7,8). These reports suggest that the SP is slightly more effective than the IP regimen. In this retrospective study, the overall survival of the IP and SP groups were very similar despite the higher RR and longer PFS of the SP group compared with the IP group. Furthermore, in the subset with target lesions, the SP group also exhibited a higher RR and slightly better PFS than the IP group. Although there was a little difference in patient backgrounds between the IP and SP groups such as the rate of PS 0 and one metastatic organ site that was in favor of the IP regimen, the SP group showed better MST and PFS than the IP group. Because our study was retrospective and small, we have too many limitations to draw conclusions from these results; however, we could find no superiority of the IP regimen to SP regimen from our results.

In the subsequent chemotherapy, >85% of the patients in both groups received second-line chemotherapy and more than half of them had the crossover treatment strategy between S-1 and CPT-11. Survival data of both groups in our study were better than previous reports (3,4). In colon cancer, it is considered to be important for the prolongation of survival to use all three active drugs, 5-FU, CPT-11 and oxaliplatin during the whole treatment course (9). Similarly, the subsequent treatment may have some impact on the overall survival of patients with advanced gastric cancer.

The incidence of patients' refusal for further treatment was higher in the IP group than the SP group. Although the incidence of Grade 3 or 4 toxicity was similar in both groups, the toxicity profile differed between them. The incidence of Grade 2 nausea, anorexia and diarrhea was observed to be 41, 39 and 9%, respectively, in the IP group and 6, 22 and 6% in the SP group. These differences in the incidence of mild symptomatic toxicities might cause patients' refusal of treatment. Thus, SP seems more feasible than IP.

In conclusion, our results demonstrate a better efficacy and feasibility of SP than IP for advanced gastric cancer patients, with or without a target lesion. The presence or absence of a target lesion cannot be used to choose between the IP and SP chemotherapy regimens.

Conflict of interest statement

None declared.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
2. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37–41.

3. Boku N, Yamamoto S, Shirao K, Doi T, Sawaki A, Koizumi W, et al. Randomized phase III study of 5-fluorouracil (5-FU) alone versus combination of irinotecan and cisplatin (CP) versus S-1 alone in advanced gastric cancer (JCOG9912). *Proc ASCO* 2007;25:18S.
4. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;9:215–21.
5. Boku N, Ohtsu A, Shimada Y, Shirao K, Seki S, Saito H, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. *J Clin Oncol* 1999;17:319–23.
6. Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, et al. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. *Cancer* 2002;94:641–6.
7. Koizumi W, Tanabe S, Saigenji K, Ohtsu A, Boku N, Nagashima F, et al. Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. *Br J Cancer* 2003;89:2207–12.
8. Ajani JA, Lee FC, Singh DA, Haller DG, Lenz HJ, Benson AB, 3rd, et al. Multicenter phase II trial of S-1 plus cisplatin in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol* 2006;24:663–7.
9. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004;22:1209–14.

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ORIGINAL ARTICLE

A late phase II study of S-1 for metastatic pancreatic cancer

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Abstract This study evaluated the antitumor effect and safety of S-1, an oral fluoropyrimidine derivative, in patients with metastatic pancreatic cancer. Chemo-naive patients with pancreatic adenocarcinoma, and measurable metastatic lesions were enrolled. S-1 was administered orally twice daily after meals at a dose of 80, 100, or 120 mg/day for body surface areas (BSAs) of less than 1.25 m^2, between 1.25 m^2 and less than 1.5, or 1.5 m^2 or greater, respectively, for 28 consecutive days, followed by a 14-day rest. Fifteen (37.5%) of 40 patients responded to treatment, including 1 complete response and 14 partial responses. The median time to progression and the overall survival time were 3.7 months (95% confidence interval, 2.2–5.6 months) and 9.2 months (95% confidence interval, 7.5–10.8 months), respectively. The major adverse events were anorexia, fatigue, hemoglobin reduction, nausea and pigmentation change, although most were tolerable and reversible. Although disseminated intravascular coagulation occurred in two patients, the condition resolved with anticoagulant therapy. S-1 is an effective and well-tolerated drug. The effectiveness of this drug should be confirmed in a phase III study.

Keywords Pancreatic cancer · Phase II study · Chemotherapy · S-1

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Introduction

Pancreatic cancer is a major leading cause of cancer-related mortality worldwide: it ranks as the fifth leading cause of death in Japan, with an annual incidence of approximately 20,000 cases and a similar mortality rate [1]. Of all the treatments available for pancreatic cancer, only resection offers a chance for a cure. However, owing to the high frequency of local extension and/or metastatic disease at the time of diagnosis, only a small minority of patients are candidates for curative resection. Moreover, surgery alone is limited, with an unsatisfactory prognosis and a high incidence of postoperative recurrence. To improve the survival of patients with pancreatic cancer, effective non-surgical treatments are urgently needed.

A randomized controlled study demonstrated that treatment with gemcitabine exhibited a better clinical benefit response (CBR) (23.8 vs. 4.8%) and median survival period (5.65 vs. 4.41 months) than bolus 5-fluorouracil (5-FU) [2].

However, chemotherapy for pancreatic cancer must be substantially improved because gemcitabine monotherapy offers only a limited survival benefit. Gemcitabine administration via a fixed-dose-rate infusion [3] and gemcitabine-based combined regimens have been investigated, but a meaningful impact on survival, compared with that of gemcitabine monotherapy, was not obtained. Randomized phase III studies of gemcitabine plus erlotinib [4] and gemcitabine plus capecitabine [5] have demonstrated significant survival benefits, but a worldwide consensus regarding these results has not been established.

S-1 is an oral anticancer drug consisting of tegafur (FT), a prodrug of 5-FU, and two biochemical modulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) [6]. CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and allows efficacious concentrations of 5-FU to be maintained in the plasma and tumor tissues. Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract and reduces the gastrointestinal toxicity of 5-FU. S-1 has been clinically shown to have a potent antitumor activity against various solid tumors [7–15].

S-1 was also effective against human pancreatic cancer xenografts implanted into nude rats [16]. Furthermore, an early phase II study of S-1 showed promising results, with a 21% response rate and a manageable toxicity profile in 19 patients with metastatic pancreatic cancer [17]. Therefore, we conducted a multi-institutional late phase II study of S-1 to confirm these previous results.

Patients and methods

Patients

Patients with inoperable pancreatic cancer or who were unable to receive radiotherapy were considered for enrollment. The eligibility criteria were as follows: capable of oral intake, histologically or cytologically confirmed pancreatic adenocarcinoma, between 20 and 74 years old, no history of prior treatment other than pancreatic resection, measurable metastatic lesions, a Karnofsky performance status (KPS) of 80–100%, an adequate hematological profile (hemoglobin $\geq$10.0 g/dl; leukocyte count, 4,000–12,000/mm^3; neutrophil count $\geq$2,000/mm^3; platelet count $\geq$100,000/mm^3), adequate hepatic function (total bilirubin level $\leq$3 times the upper limit of normal, transaminases levels $\leq$ 2.5 times the upper limit of normal), adequate renal function (normal serum creatinine level), and a life expectancy $\geq$2 months. The exclusion criteria were as follows: participation in another clinical study; treatment with phenytoin, potassium warfarin or flucytosine; active infection; serious complications; clinically significant ascites or pleural effusion; brain metastasis; abnormal bowel movements, like watery diarrhea or chronic constipation; active secondary malignancies; pregnancy or lactation; and men who were trying to father a child. The study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice and was approved by the institutional review boards at each hospital. Written informed consent was obtained from all patients before their participation.

Treatment plan

S-1 (Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) was administered orally at a dose of 40 mg/m^2 twice daily, after breakfast and dinner, for 28 consecutive days followed by a 14-day rest one course. The three initial doses were determined according to the body surface area (BSA) as follows: BSA $<$1.25 m^2, 40 mg/dose; 1.25 m^2 $\leq$ BSA $<$ 1.5 m^2, 50 mg/dose; 1.5 m^2 $\leq$ BSA, 60 mg/dose. Treatment cycles were repeated until the appearance of disease progression, unacceptable toxicities, or the patient's refusal to continue treatment. If a grade 3 or higher hematological toxicity or a grade 2 or higher non-hematological toxicity was observed, dose reduction by 10 mg/dose (minimum, 40 mg/dose) or temporary interruption of S-1 administration was recommended. To enhance treatment efficacy, the rest period was shortened to 7 days or the dose was escalated one step during the next course (maximum, 75 mg/dose), unless adverse events were observed. If a rest period of more than 28 days was required, the study treatment was stopped. Prophylactic granulocyte colony-stimulating factor was not used.

Response and safety

Patients who received at least one dose of S-1 were evaluated for response and toxicity. Tumor response was assessed using computed tomography or magnetic resonance imaging after each course according to the Japan Society for Cancer Therapy (JSCT) Criteria [18], which are similar to the World Health Organization Criteria. Primary pancreatic lesions were considered assessable, but not measurable. The response was secondarily assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) [19]. Carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) levels were quantified in each course.

The CBR was evaluated using the KPS and pain score, as described below [2]. The KPS was recorded weekly by the attending physician. Pain was evaluated by measuring the change from the baseline pain intensity and the daily dose of morphine or morphine-equivalent (doses of analgesic agents were converted to morphine-equivalent doses,

i.e., 5.0 mg fentanyl patch = 60 mg morphine). The pain intensity was graded from 0 (no pain) to 100 (worst pain) using a visual analog scale and was recorded on a pain assessment card everyday. Patients who fulfilled at least one of the following criteria were defined as eligible for the CBR analysis: (1) baseline pain intensity $\geq$20, or (2) baseline morphine consumption $\geq$10 mg/day. Moreover, all the patients underwent a 'pain stabilization period' for 2 days to ensure that the baseline values were stable before treatment: when the variation in the morphine consumption between 2 days was within 5 mg and the variation of the pain intensity was within 10, the patient was considered eligible for inclusion in the CBR analysis. Any adverse events were evaluated for grading, duration and S-1 causality according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Physical findings were assessed weekly, blood biochemistry and urinalysis were assessed biweekly, and vital signs were assessed as necessary. An independent review committee confirmed the responses and the adverse events.

Statistics

The primary measure of efficacy was the overall response rate, as defined by the tumor measurement. Other measures included the response duration, median survival time (MST) and time to progression (TTP), according to the JSCT Criteria. Response duration was calculated from the first documentation of a response until progressive disease (PD). The MST and median TTP were estimated using the Kaplan–Meier method [20]. The threshold rate was defined as 5%, and the expected rate was set at 20% because the response rate in the previous study had been 21.1% [17]. If the response rate to S-1 was 20%, a sample size of 40 patients would ensure a power of at least 80% at a one-sided significance level of 2.5% to reject the null hypothesis that the response rate was $\leq$5%. If the lower limit of the 95% confidence interval (95% CI) of the response rate exceeded the 5% threshold, a response rate of 6 out of 40 patients would be required.

Results

Patient characteristics

Between January 2003 and April 2004, 41 patients from 7 institutions were enrolled in the present study. S-1 was not administered in 1 patient because of rapid disease progression: thus, toxicity and response were evaluated in 40 patients. The patient characteristics are listed in Table 1. Most patients had a good Karnofsky performance status of 90–100%. Among the five patients who had undergone resections, three patients received pancreaticoduodenectomies and two patients received distal pancreatectomies. The major sites of metastases were the liver and distal lymph nodes. Ten of the 40 patients fulfilled the eligibility criteria for the CBR evaluation.

Treatment

A total of 144 courses were administered to 40 patients, with a median of 3.0 courses per patient (range 1–16 courses). The S-1 dose was reduced in eight patients for the following reasons: grade 3 hepatotoxicity (one patient); grade 3 gastrointestinal toxicity, including anorexia, nausea and vomiting (one patient each); grade 2 gastrointestinal toxicity (1 patient); grade 2 abdominal pain (one patient); grade 1 pancytopenia (one patient); and a body weight loss of less than 5% (one patient: the body weight of the patient was originally close to the boundary between the 50 and 60 mg dose categories). The dose was increased in eight patients because no adverse events that might have posed an impediment to dose escalation were observed; thereafter, three of the eight patients required a dose reduction to their original dose. Thirty-five (90%) of the 39 patients who completed this study were subsequently treated with gemcitabine, although the treatment periods and responses were not monitored.

Responses and survival

The responses of the 40 patients are shown in Table 2. The overall response rate, as evaluated using the JSCT criteria, was 37.5% (95% CI 22.7–54.2%), including 1 complete response (CR) and 14 partial responses (PRs). The response in the patient who showed a CR according to the JSCT criteria was judged as a PR according to the RECIST criteria because the serum CEA level did not decrease to normal. The serum CA 19-9 level decreased by more than half in 15 (48%) of the 31 patients who had pretreatment levels over 100 U/ml, and the serum CEA level decreased by more than half in 4 (29%) of the 14 patients who had pretreatment levels over 15 U/ml. The median duration of response was 6.9 months (range 4.0–18.6 months). The median TTP, MST, and 1-year survival rate were 3.7 months (95% CI 2.2–5.6 months), 9.2 months (95% CI 7.5–10.8 months), and 32.5% (13/40), respectively (Fig. 1). S-1 treatment was ongoing in 1 of the 40 patients who showed no evidence of disease progression at the time of analysis (617 days).

Clinical benefits

The CBR scores of four (40%) of the ten evaluated patients improved after S-1 therapy. The pain intensity of all four patients decreased, although their daily analgesic consump-

Table 1 Patient characteristics

Characteristics	Median (Range)	No. of patients	(%)
No. of patients enrolled		41	
Assessable for response and toxicity		40	
Sex			
Male		21	52.5
Female		19	47.5
Age, years	59.5 (41–74)		
Karnofsky performance status, %			
100		18	45.0
90		21	52.5
80		1	2.5
First dose, mg			
40		3	7.5
50		18	45.0
60		19	47.5
Pancreatectomy			
(+)		5	12.5
(−)		35	87.5
Metastatic sites			
Liver		36	90.0
Distant lymph nodes		10	25.0
Lung		4	10.0
Peritoneum		1	2.5
CA 19-9, U/ml	1,020 (1.0–250,000)		
No. of cases with more than 100 U/ml		31	77.5
CEA, U/ml	6.95 (1.0–498)		
No. of cases with more than 15 U/ml		14	35.0

tion and KPS scores did not change. In the remaining six patients, the CBR remained unchanged in one patient and increased in five patients. The responses according to the JSCT criteria of the four patients with improved CBR scores were two PR and two no change (NC).

Safety

Treatment-related adverse events are listed in Table 3. The major adverse events were anorexia, fatigue, hemoglobin reduction, nausea, and pigmentation change; however, most

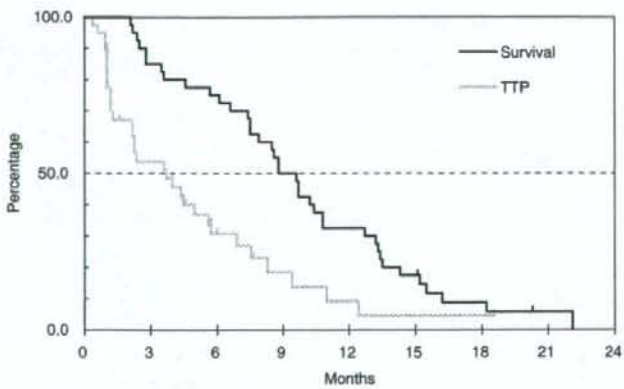

Fig. 1 Kaplan–Meier curves for overall survival (*solid line*) and time to progression (*dotted line*)

Table 2 Tumor response ($n = 40$)

Tumor response	JSCT (%)	RECIST (%)
Complete response	1 (2.5)	0 (0.0)
Partial response	14 (35.0)	15 (37.5)
No change/stable disease	11 (27.5)	11 (27.5)
Progressive disease	13 (32.5)	13 (32.5)
Not evaluable[a]	1 (2.5)	1 (2.5)
Overall response	15 (37.5)	15 (37.5)

[a] Radiographic assessment was not determined

Table 3 Treatment-related adverse events ($n = 40$): worst grade reported during the treatment period

Toxicity	Grade				Grades 1–4	Grades 3–4
	1	2	3	4	(%)	(%)
Hematological						
Leukopenia	10	7	0	0	42.5	0
Neutropenia	4	4	5	0	32.5	12.5
Hemoglobin reduction	8	13	1	1	57.5	5.0
Thrombocytopenia	13	1	1	0	37.5	2.5
Non-Hematological						
Anorexia	10	10	4	1	62.5	12.5
Nausea	11	6	3	0	50.0	7.5
Vomiting	8	6	2	0	40.0	5.0
Diarrhea	12	4	3	0	47.5	7.5
Fatigue	16	9	0	0	62.5	0
Stomatitis	9	1	0	0	25.0	0
Skin rash	6	4	0	0	25.0	0
Pigmentation change	20	0	0	0	50.0	0
DIC[a]	0	0	2	0	5.0	5.0
Colitis	0	0	1	0	2.5	2.5
Hypotension	0	0	1	0	2.5	2.5
Prothrombin time	0	0	1	0	2.5	2.5
T-bilirubin elevation	5	8	2	1	40.0	7.5
AST elevation	3	4	1	0	20.0	2.5
ALT elevation	5	4	1	0	25.0	2.5
γ-GTP elevation	0	0	1	0	2.5	2.5
Albumin reduction	5	3	0	0	20.0	0
T-protein reduction	6	2	0	0	20.0	0
Weight loss	6	1	0	0	17.5	0
LDH elevation	4	1	0	0	12.5	0

Events with a frequency of more than 10.0% or high-grade events (grades 3, 4) are listed

[a] Disseminated intravascular coagulation

of these events were tolerable and reversible. Treatment was discontinued in six patients because of treatment-related adverse events: grade 4 elevation in total bilirubin, grade 4 anorexia, grade 3 disseminated intravascular coagulation (DIC), and grade 3 colitis during the first course, grade 4 anemia (hemoglobin reduction) during the third course, and grade 2 nausea during the fourth course. Most of the events resolved with the cessation of S-1 administration, although an elevated total bilirubin level persisted in 1 patient until his death 41 days after the discontinuation of S-1 and anorexia persisted in 1 patient until the initiation of radiotherapy as a second-line treatment 13 days after the discontinuation of S-1.

Although DIC also occurred in one patient during the first course, it resolved soon after the start of anticoagulant therapy; nonetheless, the S-1 therapy had to be discontinued because of disease progression after the patient recovered from the DIC. Febrile neutropenia or treatment-related deaths did not occur. Ileus, which occurred in three patients during the early phase II study, did not occur in this study. Most of the patients were treated as outpatients.

Discussion

A variety of chemotherapy regimens for the treatment of advanced pancreatic cancer have been evaluated since the introduction of gemcitabine, which aroused renewed interest in clinical research. However, little evidence of significant activity against this disease has been demonstrated, and few agents have reproducibly provided high response rates or a meaningful impact on patient survival or quality of life.

In phase II and III studies for advanced pancreatic cancer, gemcitabine monotherapy produced response rates ranging from 4 to 17% and an MST ranging from 5.4 to 7.3 months [21, 22]. In phase II trials of oral fluoropyrimidines, UFT yielded no objective response (0/21), with an MST of 4.2 months [23], and capecitabine yielded a response rate of 9.5% (4/42), with an MST of 182 days (6.0 months) [24]. For gemcitabine combined therapy, response rates of up to 29% were reported in phase III studies, with MST values ranging from 3.74 to 9.0 months [21, 22].

An early phase II study of S-1 produced a response rate of 21% and an MST of 5.6 months [17]. The present phase II study concluded that S-1 was a promising agent for advanced pancreatic cancer, with a response rate of 37.5%, an MST of 9.2 months, and an acceptable toxicity profile. The efficacy of S-1 in the present study was more favorable than that in the previous study. The reasons for this discrepancy could not be definitively identified because of the small numbers of patients involved, although differences in the patients' backgrounds probably affected the results. A logistic regression analysis suggested that a larger proportion of female patients, fewer measurable lesions, and a lower morphine consumption, compared with the early phase II study, might have contributed to the superior response rate in the present study, although the differences were not statistically significant (data not shown). Moreover,

the larger proportion of patients receiving second-line chemotherapy may have contributed to the longer MST in the present study: the proportion of patients receiving second-line chemotherapy was 26% (5/19, 3 patients receiving 5-FU plus cisplatin, 2 patients receiving gemcitabine) in the previous study and 90% (35/39, 35 patients receiving gemcitabine) in the present study. Gemcitabine was approved for the treatment of pancreatic cancer in Japan in April 2001, after enrollment in the previous study had been completed. Although some divergences in the response rates and survival periods were noted, the results of both studies seemed to favor S-1 over other agents for the treatment of advanced pancreatic cancer.

The toxicity profiles in the previous and present studies on S-1 were similar. However, gastrointestinal toxicities like anorexia and vomiting tended to occur more frequently in the studies for pancreatic cancer than in those for other cancers. We speculated that the higher frequency of toxicity may be related to the clinical features of pancreatic cancer itself, since gastrointestinal symptoms like anorexia are observed in many patients at the time of the initial diagnosis. No treatment-related deaths were observed, but three patients developed ileus during the previous phase II study and two patients developed DIC during the present study. DIC was a noteworthy complication, although this complication can occur even in patients with pancreatic cancer who are receiving only supportive care without chemotherapy. Although the cause of the DIC could not be determined, the possibility that it was caused by the S-1 treatment cannot be excluded. Periodic monitoring of the patients' physical conditions and laboratory parameters is recommended for the early diagnosis of serious complications in patients treated outside of clinical trials, even though most patients were treated as outpatients without any serious complaints.

S-1, an oral anticancer agent, may offer clinical advantages while maintaining quality of life [25]. Since a promising anticancer effect and a relatively long MST were observed in this study, S-1 may be a potentially useful alternative to gemcitabine as a first-line drug for the treatment of advanced pancreatic cancer. Furthermore, S-1 may be useful when administered in combination with gemcitabine, since its toxicity is generally mild and its toxicological profile is distinct from that of gemcitabine. We previously conducted a phase I study to determine the recommended dose of S-1 and gemcitabine in a combination regimen for the treatment of advanced pancreatic cancer [26]. Currently, we are conducting a multi-institutional phase II study. Nakamura et al. [27] reported a 48% (16/33) response rate and an MST of 12.5 months for metastatic pancreatic cancer in a single-institute phase II study of S-1 and gemcitabine. Randomized trials are essential for determining whether chemotherapy with S-1 is equivalent or superior in efficacy to gemcitabine as an initial treatment for advanced pancreatic cancer.

In conclusion, S-1 administered as a single agent showed a promising anticancer effect with acceptable toxicity in patients with metastatic pancreatic cancer. A randomized phase III trial to evaluate the effectiveness of S-1 for advanced pancreatic cancer is warranted.

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References

1. Lowenfels AB, Maisonneuve P (2004) Epidemiology and prevention of pancreatic cancer. Jpn J Clin Oncol 34:238–244
2. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR et al (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
3. Tempero M, Plunkett W, Ruiz Van Haperen V, Hainsworth J, Hochster H, Lenzi R et al (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402–3408
4. Moore MJ (2005) Brief communication: a new combination in the treatment of advanced pancreatic cancer. Semin Oncol 32(6 Suppl 8):S5–S6
5. Cunningham D, Chau I, Stocken D, Davies C, Dunn J, Valle J et al (2005) Phase III randomised comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. Eur J Cancer Suppl 3:12
6. Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K et al (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 7:548–557
7. Shirao K, Ohtsu A, Takada H, Mitachi Y, Hirakawa K, Horikoshi N et al (2004) Phase II study of oral S-1 for treatment of metastatic colorectal carcinoma. Cancer 100:2355–2361
8. Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K et al (2000) Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. Br J Cancer 83:141–145
9. Kawahara M, Furuse K, Segawa Y, Yoshimori K, Matsui K, Kudoh S et al (2001) Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Br J Cancer 85:939–943
10. Furuse K, Kawahara M, Hasegawa K, Kudoh S, Takada M, Sugiura T et al (2001) Early phase II study of S-1, a new oral fluoropyrimidine, for advanced non-small-cell lung cancer. Int J Clin Oncol 6:236–241
11. Koizumi W, Kurihara M, Nakano S, Hasegawa K (2000) Phase II study of S-1, a novel oral derivative of 5-fluorouracil, in advanced gastric cancer. Oncology 58:191–197

12. Sugimachi K, Maehara Y, Horikoshi N, Shimada Y, Sakata Y, Mitachi Y et al (1999) An early phase II study of oral S-1, a newly developed 5-fluorouracil derivative for advanced and recurrent gastrointestinal cancers. Oncology 57:202–210
13. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T (1998) Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. Eur J Cancer 34:1715–1720
14. Inuyama Y, Kida A, Tsukuda M, Kohno N, Satake B (2001) Late phase II study of S-1 in patients with advanced head and neck cancer. Gan To Kagaku Ryoho 28:1381–1390
15. Saeki T, Takashima S, Sano M, Horikoshi N, Miura S, Shimizu S et al (2004) A phase II study of S-1 in patients with metastatic breast cancer–a Japanese trial by the S-1 Cooperative Study Group, Breast Cancer Working Group. Breast Cancer 11:194–202
16. Fukushima M, Satake H, Uchida J, Shimamoto Y, Kato T, Takechi T et al (1998) Preclinical antitumor efficacy of S-1: a new oral formulation of 5-fluorouracil on human tumor xenografts. Int J Oncol 13:693–698
17. Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C (2005) An early phase II study of S-1 in patients with metastatic pancreatic cancer. Oncology 68:171–178
18. Japan Society for Cancer Therapy (1993) Criteria for the evaluation of the clinical effects of solid cancer chemotherapy. J Jpn Soc Cancer Ther 28:101–130
19. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L et al (2000) New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205–216
20. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481
21. Kindler HL (2005) Front-line therapy of advanced pancreatic cancer. Semin Oncol 32(6 Suppl 9):S33–S36
22. Hochster HS, Haller DG, de Gramont A, Berlin JD, Philip PA, Moore MJ et al (2006) Consensus report of the International Society of Gastrointestinal Oncology on therapeutic progress in advanced pancreatic cancer. Cancer 107:676–685
23. Ueno H, Okada S, Okusaka T, Ikeda M, Kuriyama H (2002) Phase II study of uracil-tegafur in patients with metastatic pancreatic cancer. Oncology 62:223–227
24. Cartwright TH, Cohn A, Varkey JA, Chen YM, Szatrowski TP, Cox JV et al (2002) Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. J Clin Oncol 20:160–164
25. O'Neill VJ, Twelves CJ (2002) Oral cancer treatment: developments in chemotherapy and beyond. Br J Cancer 87:933–937
26. Ueno H, Okusaka T, Ikeda M, Ishiguro Y, Morizane C, Matsubara J et al (2005) A phase I study of combination chemotherapy with gemcitabine and oral S-1 for advanced pancreatic cancer. Oncology 69:421–427
27. Nakamura K, Yamaguchi T, Ishihara T, Sudo K, Kato H, Saisho H (2006) Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. Br J Cancer 94:1575–1579

≪局所進行膵癌の治療戦略≫
局所進行膵癌に対する化学療法

大川伸一*

要旨

- 局所進行膵癌に対する標準的治療については，長いあいだ論争がある．
- 米国，日本では放射線化学療法を標準治療とする傾向が強いと考えられるが，欧州では全身化学療法を標準とすることが多かった．
- 両者の治療を比較した無作為化試験は少なく，症例数も少なく，また結論もさまざまである．
- gemcitabine の登場以来，これが進行膵癌に対する標準薬となったため，局所進行膵癌にも全身化学療法が広く行われるようになった．
- gemcitabine を用いた放射線化学療法の試験もあるが，その方法，成績は一定ではない．
- 放射線化学療法と gemcitabine による全身化学療法の両者の治療成績に著明な差があるとは考えにくいが，今後は局所進行膵癌をさらに詳細に分析し，それぞれの治療に，より適した対象を見出すことが重要と考えられる．

はじめに

膵癌は早期発見が困難であり，多くの症例が診断時に遠隔転移を伴っているか切除不能な局所進行癌である[1]．局所進行膵癌とは，CT を主とする画像診断において明らかな遠隔転移を認めないが，根治切除は不可能な状態の膵癌である．すなわち一般には，上腸間膜動脈や腹腔動脈の根部に癌が明らかに進展している状態や，門脈に広範囲に浸潤している状態などであり，ほぼ UICC（The International Union Against Cancer）分類のⅢ期に等しい．

遠隔転移症例について適応となる治療法は全身化学療法であることは異論のないことであるが，新規膵癌患者の 3 割程度を占める局所進行膵癌の治療については，全身化学療法か放射線化学療法かは長いあいだ議論があり，現在でもまだ決着がついていない．しかし全身化学療法と放射線化学療法は，治療の質，期間，入院期間，起こりうる有害事象の内容などに大きな違いがあるため，どちらが推奨されるのかは臨床上，大きな問題である．

局所進行膵癌に対する放射線化学療法

局所進行膵癌に対して行われてきた放射線化学療法については，比較試験は多くはない．無作為化比較試験では 1969 年の Moertel[2]，1981 年の Moertel[3]，1988 年の GITSG（Gastrointestinal Tumor Study Group）[4]による試験で，放射線化学療法が化学療法に優っていたと報告された（Table 1）．いずれもかなり以前の試験であるが，米国はこれを根拠として今日にいたるまで，局所進行膵癌の治療として放射線化学療法を標準治療として推奨する立場をとってきた．

一方米国以外，とくに欧州では米国とは異なり，

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Table 1. 進行膵癌に対する放射線化学療法と全身化学療法の比較試験

報告者 研究グループ	報告年	症例数	放射線治療 (Gy)	化学療法	生存期間 中央値(月)	p 値
Moertel[2]	1969	32	35～40	なし	6.3	<0.05
		32	35～40	5-FU	10.4	
Moertel[3]	1981	25	60	なし	5.2	<0.01
		83	40	5-FU	9.6	
		86	60	5-FU	9.2	
GITSG[4]	1988	21		SMF	8.0	=0.02
		22	54	SMF	10.5	
Klaassen[5]	1985	44		5-FU	8.2	NS
		47	40	5-FU	8.3	
Chauffert[11]	2008	60		GEM	13.0	=0.03
		59	60	FP	8.6	
Loehrer[12]	2008	38		GEM	9.2	=0.034
		36	50.4	GEM	11.0	

GITSG：Gastrointestinal Tumor Study Group.
SMF：streptozocin, mitomycin, 5-FU.　FP：5-FU, CDDP.

Table 2. GEM 放射線化学療法の第 II 相試験

報告者	報告年	症例数	放射線治療 (Gy)	GEM 投与量 (mg/m²)	TTP (月)	1 年生存率 (%)	生存期間 中央値(月)
de Lange[8]	2002	24	24	300	7	—	10
Li[9]	2003	18	50.4～61.2	600	7.1	56	14.5
Okusaka[7]	2004	38	50.4	250	4.4	28	9.5
Murphy[10]	2007	74	20～42	1,000	6.6	46	11.2

TTP：time to progression.

上記のこれらの試験の症例数が 21 例から 86 例までの少数であること，また 1985 年の ECOG の試験[5]では有意差を認めなかったことから，放射線化学療法が必ずしも標準とはならなかった経緯がある．日本では米国の考え方に近いと考えられる．これらの放射線化学療法に用いられた薬剤は，当然ながらそれまで膵癌の key drug として長く用いられてきた fluorouracil(5-FU)が主体であった．5-FU の投与法はさまざまであり，bolus で行ったり持続投与が行われたりしたが，投与法について比較した大規模な試験はない．

1997 年に Burris ら[6]により，塩酸ゲムシタビン(gemcitabine：GEM)が進行膵癌に対する標準薬として登場してからは，これを併用薬剤とする放射線化学療法が，いくつか報告されている[7～10](Table 2)．これらの試験における GEM の投与量は，実にさまざまである．

最近では，フランスの研究グループから GEM 単独療法と比較して放射線化学療法に否定的な報告[11]がされているが，一方で 2008 年の ASCO(米国がん治療学会)では，米国の研究グループから放射線化学療法に肯定的な報告[12]もされている．

局所進行膵癌に対する化学療法の背景

過去長期間にわたり，膵癌の化学療法は 5-FU を主体として行われてきた[13～15]．奏効率は最大 28% くらい[14]でさまざまであったが，比較的奏効率のよい治療法も追試にて同様の成績をあげるこ

とが少なかったこと[13]や，survival の改善につながらない[15]，などの問題があった．

GEM が登場[6]して以来，これが標準薬となったため，欧米をはじめとして GEM を key drug とした化学療法の臨床研究が，この 10 年で盛んに行われている．しかし試験対象としての進行膵癌に，遠隔転移を伴う膵癌と局所進行膵癌を同時に含む試験が多いため，局所進行膵癌のみを扱った化学療法の第Ⅱ相試験はほとんど存在しない．両者を対象に含む試験[16,17]の内容からは，対象例のおおむね 20～30% が局所進行膵癌と考えられ，実際の臨床の現場の割合に即したものであることが多い．

局所進行膵癌の増悪様式○

局所進行膵癌の治療戦略を考えるうえで重要な点の一つは，その増悪様式であるが，一般には肝などへの遠隔転移をきたすか，または腹膜播種が多いと考えられる．一方で GEM を用いた最近の放射線化学療法の試験の報告では，局所再発率は数～50% とさまざまであり[7～10]，さらに局所の再発が生存期間に及ぼす影響については詳細な検討がされているとはいいがたく，増悪の主要因が特定された解析は少ない．

また膵癌はしばしば一つの要因だけで増悪するものではなく，画像上明らかな増悪が認められなくとも症状が増悪していく，いわゆる臨床的増悪も多い．こうした特徴から膵癌を「全身病」であると考えると，治療法の評価は，一般にはやはり生存期間で行うことになろう．

局所進行膵癌に対する全身化学療法○

前述したように局所進行膵癌の全身化学療法の評価は，放射線化学療法との比較試験で解析されていることが多い[4～5,11,12]．あるいは，遠隔転移のある膵癌と局所進行膵癌の両者を対象にした試験の subgroup 解析で述べられている[16,17]．その生存期間の成績を大まかにまとめると，化学療法単独の生存期間中央値は多くが約 8～10ヵ月くらいであろう．これらは前述した GEM を用いた最近の放射線化学療法の成績(Table 2)に対して，やや劣るようにもみえるが，一般には全身化学療法より放射線化学療法のほうが治療のための入院期間が長いことや有害事象の点などから，その差は結局著明なものではないと思われる．

しかし一方で，試験の endpoint である生存期間の比較だけでは治療効果の詳細な意義がつかめない点もある．たとえば長期間にわたり明らかな遠隔転移をきたさない例に対しては，放射線化学療法が有用であり，生存期間を延長させている可能性がある．この点に注目して，まず局所進行膵癌に全身化学療法を数コース行い，そのあいだに遠隔転移をきたさない症例だけを対象にして放射線化学療法を行う方法も注目されている[18]．

おわりに○

局所進行膵癌の標準治療が放射線化学療法か全身化学療法かは，大規模な第Ⅲ相試験が困難であること，放射線治療の quality control が問題であること，さらには局所進行膵癌の中でも進行度に幅があること，すなわち小さな転移が隠されている例が少なからず存在することなどから，結論を導くにはまだ時間を要するため，しばらくは controversial な状態が続くと予想される．

今後，さらに多くの臨床研究にて詳細な分析を積み重ねることにより，全身化学療法が推奨される対象と放射線化学療法により恩恵を受けられる対象を特定できるようになれば，難治癌である膵癌治療の進歩に，また一歩貢献できるであろう．

文　献○

1) Evans DB et al：Cancer of the pancreas. Cancer：principles & practice of oncology, 6 Ed, ed by DeVita VT Jr et al, Lippincott Williams & Wilkins, Philadelphia, p1126-1161, 2001
2) Moertel CG et al：Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet **2**：865, 1969
3) Moertel CG et al, The Gastrointestinal Tumor Study Group：Therapy of locally unresectable pancreatic carci-

noma：a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads＋5-fluorouracil), and high dose radiation＋5-fluorouracil. Cancer **48**：1705, 1981
4) Gastrointestinal Tumor Study Group：Treatment of locally unresectable carcinoma of the pancreas：comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst **80**：751, 1988
5) Klaassen DJ et al：Treatment of locally unresectable cancer of the stomach and pancreas：a randomized comparison of 5-fluorouracil：an Eastern Cooperative Oncology Group study. J Clin Oncol **3**：373, 1985
6) Burris Ⅲ HA et al：Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer：a randomized trial. J Clin Oncol **15**：2403, 1997
7) Okusaka T et al：Phase Ⅱ study of radiotherapy combined with gemcitabine for locally advanced pancreatic cancer. Br J Cancer **91**：673, 2004
8) de Lange SM et al：Gemcitabine-radiotherapy in patients with locally advanced pancreatic cancer. Eur J Cancer **38**：1212, 2002
9) Li CP et al：Concurrennt chemoradiotherapy treatment of locally advanced pancreatic cancer：gemcitabine versus 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys **57**：98, 2003
10) Murphy JD et al：Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys **68**：801, 2007
11) Chauffert B et al：Phase Ⅲ trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance with gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Defenitive results of the 2000-01 FFCD/SFRO study. Annal Oncol, 2008, May 7, Epub ahead of print
12) Loehrer PJ et al：A randomized phase Ⅲ study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer：E-4201. J Clin Oncol **26**[15S]：214s, 2008 (Suppl, 2008ASCO abs4506)
13) Abbruzzese JL：Past and present treatment of pancreatic adenocarcinoma：chemotherapy as a standard treatment modality. Seminars in Oncology **29** (6) [Suppl 20]：2, 2002
14) Carter SK et al：The integration of chemotherapy into a combined modality approach for cancer treatment：Ⅵ. pancreatic adenocarcinoma. Cancer Treat Rev **3**：193, 1975
15) Ducreux M et al：A randomized trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma. Ann Oncol Aug **13**：1185, 2002
16) Louvet C et al：Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer：results of a GERCOR and GISCAD phase Ⅲ trial. J Clin Oncol **23**：3509, 2005
17) Abou-Alfa GK et al：Randomized phase Ⅲ study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer：J Clin Oncol **24**：4441, 2006
18) Rana et al：Neoadjuvant chemotherapy improves outcomes of chemoradiotherapy for locally advanced pancreatic cancer. J Clin Oncol **24** (18s)：187s, 2006 (Suppl, 2006 ASCO abs 4036)

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—症例報告—

遺伝子解析により確認し得た，盲腸癌術後膵転移の1切除例

村田依子　大川伸一　天野　歩
上野　誠　宮川　薫[1]　塩澤　学
杉政征夫[2]　林　宏行[3]　宮城洋平[4]

要旨：症例は64歳女性．2002年盲腸癌穿孔のため回盲部切除術を施行され，高分化腺癌，ss，ly0，v0，n（−），stage IIであった．2005年腹部CT検査にて膵尾部に径2cmの腫瘤が出現し，膵体尾部切除，脾合併切除術を施行した．膵腫瘤は中分化腺癌で盲腸癌と類似しており，また*p53*，*k-ras*遺伝子ともにpoint mutationが一致し，盲腸癌の膵転移と診断された．

索引用語：転移性膵腫瘍，大腸癌膵転移，切除例，鑑別，遺伝子解析

はじめに

転移性膵腫瘍の切除例は少なく，報告例の多くは腎細胞癌の膵転移症例であり，大腸癌膵転移の切除例は極めてまれである．転移性膵癌と原発性膵管癌の鑑別は，画像上はもちろん，病理学的にも困難であることも多く，臨床経過と組織学的所見から総合的に判断するしかないと考えられていた[18]．今回われわれは，膵腫瘍と盲腸癌の遺伝子解析を行い，point mutationの一致を確認することにより，盲腸癌の膵転移であることを確認し得たので，本邦報告例を集積し文献的考察を加え報告する．

I　症　例

症例：64歳　女性．

主訴：なし．

既往歴：61歳　盲腸癌穿孔にて回盲部切除術高分化腺癌，ss，ly0，v0，n（−），stage II．

嗜好歴：飲酒；機会飲酒　喫煙；なし．

家族歴：兄　膵癌．

現病歴：2002年7月腹痛のため他院受診．盲腸癌穿孔と診断され，同日緊急回盲部切除術およびD3郭清術を施行された．術直前の血清CEA 5.5ng/ml，血清CA19-9 38.4u/mlであった．術中所見で肉眼的に後腹膜浸潤を認めたため，術後補助化学療法を2回施行されたが，その後通院を自己中断していた．2005年8月近医で血清CEA値上昇を指摘され，当院紹介受診．上部・下部消化管内視鏡検査所見上異常を認めず，腹部CT検査にて膵尾部に腫瘤を認めたため，精査加療目的に入院となった．

入院時現症：身長155cm　体重52kg（増減なし）血圧131/76mmHg　脈拍80/min（整）体温36.4℃．頸部，心肺に異常なし．表在リンパ節触知せず．腹部正中に手術瘢痕あり．腹部は平坦，軟．腫瘤触知せず．下肢浮腫なし．神経学的異常所見なし．

入院時検査所見（Table 1）：末梢血液，生化学所見は異常を認めず．血清CEA　21.9ng/mlと高値の他は，血清CA19-9 19.6u/ml，DUPAN-2 58 U/mlと正常範囲内であった．

腹部造影CT（Figure 1）：膵尾部に約2cmの辺縁不整で内部がlow densityの腫瘤を認めた．

内視鏡的逆行性膵管造影（Figure 2）：主膵管が膵体部から二股に分かれるanomalyを認め

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Table 1. 入院時検査所見

Hematology		Blood Chemistry	
WBC	6000 /μl	TP	7.8 g/dl
Neu.	55.2 %	Alb	4.6 g/dl
Lym.	38.9 %	AST	33 U/l
Mono.	3.7 %	ALT	36 U/l
Eo.	1.7 %	LDH	204 U/l
Baso.	0.5 %	ALP	138 U/l
RBC	420 /μl	γ-GTP	44 U/l
Hb	12.6 g/dl	Amy	80 U/l
Plt	24.9 /μl	elastase 1	400 ng/dl
		Cr	0.67 mg/dl
Coagulation		BUN	9.8 mg/dl
PT	11.3 sec	Na	139 mEq/l
	88 %	K	4.1 mEq/l
APTT	26.3 sec	Cl	101 mEq/l
		Glu	100 mg/dl
Tumor Marker		CRP	0.06 mg/dl
CEA	21.9 ng/ml		
CA19-9	19.6 u/ml	Hormone	
DUPAN-2	58 U/ml	Insulin	4.09 μU/ml
		Glucagon	95 pg/ml
		Gastrin	380 pg/ml

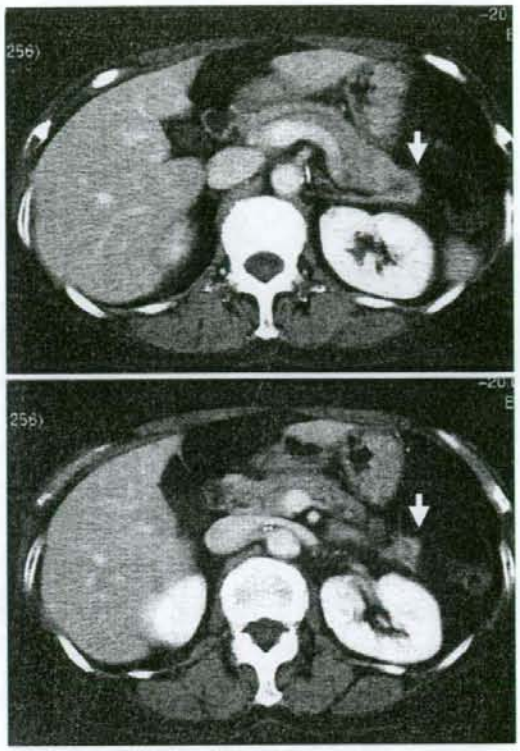

Figure 1. 腹部造影CT：膵尾部に径2cmの辺縁不整で内部がlow densityの腫瘤を認めた.

た．明らかな途絶は認めなかったが，尾側の2次膵管は拡張しており，頭側に圧排されていた．

FDG-PET（Figure 3）：膵尾部の病変に一致して，FDGの異常集積を認めた．口腔内左側にも集積を認めたが，頭頸部の精査にて異常を認めなかった．

2カ月後の腹部Dynamic CT（Figure 4）：膵尾部腫瘤は3×2cmに増大し，早期相でlow density，後期相でiso densityを示した．また辺縁不整で周囲に毛羽立ちを認め，周囲浸潤が疑われ，また左副腎への浸潤も疑われた．

また尾側のスライスでは，下膵リンパ節（#18）が1.5cmに腫大していた．

2カ月後の血清CEA値は29.0ng/mlと，初診時の血清CEA 21.9ng/mlと比べ，軽度上昇した．血清CA19-9値は31.3u/mlと正常範囲内であった．

鑑別診断として，原発性膵管癌と盲腸癌術後の膵転移が考えられた．ERCP上膵管に明らかな途絶が認められず，また血清CEA値の上昇が緩徐で，血清CA19-9値が正常であることからも，原発性膵管癌よりも盲腸癌の膵転移が疑われた．しかし画像検査上両者の鑑別は困難で，膵体尾部腫瘍，下膵リンパ節転移，左副腎転移の術前診断で，11月膵体尾部切除，脾合併切除術を施行した．

術中所見：腹膜播種は認めなかった．腫瘤は膵外発育しており，横行結腸に浸潤していたため，横行結腸も部分切除した．

切除標本（Figure 5）：膵尾部の腫瘤は40×35×20mmで，黄白色調のやや境界不明瞭な腫瘤であった．

病理組織学的所見（Figure 6）：膵腫瘍は円柱形細胞よりなる中分化腺癌で，壊死物質を含む篩状構築を主体としており，結腸癌の転移を疑わせる像であり，以前の盲腸癌標本と類似した組織像であった．腫瘍の上皮内進展やPanIN（pancreatic intraepithelial neoplasia）の所見を認めず，また腫瘍周囲の膵組織に脂肪性壊死の所見は見られず，積極的に膵原発を示唆する所見は見られず，

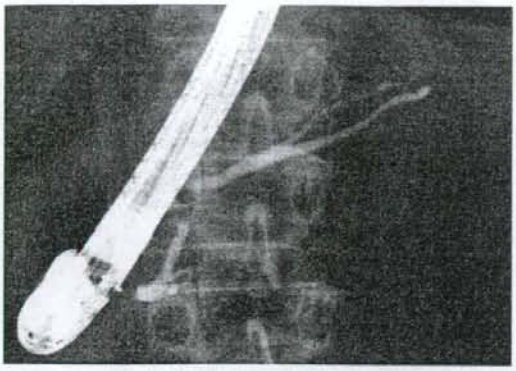

Figure 2. 内視鏡的逆行性膵管造影：主膵管が膵体部から二股に分かれるanomalyを認めた．明らかな途絶は認めなかったが，尾側の2次膵管は拡張しており，頭側に圧排されていた．

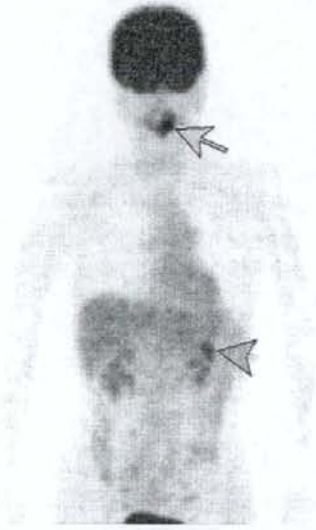

Figure 3. FDG-PET：膵尾部の病変に一致してFDGの異常集積（SUVmax = 4.6）を認めた．

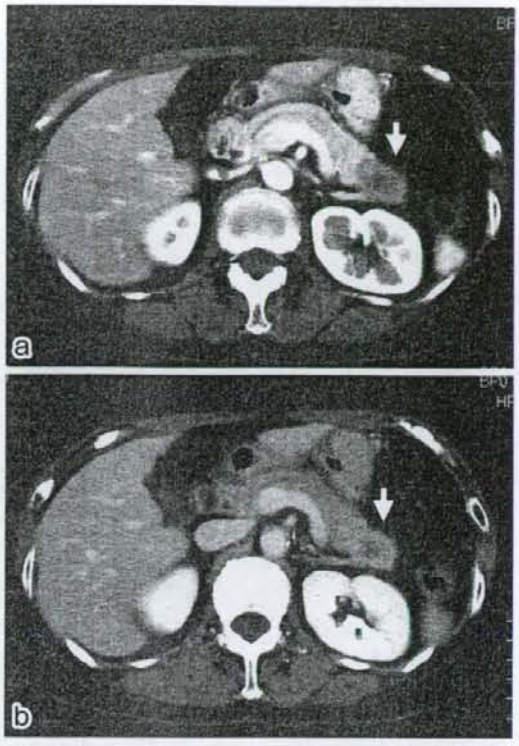

Figure 4. 2カ月後の腹部Dynamic CT　a：動脈相　b：平衡相．膵尾部腫瘤は3×2cmに増大し，早期相でlow density，後期相でiso densityを示した．辺縁不整で周囲に毛羽立ちを認め，また左副腎への転移も疑われた．

盲腸癌の膵転移と診断した．また下膵リンパ節転移（#18）と腸管傍リンパ節転移（#221），左副腎転移も認められた．

遺伝子解析（Figure 7）：盲腸癌と膵腫瘍のパラフィン切片よりDNAを抽出し，PCRで増幅しDirect Sequenceによりそれぞれの腫瘍に同じ変異が検出できるか，遺伝子変異解析を行った．

*p53*遺伝子は，いずれの腫瘍もcodon 171の1st letterのグアニンからチミンへの変異を検出し，コードするアミノ酸がGAG（グルタミン酸）からTAG（stop codon）に変化していた．*k-ras*遺伝子は，いずれの腫瘍もcodon 13の2nd letterのグアニンからアデニンへの変異を検出し，コードするアミノ酸がGGC（グリシン）からGAC（アスパラギン酸）に変化していた．*p53*遺伝子と*k-ras*遺伝子に認めたpoint mutationが一致していたこと，また一般に*k-ras*遺伝子変異は，大腸癌や原発性膵管癌の両者に見られるが，原発性膵管癌ではcodon 12の変異であるのに対し[20]，本症例ではcodon 13の変異であったことから，膵腫瘍は盲腸癌の転移と診断された．

術後経過：膵転移巣切除後，血清CEA値はすみやかに低下した．術後補助化学療法を勧めたが，患者が拒否．術後3カ月のCT検査で多発肺

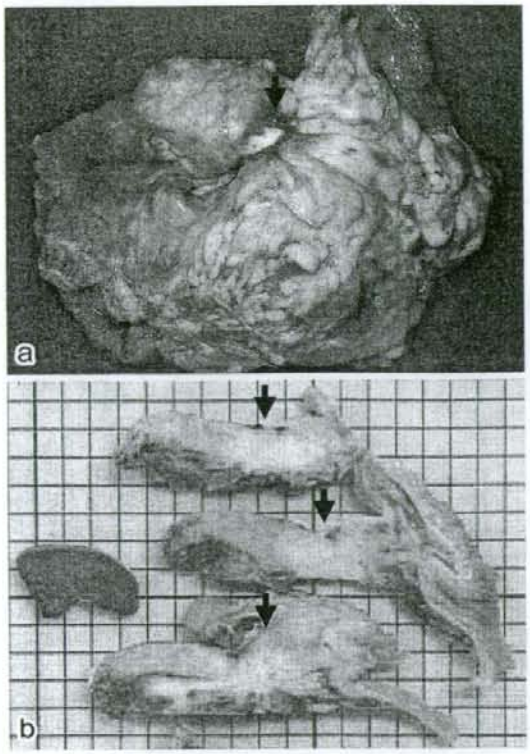

Figure 5. 切除標本の肉眼的所見　a：腫瘤は膵外発育しており，横行結腸に浸潤していた．　b：膵尾部の腫瘤は40×35×20mmで，黄白色調のやや境界不明瞭な腫瘤であった．

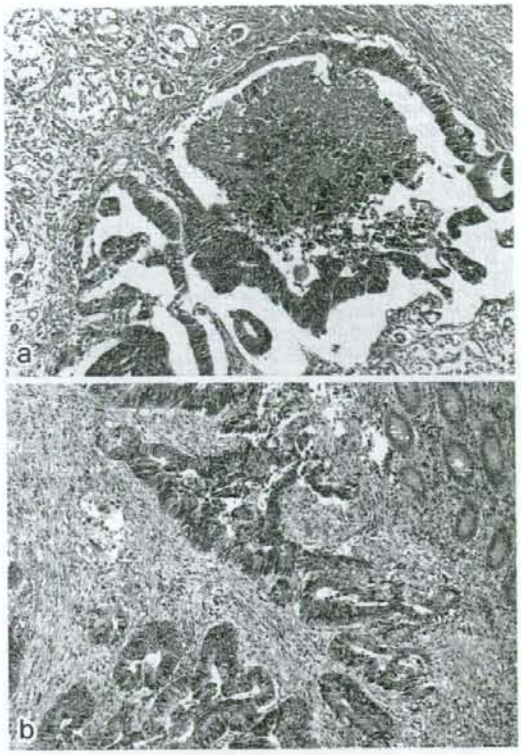

Figure 6. 病理組織学的所見　aに膵腫瘍，bに盲腸癌の組織像を示す（HE染色 ×40）．膵腫瘍は，円柱形細胞からなる中分化腺癌で，壊死物質を含む篩状構築を主体としており，組織構築や細胞形態が盲腸癌と類似していた．腫瘍周囲の膵組織に脂肪性壊死の所見も認められなかった．

転移が出現したため，化学療法を開始した．術後18カ月現在，外来通院中である．

II 考　察

小塚ら[1]によると，剖検例での悪性腫瘍の膵転移は21.7%（714例中154例）に認められたと報告され，決してまれな病態ではない．しかしその中には連続浸潤や腹膜播種によるものも含まれているため，孤立性の膵転移の正確な頻度は不明である．小塚らは，膵転移の最も頻度の高い原発巣は胃癌（37.0%　154例中57例）であると報告しているが，膵への転移形式は，胃癌からの連続浸潤および膵周囲リンパ節からの膵実質への侵入によるものが多いと述べている．大腸癌の膵転移は1.3%（154例中2例）であったと報告され，大腸癌が膵に転移することはまれである．

一方，膵転移の切除例の報告では，腎細胞癌からの転移が多い．大腸癌の膵転移が外科的切除の対象となる症例は非常にまれであり，1990年以降本邦での大腸癌膵転移の切除例の報告は，われわれが医学中央雑誌で検索し得た限りで自験例を含め，20例に過ぎなかった（Table 2）[2)~19)]．20例の年齢中央値65歳，男/女　9/11例，原発巣は直腸が11例と多く（直腸癌と結腸癌の重複例[10)]を除く），肺転移にて肺切除術後の経過中に，膵転移が発見される症例が12例と多かった．原発巣切除から膵転移切除までの期間中央値は40カ月で，大腸癌の比較的slow growingな特徴を反映してか，原発巣切除後長期経過後に膵転移が発見される傾向が認められた．

膵への転移経路として小塚ら[1]は，①近接臓器からの連続的波及，②膵周囲リンパ節からのリン

CK20+/CK7−の場合，原発巣が大腸である確率が78.41%，CK20+/CK7+の場合，胆嚢・膵臓である確率が74.85%であると報告している．

自験例において，盲腸癌と膵腫瘍の切除標本でCK20とCK7を用いて免疫染色を行ったところ，盲腸癌，膵腫瘍ともにCK20−/CK7−であった．Tot[21]によると，転移巣がCK20−/CK7−の場合，原発巣が大腸である確率は42.56%，胆嚢・膵臓である確率は11.38%であるとし，CK20−である場合は，原発巣の鑑別は困難であると結論付けている．

またLauら[22]は，Mucinの蛋白成分をコードする遺伝子である，MUC1，MUC2，MUC5ACに対するモノクローナル抗体による鑑別方法を報告している．原発性膵管癌ではMUC1（+），MUC2（−），MUC5AC（+）となることが多いのに対し，大腸癌はさまざまなパターンが見られ，一貫した表現型がない．そのため，原発性膵管癌の表現型以外になれば，大腸癌膵転移の可能性が高いと診断されるが，厳密ではない．

*p53*遺伝子変異には，いくつかのhot spotはあるものの，その変異はDNA結合領域に相当する部分を中心に幅広く変異が分布することから，その遺伝子変異が一致するか否かは，肝癌などを中心に，多発性病変のclonalityの判断などに使われてきた実績がある[23]．*k-ras*遺伝子変異は，大腸癌，膵癌のいずれにも高頻度で見られるため，その存在自体は両者の鑑別に役立たない．一方，文献的には，*k-ras*遺伝子のcodon 13のGGCがGACに変わるpoint mutationは，大腸癌の*k-ras*遺伝子変異のおよそ1/3に見られるが，膵癌78例の解析では全く見られなかったとされている[20][24][25]．したがって，大腸癌での*k-ras*遺伝子変異がcodon 13に存在した場合に限っては，膵原発腫瘍との鑑別に有力な1つの指標となる．今回の膵腫瘍で*p53*遺伝子変異と*k-ras*遺伝子codon 13の遺伝子変異の両方が一致していたということは，強く大腸癌の転移を示唆するものと判断される．

今回われわれは，*p53*遺伝子と*k-ras*遺伝子に認めたpoint mutationの一致を確認することによって，膵腫瘍が大腸癌の転移であることを確認し得た．大腸癌膵転移と原発性膵癌では術後の化学療法も異なり，また大腸癌膵転移の切除例では術後生存期間41カ月と長期生存例も報告されることから[11]，両者を厳密に鑑別することは重要であると思われた．

文　献

1) 小塚貞雄，坪根幹夫，滝　正：転移性膵癌の病理学的研究．胆と膵　11；1531-1535：1980
2) 湯浅典博，二村雄次，早川直和，他：直腸癌切除術後の転移性膵頭部癌の1切除例．日本消化器外科学会雑誌　23；1191-1195：1990
3) 横山伸二，棚田　稔，佐伯英行，他：切除可能であった直腸癌原発転移性膵癌の1例．癌の臨床　41；77-82：1995
4) 関　誠，堀　雅春，上野雅資，他：転移性膵癌の画像診断上の特徴．膵臓　10；437-446：1995
5) 久吉隆郎，天野純治，難波　亨，他：両側肺転移巣切除後に膵転移巣を切除しえた直腸癌の1例．日本臨床外科学会雑誌　56；1495：1995
6) 清水泰博，安井健三，森本剛史，他：大腸癌膵転移の1切除例．膵臓　13；316-321：1998
7) Inagaki H, Nakao A, Ando N, et al：A case of solitary metastatic pancreatic cancer from rectal carcinoma：a case report. Hepatogastroenterology 45；2413-2417：1998
8) 高倉範尚，志摩泰生，八木孝仁，他：大腸癌膵転移の1切除例と本邦報告例の検討．膵臓　14；513-519：1999
9) 石樽　清，川瀬義久，金住直人，他：切除しえた転移性膵腫瘍の3例．日本消化器外科学会雑誌　33；1686-1690：2000
10) 瀧沢泰彦，黒川　勝，持木　大，他：大腸癌膵転移の1切除例．日本消化器外科学会雑誌　34；132-136：2001
11) 鈴村　潔，山口晃弘，磯谷正敏，他：十二指腸と横行結腸に瘻孔を形成した大腸癌膵頭部転移の1切除例．日本消化器外科学会雑誌　34；1665-1669：2001
12) 広瀬邦弘，小林裕明，渡辺義人，他：大腸癌膵転移の1切除例．日本臨床外科学会雑誌　62；2587：2001
13) 菅原　元，山口晃弘，磯谷正敏，他：上行結腸癌異時性膵転移の1切除例．日本消化器外科学会雑誌　35；682-686：2002
14) 米山泰生，貝沼　修，谷口徹志，他：3回の再発切除後，切除しえた直腸癌膵転移の1例．日本消化器外科学会雑誌　35；214-218：2002
15) 岡田邦明，近藤征文，石津寛之，他：盲腸癌術

後膵・脾転移の1切除例．日本大腸肛門病学会雑誌　55；366-370：2002
16) 森　一成，佐々木政一，白井康嗣，他：肺・脳・膵転移巣を切除した直腸癌の1例．日本臨床外科学会雑誌　64；700-704：2003
17) 遠藤　健，松山秀樹，上野貴史，他：下行結腸切除後の転移性膵腫瘍の1例．日本臨床外科学会雑誌　65；2465-2467：2004
18) 亀田久仁郎，盛田知幸，野村直人，他：直腸癌術後5年目に膵転移をきたした1例．日本臨床外科学会雑誌　65；1929-1932：2004
19) 稲垣　均，松井隆則，小島　宏，他：直腸癌原発の孤立性転移性膵腫瘍の1切除例．日本消化器外科学会雑誌　37；692-696：2004
20) Bos JL：Ras oncogenes in human cancer：a review. Cancer Res 49；4682-4689：1989
21) Tot T：Adenocarcinomas metastatic to the liver：the value of cytokeratins 20 and 7 in the search for unknown primary tumors. Cancer 85；171-177：1999
22) Lau SK, Weiss LM, Chu PG：Differential expression of MUC1, MUC2, and MUC5AC in carcinomas of various sites：an immunohistochemical study. Am J Clin Pathol 122；61-69：2004
23) Matsumoto Y, Fujii H, Matsuda M, et al：Multicentric occurrence of hepatocellular carcinoma：diagnosis and clinical significance. J Hepatobiliary Pancreat Surg 8；435-440：2001
24) Almoguera C, Shibata D, Forrester K, et al：Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell 53；549-554：1988
25) Smit VT, Boot AJ, Smits AM, et al：KRAS codon 12 mutations occur very frequently in pancreatic adenocarcinomas. Nucleic Acids Res 16；7773-7782：1988

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A resected case of metastatic pancreatic cancer from cecal carcinoma

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A 64-year-old woman underwent an ileocecectomy in July 2002 for ruptured cecal carcinoma, which was a well-differentiated adenocarcinoma, stage II, ss, ly0, v0, n (−). In August 2005, abdominal CT revealed a tumor 20mm in diameter in the pancreatic tail, therefore, a distal pancreatectomy and splenectomy were performed. The pancreatic tumor resembled the moderately differentiated cecal adenocarcinoma, both having *p53* and *k-ras* point mutations in common, and it was diagnosed as a metastasis of the cecal carcinoma.

Advanced pancreatic cancer: the use of the apparent diffusion coefficient to predict response to chemotherapy

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ABSTRACT. The purpose of this study was to determine if the apparent diffusion coefficient (ADC) on diffusion-weighted MRI could predict the response of patients with advanced pancreatic cancer to chemotherapy. Diffusion-weighted MRI was performed in 63 consecutive patients with advanced pancreatic cancer who were subsequently treated with chemotherapy. The ADC values of the primary tumour with a middle *b*-value (400 s mm^{-2}) and a high *b*-value (1000 s mm^{-2}) were determined; cystic or necrotic components were avoided. The patients were classified into two groups: (i) those with progressive disease and (ii) those who were stable 3 months and 6 months after initial treatment. The groups were compared with respect to the ADC and clinical factors, including gender, age, Union International Contre le Cancer (UICC) stage, initial tumour size and chemotherapy agents used. Local tumour progression rates were evaluated using the Kaplan–Meier method. The middle *b*-value ADC of the pancreatic cancers ranged from 0.93–2.42 $\times 10^{-3}$ mm^2 s^{-1} (mean, 1.50 $\times 10^{-3}$ mm^2 s^{-1}), and the high *b*-value ADC ranged from 0.72–1.88 $\times 10^{-3}$ mm^2 s^{-1} (mean, 1.20 $\times 10^{-3}$ mm^2 s^{-1}). The high *b*-value ADC was significantly different between the progressive and stable groups at 3 months' and 6 months' follow-up ($p=0.03$ and $p=0.04$, respectively). The rate of tumour progression was significantly higher in those with a lower high *b*-value ADC than in those with a higher *b*-value ADC (median progression time, 140 days *vs* 182 days; $p=0.01$). In conclusion, a lower high *b*-value ADC in patients with advanced pancreatic cancer may be predictive of early progression in chemotherapy-treated patients.

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Pancreatic cancer is often diagnosed when the disease is in an advanced stage. Currently, radical surgery is the only curative therapy for pancreatic cancer; however, only 5–20% of patients present with potentially resectable disease [1–3]. Patients with inoperable pancreatic cancer have a limited survival rate, which averages only 3–4 months [4]. For locally advanced, unresectable and metastatic disease, palliative treatment with chemotherapy or chemoradiation is the only option. The results of chemotherapy for pancreatic cancer have generally been disappointing [5]. Recently, however, systemic chemotherapy with gemcitabine or gemcitabine plus platinum, or chemotherapy plus radiation, was reported to have some positive effects (1-year survival, 18–36%) [6–8]. Indications for chemotherapy should be carefully evaluated because of the relatively high risk of complications and side effects. Therefore, prognostic factors permitting the identification of patients who will benefit from such treatment would be clinically useful [9].

Diffusion-weighted MRI is a technique in which phase-defocusing and -refocusing gradients are used to evaluate the rate of microscopic water diffusion within tissue. Quantitative measurements of the diffusivity of water are described by the apparent diffusion coefficient (ADC). Investigators have reported the usefulness of ADC measurement for characterizing tumours [10–15]. The ability to measure the rate of water diffusion within tissue is important, as water diffusion is frequently altered in various disease processes and may reflect physiological and morphological characteristics, such as cell density and tissue viability [12, 16]. The results of several studies have suggested that the initial ADC of a tumour can serve as a predictive parameter for a patient's response to chemotherapy [12, 13, 15, 17]. Therefore, a method that enables pre-treatment imaging assessment of tumour malignancy and which would allow a more effective therapeutic strategy to improve prognosis would be of considerable clinical benefit. To the best of our knowledge, the predictive value of ADC in patients with advanced pancreatic cancer has not been reported. The purpose of this study was to evaluate the use of ADC to predict the response of patients with advanced pancreatic cancer to chemotherapy.

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Methods and materials

Patients

From July 2003 to August 2006, 63 consecutive patients (31 male, 32 female; mean age, 64.6 years; age range, 43–83 years) with advanced pancreatic cancer who had