With this imperative, we surveyed the actual cost of PC treatment especially with respect to the difference after the introduction of a new drug, GEM. To our knowledge, this is the first report of a cost analysis of PC in Japan.

PATIENTS AND METHODS

PATIENTS

Since the day of our hospital opening in July 1992, we have recorded all patients admitted to our division. This database has been updated generally three times a week at our morning conference. We obtained an invasive ductal PC patient list from the database, and surveyed all case records between 1 April 2000 and 30 March 2002 (April 2001 ± 1 year) in the list. The reason we chose this period was to investigate the impact of GEM, which has been introduced to Japanese hospitals since April 2001. We collected each patient's baseline data at the time of diagnosis and their treatment histories. These included gender, age, computed tomography (CT) stage, site of metastasis, performance status according to the Eastern Cooperative Oncology Group criteria, serum level of carcinoembryonic antigen and carbohydrate antigen (CA) 19-9, primary treatment modalities, treatment costs (calculated from patient receipts), and date and cause of death.

TREATMENT

According to the CT stage at presentation, patients with resectable disease underwent resection, and we did not perform any adjuvant therapies until recurrence after surgery. As for locally advanced disease, we performed a combination of intraoperative and external-beam radiotherapy with 5-FU before April 2001 (9). After April 2001, we performed hypofractionated external-beam radiotherapy followed by GEM chemotherapy in selected patients with locally advanced PC (10). We had performed single agent chemotherapy for metastatic or recurrent PC in general by using 5-FU before April 2001, and GEM thereafter (7). Until November 2000, combination therapy of hepatic arterial infusion of 5-FU and external-beam radiation for the primary tumor had been performed in selected patients with no metastases other than in the liver (11).

Patients received a detail explanation about the studies and gave written informed consent after approval of the protocols by the Institutional Review Board of the National Cancer Center.

TREATMENT COST

In Japan, upon joining an organization, the employees and the families of those employed by government offices, and the private sector and public organizations automatically join the health insurance program. People who are not members of the Health Insurance Union have been required to join the National Health Insurance program, which is operated by municipalities throughout the nation, since 1961. The costs for medical services are regulated by the government and are the same throughout Japan, and people can receive medical services with 20–30% of the medical costs as their payment, based on this social security system.

Treatment costs are calculated from patient receipts of our hospital. Other than the uniform treatment costs regulated by the government, the costs in the current study included various actual expenses, such as private room charges, the cost of daily meals during hospitalization and medical certificates for private health insurance. Namely, the total costs meant total payments to the hospital for patients who did not join the Japanese health insurance system.

In the current study, treatment costs were described in terms of United States dollars ($) with the exchange rate at the time of data fixation, 30 June 2004, i.e. $1 = 109 Japanese yen (¥). For example, the cost of pancreaticoduodenectomy is $4825 (¥526 000), and 1 gram of GEM is $255 (¥27 825), in Japan.

ANALYSIS AND STATISTICS

We surveyed the treatment costs and survival data of patients, and examined the relationship among patients' characteristics, treatment costs and survival time. Total treatment cost from the first hospitalization to the death or 30 June 2004 (date of the data fixation), including all costs of every hospital visits and the last hospitalization for terminal care, was defined as the total treatment cost over a lifetime (TCL) in the current study.

Overall survival was measured from the first day of treatment to the date of death or last contact. All patients were censored on 30 June 2004, 14 months after treatment of the last patient. Survival curves were calculated by the Kaplan–Meier method. Differences in survival among subgroups classified by each factor were evaluated by log-rank tests.

Since the treatment costs were not shown to have a normal distribution, the Mann–Whitney test was used to compare the overall differences of them among the subgroups. Frequency analysis was performed with Fisher's exact test for 2×2 tables, and with the χ^2-test for 3×2 tables.

All analyses were performed using the statistical software SPSS 11.0J for Windows. Statistical significance was defined as a two-sided P-value of 0.05 or less.

RESULTS

A total of 113 PC patients were admitted during the 2 years survey. Among the 113 patients, the TCL was calculated in 54 patients, i.e. 49 who died in our hospital and 5 who were alive until 30 June 2004. The TCL was not available in the remaining 59, mainly because they went to other hospitals for terminal care. There was no difference in their backgrounds and the survival between the former 54 and the latter 59 (Table 1) other than the pretreatment CA 19-9 level, which was higher in the former 54.

In the 54 patients, TCL ranged from $4586 to $89 681 and the quartiles at 25, 50 and 75% were $24 046, $35 351 and $48 119, respectively. According to the CT stage, the median of TCL and survival time were $43 865 and 26.5 months for the resectable, $29 255 and 10.0 months for the locally

Table 1. Characteristics of 113 patients who were admitted between 1 April 2000 and 30 March 2002

Total treatment cost over a lifetime	Available (n = 54)	Not available (n = 59)	P-value
Gender			
Man	36	35	0.442†
Woman	18	24	
Age			
Median	59.5	65	0.076‡
CT stage			
Resectable	14	15	0.713§
Locally advanced	21	27	
Metastatic	19	17	
Performance status			
0 or 1	50	55	1.000†
2 or 3	4	4	
Location of the primary tumor			
Head	25	34	0.261†
Body-tail	29	25	
CEA (ng/ml)¶			
Median	7.4	6.8	0.496‡
CA 19-9 (U/ml)#			
Median	510.5	108	0.038‡
Primary treatment			
Surgery	14	15	0.335§
Chemoradiotherapy	20	29	
Chemotherapy or supportive care	20	15	
Survival time (month)			
Median	8.6	8.7	0.603*
95% Confidence interval	6.3–10.9	7.1–10.3	

*Log-rank test; †Fisher's exact test; ‡Mann–Whitney test; §χ^2-test; ¶carcinoembryonic antigen; #carbohydrate antigen 19-9.

Table 2. Characteristics of 54 patients who were completely followed in our hospital

Date of the first admission	Before April 2001 (n = 26)	After April 2001 (n = 28)	P-value
Gender			
Man	17	19	1.000†
Woman	9	9	
Age			
Median	59.5	65	0.206‡
CT stage			
Resectable	9	5	0.017§
Locally advanced	5	16	
Metastatic	12	7	
Performance status			
0 or 1	24	26	1.000†
2 or 3	2	2	
Location of the primary tumor			
Head	11	14	0.597†
Body-tail	15	14	
CEA (ng/ml)			
Median	4.75	9.65	0.063‡
CA 19-9 (U/ml)#			
Median	419	585	0.441‡
Primary treatment			
Surgery	9	5	0.107§
Chemoradiotherapy	11	9	
Chemotherapy or supportive care	6	14	
Gemcitabine chemotherapy over a lifetime			
Present	0	19	0.000†
Absent	26	9	

†Fisher's exact test; ‡Mann–Whitney test; §χ^2-test; ¶carcinoembryonic antigen; #carbohydrate antigen 19-9.

advanced, and \$30 676 and 4.8 months for the metastatic, respectively.

Differences After April 2001

Among the 54 patients available for TCL analysis, 26 were admitted before April 2001 (Group A) and the remaining 28 were admitted thereafter (Group B). The patients' characteristics in each group are shown in Table 2. The frequencies of locally advanced disease and gemcitabine chemotherapy were higher in Group B. As for the patients with locally advanced disease, GEM chemotherapy have been an alternative treatment choice in our hospital since April 2001. Accordingly, there was no significant difference between Groups A and B in the other baseline background factors, including primary treatment.

Table 3 shows several costs and survival times in Groups A and B. The total cost for anticancer agents was significantly higher in Group B than in Group A, whereas there were no significant differences as for overall survival and TCL between the groups. Among the cost of anticancer agents, a fraction of that in the outpatient clinic was the main cause that made the cost in Group B significantly higher than in Group A. Although there was no significant difference in hospital stay in the first admission between the two groups, the cost for the first admission in Group A tended to be high compared to that in Group B. The cost for the first admission included various imaging tests (Table 4). An average number of imaging tests per patient in the first admission was 5.0 in Group A and 3.9 in Group B. In 40 patients with locally advanced or metastatic disease, the median cost and hospital stay in the first admission in Group B (\$11 493 and 37 days, respectively) were lower than those in Group A (\$22 218 and 59 days,

Table 3. Treatment costs and survival of 26 patients who were admitted before gemcitabine introduction (April 2001) and 28 admitted thereafter

Date of the first admission	Before April 2001 (n = 26)	After April 2001 (n = 28)	P-value
Survival time (month)			
Median	7.4	8.8	0.952†
95% Confidence interval	5.5–9.3	4.5–13.2	
Total treatment cost over a lifetime ($)			
Minimum	10 028	4586	0.604‡
25 percentile	27 284	23 768	
Median	35 744	35 226	
75 percentile	47 989	50 680	
Maximum	89 681	61 400	
Total treatment cost/survival time ($/month)			
Minimum	895	331	0.307‡
25 percentile	2016	1654	
Median	3828	3182	
75 percentile	6957	4912	
Maximum	12 366	31 296	
Total cost for anticancer agents ($)			
Minimum	0	0	0.046‡
25 percentile	1603	3326	
Median	3136	5728	
75 percentile	4974	10 163	
Maximum	19 770	43 569	
Percentage of anticancer agents in total cost			
Minimum	0%	0%	0.022‡
25 percentile	5.4%	8.5%	
Median	9.7%	15.5%	
75 percentile	13.7%	25.4%	
Maximum	38.7%	80.3%	
Cost for anticancer agents in admission ($)			
Minimum	0	0	0.216‡
25 percentile	1334	1175	
Median	2596	1951	
75 percentile	4111	3174	
Maximum	11 314	10 759	
Cost for anticancer agents in outpatient clinic ($)			
Minimum	0	0	0.016‡
25 percentile	0	0	
Median	26	2898	
75 percentile	365	6005	
Maximum	14 190	42 426	
Hospital stay in the first admission (days)			
Minimum	10	5	0.232‡
25 percentile	38	25	
Median	59	46	
75 percentile	74	65	
Maximum	134	140	
Cost for the first admission ($)			
Minimum	369	1882	0.097‡
25 percentile	11 379	8663	
Median	22 313	13 217	
75 percentile	29 480	22 135	
Maximum	47 544	47 636	

†Log-rank test; ‡Mann–Whitney test.

Table 4. The frequency of various imaging tests in the first admission before and after introduction of gemcitabine

Date of the first admission	Before April 2001 (n = 26) (%)	After April 2001 (n = 28) (%)
Abdominal ultrasonography	100	100
Computed tomography	100	100
Magnetic resonance imaging	96	100
Upper abdominal fiberscopy	69	29
Colon fiberscopy	12	7
Endoscopic retrograde cholangiopancreatography	54	11
Endoscopic ultrasonography	19	4
Angiography	54	25
Positron emission tomography	23	14

respectively), although the differences were not statistically significant (P = 0.055 and P = 0.156, respectively).

DISCUSSION

As known from previous reports (12,13), the disease stages are correlated with PC treatment costs in Japan. When compared to the total treatment cost of metastatic disease, that of locally advanced and resectable disease was 1.2- to 1.6-fold and 1.6- to 1.9-fold higher, respectively (Table 5). The relative relationship between disease stage and treatment cost was at almost the same proportion in the three countries. As for the absolute treatment costs, however, there were relatively large differences among the three. The average cost of PC treatment in Japan was about twice of that in Sweden, and three quarters of that in the United States. This is probably due to differences of social security and health insurance systems in each country.

Other than the survey of actual PC treatment costs in Japan, economic and medical differences after the introduction of GEM were our main interest in the current study. Before conducting the current study, we hypothesized that the TCL had gone up since the introduction of the expensive new drug, GEM.

However, the TCL did not increase as a result of GEM introduction. Possible reasons were simplification in pretreatment imaging examinations, shorter hospitalization and an early outpatient-based treatment. The frequency of imaging tests before treatment decreased except for ultrasonography, CT and magnetic resonance imaging after the GEM introduction. Because we were aware that the three imaging tests were necessary and sufficient for staging evaluation after the GEM introduction, other invasive examinations, such as endoscopic retrograde cholangiopancreatography or angiography, were optional, especially in advanced cases. Moreover, hospitalization becomes shorter because GEM chemotherapy is feasible for an outpatient treatment. Accordingly, total costs for anticancer agents increased after GEM, especially in the outpatient clinic fraction.

Table 5. International cost comparison of pancreatic cancer treatment

Average	Resectable disease	Locally advanced disease	Metastatic disease	Country (reference)
$19 499	$27 161	$22 671	$14 277	Sweden (11)
$35 892	$46 250	$34 626	$29 658	Japan (current study)
$48 803	$65 335	$54 717	$35 809	United States (12)

The exchange rate is set to the average in 2000, i.e. $1 = €1.029 = ¥106.

To reduce the costs of cancer treatment, therefore, simplification in examinations and shortening of hospitalization may be effective. However, those efforts may have an apparent limitation, because new expensive agents, such as bevacizumab, will increase the PC chemotherapy costs in the near future, as seen in colorectal cancer chemotherapy costs at present.

In summary, the total cost of PC treatment correlated well with disease staging, and there was no international difference in its proportion. The total costs after GEM did not tend to be high in our hospital, probably because of the simplification in examinations and short hospitalization. We believe it will be necessary to promote cost analysis and to make an effort to reduce treatment costs as well as to develop new effective and expensive agents, because health care resources are becoming scarce in many countries.

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GASTROENTEROLOGY

Impact of gemcitabine on the treatment of metastatic pancreatic cancer

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Abstract

Background and Aim: A previous randomized trial showed gemcitabine was superior to 5-fluorouracil in overall patient survival. However, the incremental improvement in survival was minimal. It is 2.5 years since gemcitabine has become available for the treatment of pancreatic cancer in clinical practice in Japan. The current study was conducted to examine whether treatment outcomes have changed since the introduction of gemcitabine therapy.

Methods: Ninety-one consecutive patients with metastatic pancreatic cancer treated with systemic chemotherapy at the National Cancer Center Hospital East were surveyed. Patients admitted before April 2001 received 5-fluorouracil, and those admitted subsequently received gemcitabine. The patients were divided into the gemcitabine group ($n = 50$) and the non-gemcitabine group ($n = 41$), and these groups were compared for five outcomes, objective response rate, non-progressive disease rate, carbohydrate antigen (CA)19-9 response rate, actual survival time, and difference between estimated and observed survivals. The estimated survival time was determined using the prognostic index reported in the previous study.

Results: Except for the objective response rate, the four other outcomes in the gemcitabine group were significantly superior to those in the non-gemcitabine group. The frequency of non-progressive disease, CA19-9 response, and favorable prognosis compared with the estimated survival, were 58%, 22%, and 60%, respectively, in the gemcitabine group, and 22%, 6%, 30%, respectively, in the non-gemcitabine group. The median survival time in the gemcitabine and non-gemcitabine group was 5.73 and 2.87 months, respectively.

Conclusion: It is suggested that there was a definite improvement in pancreatic cancer treatment after gemcitabine was introduced.

Key words: carbohydrate antigen 19-9, chemotherapy, gemcitabine, pancreatic neoplasm, prognosis.

INTRODUCTION

Pancreatic cancer (PC) is the fifth leading cause of cancer deaths in Japan, and in 1999, there were 18 654 deaths from this malignancy.[1] Although surgical resection is the only curative modality for this malignancy, most patients have unresectable disease at the time of diagnosis. For a long time, chemotherapy for PC had only limited value in clinical practice, and there had been no regimen superior to 5-fluorouracil (5-FU) therapy alone.[2,3] In the late 1990s, however, gemcitabine (GEM) was introduced as a PC chemotherapy. Gemcitabine therapy showed significantly better results in the clinical benefit response rates and survival in the randomized trial compared with 5-FU.[4,5] Accordingly, GEM has been accepted as first-line chemotherapy for advanced PC in many countries. In Japan, GEM was approved by the Government after a phase 1 trial in Japanese patients[6] and was introduced into hospitals as a practical therapy in April 2000.

In this retrospective study, we surveyed all metastatic PC patients treated with systemic chemotherapy at the

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National Cancer Center Hospital East, to examine whether treatment outcomes have changed since the introduction of GEM therapy.

METHODS

Patients

Between July 1992 and April 2003, 91 consecutive patients with metastatic PC received chemotherapy in the Division of Hepatobiliary and Pancreatic Medical Oncology at the National Cancer Center Hospital East. Among them, 74 received single-agent chemotherapy (5-FU or GEM). The remaining 17 received chemotherapy as part of multicenter clinical trials: phase 2 studies of cisplatin and 5-FU[7] in 10, docetaxel[8] in three, and irinotecan in four.

Histological or cytological confirmation of exocrine PC was obtained from all patients before chemotherapy. In addition, clinical trial patients were required to meet the eligibility criteria determined by each protocol. Briefly, they included: no previous chemotherapy; good performance status (PS); adequate bone marrow, renal, and hepatic function; no serious complications; and receipt of written informed consent.

Chemotherapy

In clinical practice, patients admitted before April 2001 received 5-FU, and those admitted subsequently received GEM. The 5-FU 600 mg/m^2 was administered over 2 h once weekly, or GEM 1000 mg/m^2 was administered over 30 min weekly, three times every 4 weeks. In clinical trials, details of the regimen are shown in the references. In brief: 5-FU 500 mg/m^2 for 5 days and cisplatin 80 mg/m^2 on the first day every 4 weeks;[7] docetaxel 60 mg/m^2 every 3–4 weeks;[8] and irinotecan 100 mg/m^2 weekly, three times every 4 weeks. In each regimen, chemotherapy was continued until evidence of disease progression. Follow-up computed tomography (CT) was performed after every course to objectively assess tumor response according to World Health Organization criteria.[9]

Data collection

We surveyed all case records of the 91 patients and collected each patient's baseline data including potential prognostic value[10–12] and their treatment outcomes. These were: regimen of chemotherapy; age; gender; PS according to the Eastern Cooperative Oncology Group criteria; presence or absence of prior surgery; location of the primary tumor; site of distant metastasis; presence or absence of measurable lesion; serum levels of carcinoembryonic antigen (CEA)[10] and C-reactive protein (CRP)[11] before chemotherapy; serial serum levels of carbohydrate antigen 19–9 (CA19-9) before and after chemotherapy;[12] serial CT reports; the first day of chemotherapy; and the date of death or last contact.

Treatment responses were evaluated using CT and serial change of serum CA19-9.

The CT response criteria were as follows: a complete response (CR) required the disappearance of all measurable disease for more than 28 days, during which time no new lesions could appear; a partial response (PR) required reduction of greater than 50% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions lasting for more than 28 days, during which time no new lesions could appear; stable disease (SD) required reduction of less than 50% or an increase of less than 25% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions lasting for more than 28 days, during which time no new lesions could appear; and progressive disease (PD) was defined as an increase of more than 25% in the sum of the products of the greatest perpendicular dimensions of all measurable lesions or the development of any new lesions. In the current study, we evaluated the primary pancreatic tumor by CT, but did not regard it as the measurable lesion.

When patients had an abnormal serum CA19-9 level of 100 U/mL or greater before chemotherapy, we defined a CA19-9 responder as a patient whose serum CA19-9 level was reduced by greater than 50% within 2 months after the initiation of chemotherapy.[12]

Statistics and analysis

We divided patients into the GEM or non-GEM group according to their regimen, and compared patient backgrounds, treatment responses and survival time between the two groups.

The frequency of each variable of the patient's background was analyzed using the chi-squared test. Continuous variables were grouped by a convenient value near the median value (age) or potential prognostic values (CEA, CA19-9, and CRP).

In the current study, an objective response was reported as a rate of patients with CR + PR divided by all patients in each group. The non-PD rate was also reported as a rate of patients with CR + PR + SD divided by all patients in each group. The CA19-9 response rate was defined as responders divided by all patients with a CA19-9 level of 100 U/mL or greater before chemotherapy in each group. The frequency of each response was analyzed by the chi-squared test.

Overall survival was measured from the first day of chemotherapy to the day of death or the last day of follow up. Survival curves were calculated by the Kaplan–Meier method.[13] Differences in survival were evaluated by log–rank tests. We calculated the prognostic index in each patient using to an equation reported previously.[12] The equation for the index was as follows: $1.144 \times$ (0 for CRP less than 5 mg/dL and 1 for CRP of 5 mg/dL or greater) + $1.029 \times$ (0 for a PS of 0–1 and 1 for a PS of 2–3) + $0.538 \times$ (0 for CA19-9 <10 000 U/mL and 1 for CA19-9 of ≥10 000 U/mL). The pretreatment CA19-9 was not available in one patient so calculations were performed for the remaining 90. We estimated each patient's median survival time in months using this

index: 5.2, 2.6, and 1.4 in the good, intermediate, and poor prognosis groups, respectively, and compared this with his or her observed survival time. When an observed survival time was longer than the estimated one, we regarded it as a favorable prognosis. Censored cases within the estimated median survival time were not regarded as evaluable cases. The frequency of patients with favorable prognosis in each group was analyzed by the chi-squared test.

All analyses were performed using the statistical software SPSS 11.0 J for Windows. Statistical significance was defined as a two-sided *P*-value of 0.05 or less.

RESULTS

Among the 91 patients, 41 were from the non-GEM group and 50 were from the GEM group. Patient characteristics in each group were very similar to each other and are shown in Table 1. Of the nine patients with no measurable lesion, four had ascites with malignant cells other than the primary pancreatic tumor. The remaining five had minute liver metastasis (two patients) and/or peritoneal dissemination (four patients) at the time of laparotomy. Five had recurrent cancer after resection of the primary tumor with curative intent. Of these five, four had distant metastasis with no evidence of local recurrence.

Treatment responses are summarized in Table 2. There was no significant difference in the objective response between the two groups. The non-PD rate in the GEM group (58%) was significantly higher ($P = 0.011$) than that in the non-GEM group (22%). The CA19-9 response rate was evaluated in 72 patients, because pretreatment CA19-9 was not 100 U/mL or greater in the remaining 19. Serial CA19-9 changes after chemotherapy was not available in 17 patients mainly due to their early deterioration. These 17 patients were regarded as non-responders. The CA19-9 response rate in the GEM group was also significantly higher than that in non-GEM group.

Of the 91 patients studied, 81 died and 10 were still alive at the time of writing (December 2003). Six patients (7%) were lost to follow up after observation with a median of 4.3 months. Median survival time in

Table 1 Baseline characteristics of patients in the gemcitabine (GEM) and non-GEM groups

	Non-GEM ($n = 41$)	GEM ($n = 50$)	*P*-value
Age (years)			
Median (range)	60 (28–76)	59 (34–78)	
>60	21 (51%)	29 (58%)	0.534
Sex			
Male	27 (66%)	34 (68%)	1.000
Female	14	16	
Primary tumor			
Head	14 (34%)	10 (20%)	0.153
Body-tail	25	37	
Post-resection	2	3	
Eastern Cooperative Oncology Group performance status			
0, 1	36 (88%)	45 (90%)	0.750
2, 3	5	5	
Site of metastasis			
Liver	36 (88%)	42 (84%)	0.766
Peritoneum	5	10	
Lymph node	5	3	
Lung	5	2	
Bone	1	1	
Soft tissue	1	1	
Measurable lesion			
Present	39 (95%)	43 (86%)	0.177
Absent	2	7	
Carcinoembryonic antigen (ng/mL)			
Median (range)	7.9 (1.5–9082)	12 (1.5–238)	
>10 ng/mL	17 (41%)	32 (64%)	0.056
Carbohydrate antigen 19-9 (U/mL)			
Median (range)	2046 (1–314 070)	1737 (1–38 712)	
>10 000 U/mL	9 (22%)	7 (14%)	0.406
C-reactive protein (mg/dL)			
Median (range)	0.8 (0–13.2)	0.7 (0–29.2)	
>5 mg/dL	5 (12%)	9 (18%)	0.564

Table 2 Treatment responses of patients in the gemcitabine (GEM) and non-GEM groups

	Non-GEM ($n = 41$)	GEM ($n = 50$)	P value
Computed tomography response			
Partial response	1 (2%)	5 (10%)	0.217
Stable disease	8	24	
Progressive disease	18	8	
Not evaluable	14	13	
Serial carbohydrate antigen 19-9			
Pretreatment level >100 U/mL	33	39	
Responder	2 (6%)	11 (22%)	0.029
Non-responder	31	28	

GEM group was 5.73 months with 95% confidence interval (CI) between 3.95 and 7.51. It was significantly longer ($P = 0.0004$) than that in non-GEM group (median; 2.87, 95% CI; 1.72–4.02) (Fig. 1).

According to the calculating prognostic index,[12] we divided the 90 patients into three groups: good ($n = 61$), intermediate ($n = 24$), and poor prognosis groups ($n = 5$). Survival curves in the three prognostic groups showed the index had a good validity ($P = 0.0069$). Because there were three censored cases within the estimated median survival time, we compared each patient's estimated and observed survival time in the remaining 87 (Table 3). Of 47 patients in the GEM group, 28 (60%) showed favorable prognosis, and the frequency was significantly higher than that (12 of 40 patients, 30%) in the non-GEM group ($P = 0.009$).

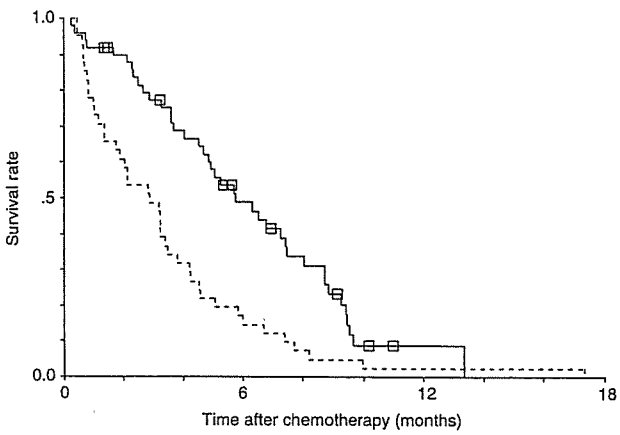

Figure 1 Survival curves of patients in the (—) gemcitabine (GEM) group ($n = 50$) and the (---) non-GEM group ($n = 41$). (□) Censored cases.

DISCUSSION

Gemcitabine was shown to be superior to 5-FU both in the clinical benefit response and in overall patient survival.[5] However, the incremental improvement in overall survival seen with GEM was minimal. In Japan, GEM had been available for the treatment of PC in clinical practice 2.5 years. In the current study, we surveyed PC treatment outcomes to focus on the change before and after the introduction of GEM.

We studied five outcomes: the objective response rate, non-PD rate, CA19-9 response rate, actual survival time, and difference between estimated and observed survivals. The advantage of GEM was demonstrated for four of these outcomes, but was not demonstrated for the objective response rate. The objective response of 8% in the current study was similar to previous findings of GEM monotherapy.[4,5] Despite this poor activity for tumor shrinkage, we favored GEM because of its clinical benefit and manageable toxicity, which were difficult to evaluate in a retrospective analysis. There was a definite antitumor effect in the GEM group, which was indicated by non-PD and CA19-9 response rates, but it was not strong enough to cause evident tumor shrinkage.

We had to make survival comparison analyses carefully because various biases could not be excluded completely in a retrospective study. Although this single institution study warranted all patients to have the same initial staging examinations, monitoring, and approach to supportive care, historical changes of treatment strategy might cause some biases. At first, we compared survival of all (locally advanced and metastatic) patients who received chemotherapy alone. Before the introduction of GEM, we had treated locally advanced patients by intraoperative radiotherapy trials.[14,15] These trials revealed that occult metastases were found in one-third of the patients with CT-staging locally advanced disease at the time of laparotomy. We thereafter selected only good candidates for chemoradiotherapy, whereas 5-FU based concurrent chemoradiotherapy was the standard treatment for locally advanced PC.[16–18] As a result, we treated more CT-staging locally advanced patients with GEM compared with non-GEM chemotherapy. Accordingly, we focused on metastatic PC patients in the current final analysis. The introduction of the prognostic model proposed previously[12] was also used to avoid the biases. The advantage of GEM was significant in the two comparisons. At the initiation of analysis we expected that there would be a subtle difference because the survival advantage of GEM over 5-FU was reported to be only 1 month in a previous randomized trial.[5]

Table 3 Difference between estimated and observed survival time of patients in the gemcitabine (GEM) and non-GEM groups

Prognostic index	Estimated survival time (months)	Non-GEM ($n = 40$) Observed survival time <EST	Non-GEM ($n = 40$) Observed survival time >EST	GEM ($n = 47$) Observed survival time <EST	GEM ($n = 47$) Observed survival time >EST
0	5.2	17	7	15	20
0.538	2.6	4	3	1	2
1.029		2	1	0	0
1.144		3	1	1	2
1.567		1	0	0	1
1.682		0	0	1	0
2.173	1.4	0	0	1	2
2.711		1	0	0	1
		28	12 (30%)	19	28 (60%)

EST, estimated survival time.

There is an evident limitation in the comparison of treatments in such a retrospective study. Various historical changes, such as technical improvement of diagnostic modalities, staging methods, supportive treatments and so on, usually result in better patient survival in addition to anticancer treatment; however, we observed some good responses since the introduction of GEM treatment. From the current analysis, we suggest that there was a definitive improvement of PC treatment following the introduction GEM.

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Original Article

Prognostic Factors in Patients with Gemcitabine-Refractory Pancreatic Cancer

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Objective: The purpose of this study was to identify prognostic factors in patients with gemcitabine-refractory pancreatic cancer and to determine criteria for selecting candidates for second-line treatment.
Methods: The records of 74 patients who were treated with gemcitabine (GEM) and followed up until disease progression were reviewed retrospectively. Sixteen clinical variables at the time of disease progression after GEM chemotherapy were chosen for analysis in this study. Univariate and multivariate analyses were conducted to identify prognostic factors associated with survival.
Results: At the time of analysis, 71 patients had died because of tumor progression. The overall median survival time was 5.1 months after first-line chemotherapy with GEM was initiated. Median survival time after disease progression was 2.0 months. Three factors, performance status, peritoneal dissemination and C-reactive protein level, were identified as independent prognostic factors in multivariate analysis. Median survival time in the good prognosis group (patients with performance status 0 or 1, no peritoneal dissemination and C-reactive protein <5.0 mg/dl) was 3.4 months.
Conclusions: Performance status, serum level of C-reactive protein and peritoneal dissemination were identified as important prognostic factors in patients with GEM-refractory pancreatic cancer. These factors should be considered in determining the treatment following first-line chemotherapy in patients with advanced pancreatic cancer.

Key words: pancreatic neoplasms – gemcitabine – prognosis – salvage therapy

INTRODUCTION

Pancreatic cancer (PC) is the fifth leading cause of cancer deaths in Japan, with approximately 19 000 patients dying from this disease every year (1). Unfortunately, the majority of patients present with the disease already in an unresectable state at the time of diagnosis, due to locally advanced or metastatic spread. In recent years, gemcitabine (GEM), which is associated with more clinical benefits and better survival compared with 5-fluorouracil, has been widely used as a standard first-line chemotherapy agent for unresectable PC (2). Molecular targeted agents have also been developed for pancreatic cancer. It has been demonstrated that erlotinib combined with GEM improve survival (3). Moreover, another epidermal growth factor receptor (EGFR)-inhibitor, namely cetuximab, has been tried in phase II study (4). The efficacy of GEM is still unsatisfactory, and therefore the prognosis for patients remains poor, with a median survival time (MST) of around 6 months. In order to improve survival, it is necessary to develop not only a more effective first-line regimen, but also effective agents for second-line chemotherapy.

Generally PC progresses rapidly, and a patient's general condition often deteriorates too rapidly to perform any additional chemotherapy after failure of first-line treatment with GEM. Some patients may suffer from more serious adverse effects during second-line chemotherapy compared

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with first-line chemotherapy. Therefore, second-line chemotherapy is difficult to establish and should be initiated with more care than first-line. It is necessary to clarify the natural prognosis for patients with GEM-refractory PC in order to appropriately treat patients with either additional chemotherapy or best supportive care. Furthermore, identification of prognostic factors after GEM failure can help conducting clinical trials for promising second-line chemotherapy agents in patients with advanced PC. Thus, in the present study we investigated survival and prognostic factors in GEM-refractory PC patients and clarified criteria for selecting appropriate candidates for second-line therapy.

PATIENTS AND METHODS

Patients

In Japan, GEM was approved for the treatment of PC by the Ministry of Health, Labor, and Welfare in April 2001. GEM-refractory pancreatic cancer was defined as PC that progresses after chemotherapy with GEM. A total of 210 patients with histologically or cytologically confirmed unresectable PC who had received no other treatment were admitted to our hospital between April 2001 and March 2004. Forty patients were treated with chemoradiotherapy, 33 received palliative treatment and 137 were treated with systemic chemotherapy. Of the 137 patients who received systemic chemotherapy, 100 patients were treated with GEM alone, and 37 were treated with other regimens as part of clinical trials. Twenty-six of the 100 patients treated with GEM alone were excluded from analysis in this study because they were transferred to other hospitals and could not be followed up until disease progression. Data from the remaining 74 patients were analyzed in the current study. These patients were consistent with the criteria of GEM-refractory pancreatic cancer.

Treatment and Assessment of Efficacy

GEM as the first-line chemotherapy agent was administered weekly at a dose of 1000 mg/m^2 in a 30-min intravenous infusion for three consecutive weeks, followed by a week of rest. Treatment was continued until disease progression, patient refusal, or unacceptable toxicity.

Tumor response was evaluated by enhanced computed tomography (CT) or magnetic resonance imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) at least every 8 weeks. Disease progression was defined as confirmation of progressive disease (PD) on the RECIST or clinical deterioration of the patient's general condition.

Factors Analyzed

Sixteen clinical variables at the time of disease progression after GEM chemotherapy were chosen in this study. Each variable was divided into two categories based on previous investigations (5–11) as follows: age (<65 or ≥65 years), sex (male or female), performance status (PS; 0, 1 or 2–4), white blood cell count (<10,000 or ≥10 000/μl), hemoglobin level (<8.0 or ≥8.0 g/dl), platelet count (<100 000 or ≥100 000/μl), serum total bilirubin level (<2.0 or ≥2.0 mg/dl), serum albumin level (≤2.8 or >2.8 g/dl), serum lactate dehydrogenase level (<400 or ≥400 IU/l), serum C-reactive protein (CRP) level (<5.0 or ≥5.0 mg/dl), serum creatinine level (<1.0 or ≥1.0 mg/dl), size of primary tumor (<50 mm or ≥50 mm), liver metastasis (presence or absence), ascites or peritoneal dissemination (presence or absence), serum carcinoembryonic antigen (CEA) level (<100 or ≥100 ng/ml), and serum carbohydrate antigen 19-9 (CA 19-9) level (<10 000 or ≥10 000 U/ml). PS was evaluated according to the Eastern Cooperative Oncology Group criteria. The size of the primary tumor was measured by enhanced CT. Peritoneal dissemination was defined as recognition of peritoneal nodules in CT scans or accumulation of ascites.

Statistical Methods

Overall survival for first-line GEM treatment was calculated from the day chemotherapy was started to either the day of death or the last day of follow-up. Overall survival after progression was calculated from the day when disease progression was confirmed with imaging examinations to either the day of death or the last day of follow-up. Patients whose disease progression was not evaluated with imaging examinations because of rapid general deterioration were also included in this study and the day GEM chemotherapy was determined to terminate was defined as the day of disease progression. Survival data were analyzed using the Kaplan–Meier method. Differences in survival were evaluated by log-rank tests. The Cox proportional hazards model was used to determine the most significant variables related to survival. Forward and backward stepwise regression procedures based on the partial likelihood ratio were used to determine the major independent predictors of survival. Statistical analyses were performed using the SPSS II 11.0J software package for Windows (SPSS Japan, Tokyo, Japan). All P values presented in this report are of the two-tailed type; $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics are shown in Table 1. Seventy (94.6%) of the 74 patients had distant metastasis. In response to the initial treatment with GEM, three patients showed a partial response, 39 showed a stable disease; 23 patients, however, showed a progressive disease. The remaining nine were not evaluable with imaging examinations because of rapid general deterioration due to disease progression.

Table 1. Patient characteristics

Characteristics	No. of patients (%)
Age [median (range)]	61.5 (37–90)
Gender	
Male	44 (59.5)
Female	30 (40.5)
Performance status	
0–1	49 (66.2)
2–4	25 (33.8)
Primary tumor site	
head	23 (31.1)
	51 (68.9)
Distant metastasis	
absent	4 (5.4)
present	70 (94.6)
liver	56
peritoneum	23
lung	8
distant lymph node	15
adrenal gland	2
bone	2
ovary	1
Carbohydrate antigen 19-9 (U/ml)	
[median (25–75 percentile)]	1974.5 (305.8–5886.5)
Carcinoembryonic antigen (ng/ml)	
[median (25–75 percentile)]	15.7 (7.7–40.3)

The overall response rate to first-line chemotherapy with GEM alone was thus 4.1% (95% CI: 0.1–11.4%).

Treatment after Failure of GEM Chemotherapy

Generally, we prioritized using agents on clinical trials (e.g. phase I) for treatment after GEM chemotherapy had failed. However, chemotherapy using GEM alone continued if patients were in good general condition, even after disease progression was evident during imaging examinations. Best supportive care alone was provided for patients who refused to continue chemotherapy or in whom general condition deteriorated.

After disease progression, of the 74 patients, 14 (18.9%) continued GEM chemotherapy, two (2.7%) participated in a phase I study of a new anti-cancer agent, and the remaining 58 (78.4%) patients received best supportive care.

Survival

At the time of analysis, 71 patients had died from tumor progression. Overall MST was 5.1 months after first-line chemotherapy with GEM was initiated (Fig. 1). MST after disease progression was 2.0 months (95% CI: 1.7–2.4 months) (Fig. 2).

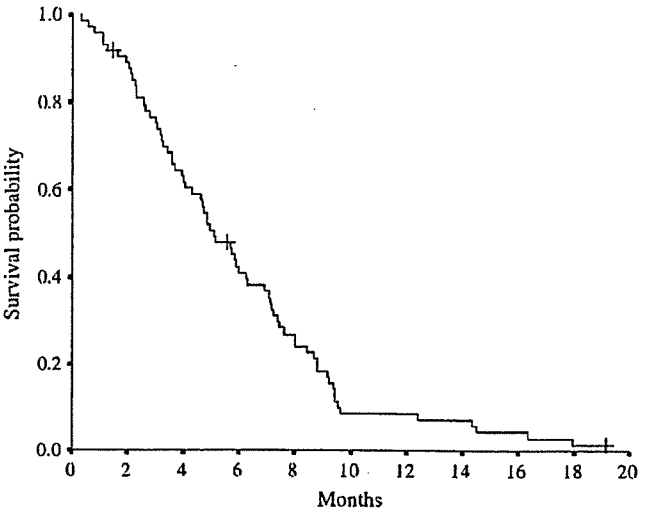

Figure 1. Overall survival curve for 74 pancreatic cancer patients from the day of the start of gemcitabine chemotherapy. The 'plus' sign indicates censored cases. Median survival is 5.1 months.

Univariate Analysis

Among the 16 variables, seven variables were identified as being significantly associated with shorter survival time: PS of 2–4, platelet count of $<100\ 000/\mu l$, serum total bilirubin level of ≥ 2.0 mg/dl, serum albumin level of <2.8 g/dl, serum CRP level of ≥ 5.0 mg/dl, presence of peritoneal dissemination and serum CA 19-9 level of $\geq 10\ 000$ U/ml (Table 2).

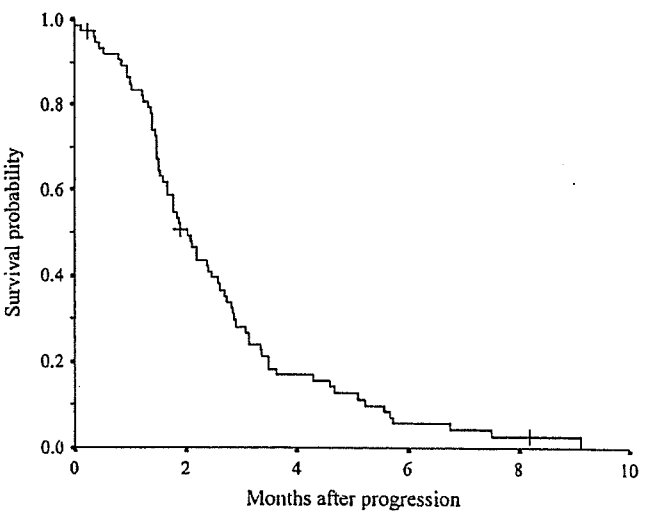

Figure 2. Overall survival curve for 74 pancreatic cancer patients after progression of the first-line of GEM chemotherapy. The 'plus' sign indicates censored cases. Median survival is 2.0 months.

Table 2. Univariate analysis

Variable	*n*	Median survival (months)	*P*-value
Age			
<65	47	1.9	0.9853
≥65	27	2.1	
Sex			
Male	30	2.6	0.2441
Female	44	1.8	
Performance status			
0–1	49	2.6	0.0007
2–4	25	1.5	
White blood ell			
<10 000/mm^3	68	1.9	0.9720
≥10 000/mm^3	6	2.6	
Hemoglobin			
<8.0 g/dl	9	1.6	0.1953
≥8.0 g/dl	65	2.1	
Platelet			
<100 000/μl	7	1.4	0.0498
≥100 000/μl	67	2.1	
Total bilirubin			
<2.0 mg/dl	65	2.0	0.0479
≥2.0 mg/dl			
Albumin			
<2.8 g/dl	15	1.5	0.0023
≥2.8 g/dl	59	2.2	
Lactate dehydrogenase			
<400 IU/l	65	2.1	0.1053
≥400 IU/l	9	1.7	
C-reactive protein			
<5.0 mg/dl	56	2.4	<0.0001
≥5.0 mg/dl	18	1.4	
Serum creatinine			
<1.0 mg/dl	62	2.2	0.5390
≥1.0 mg/dl	12	1.7	
Primary tumor size			
<50 mm	40	2.2	0.1402
≥50 mm	34	1.8	
Liver metastasis			
Absent	18	1.6	0.6471
Present	56	2.1	
Carcinoembryonic antigen			
<100 ng/nl	59	2.2	0.3337
≥100 ng/ml	15	1.7	
Carbohydrate antigen 19-9			
<10 000 U/ml	62	2.1	0.0077
≥10 000 U/ml	12	1.4	

Multivariate Analysis

Multivariate regression analysis was conducted for the seven variables found to have prognostic significance in univariate analysis. Three factors, PS, peritoneal dissemination and CRP, were identified as independent prognostic factors (Table 3). In order to apply these findings to clinical practice, the patients were divided into two groups: the good prognosis group (patients with PS 0 or 1, no peritoneal dissemination and CRP <5.0 mg/dl) and the poor prognosis group (positive for at least one of the three prognostic factors). MST in the good prognosis group was 3.4 months, with the 95% CI ranging from 2.6 to 4.1 months, and MST in the poor prognosis group was 1.5 months, with the 95% CI ranging from 1.4 to 1.6 months (Fig. 3). Twenty-nine patients (39.1%) were included in the good prognosis group.

DISCUSSION

For patients with advanced PC treated with GEM chemotherapy alone, the prognosis is around 6 months. In the present study, median survival was 5.1 months (95% CI: 4.0–6.2 months), which may be worse than that of previous reports. This may be because patients with better conditions were enrolled in clinical trials, such as chemoradiotherapy of new agents. The patients included in this study were treated with GEM as clinical practice, and these patients might have unfavorable factors for survival. For example, PS of these patients were 39 in score 0, 25 in score 1, 10 in score 2. As a result, overall survival of patients included in this study might be worse than that of some previous clinical trials of GEM chemotherapy for patients with advanced PC.

The efficacy of GEM is still poor and it is important not only to develop more effective first-line therapy but to develop effective second-line chemotherapy. No effective second-line chemotherapy has yet been established; however, clinical trials to develop promising second-line chemotherapy are ongoing. In some patients, systemic condition

Table 3. Significant prognostic factors identified by multivariate analysis using Cox proportional hazards model

Variables	*n*	Hazard ratio	95% CI	*P* value
C-reactive protein				
<5.0 mg/dl	56	1		
≥5.0 mg/dl	18	3.291	1.681–6.444	0.001
Performance status				
0–1	49	1		
2–4	25	2.522	1.404–4.529	0.002
Peritoneal dissemination				
Absent	51	1		
Present	23	1.988	1.052–3.757	0.034

CI, confidence interval.

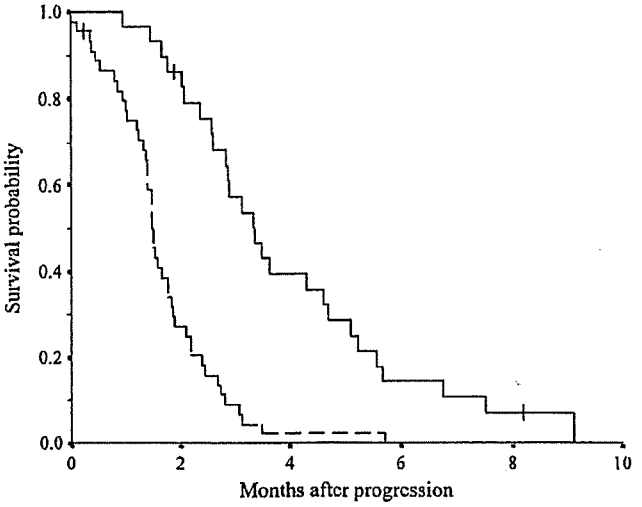

Figure 3. Survival curves for two groups divided: good prognosis group (patients with performance status 0–1, no peritoneal dissemination and C-reactive protein <5.0 mg/dl); and poor prognosis group (positive for at least one among three prognostic factors). Plain line indicates good prognosis group. Dotted line indicates poor prognosis group. There is a significant difference in survival between two groups ($P < 0.0001$). The 'plus' sign indicates censored cases.

rapidly deteriorates after GEM failure and not all patients are suitable candidates for second-line chemotherapy. In the present study, we clarified the prognosis and prognostic factors in patients with GEM-refractory PC, and identified appropriate candidates for second-line chemotherapy.

In this study, three factors, PS, peritoneal dissemination and CRP, were identified as independent prognostic factors in patients with GEM-refractory PC. PS has been widely used to evaluate physical conditions of many cancer patients. It has been recognized as an important prognostic factor in many malignancies. Other studies have similarly found that PS has prognostic value in advanced or metastatic PC after first-line chemotherapy (5–7). Because general conditions of patients with PC often rapidly deteriorate after first-line chemotherapy, the indication of second-line chemotherapy should be limited to good performance patients.

Peritoneal dissemination was also recognized as a prognostic factor in this study. PC spreads easily into the peritoneal cavity, resulting in uncontrollable massive ascites and in deterioration of general condition. In an analysis of prognostic factors in patients with metastatic PC from the start of first-line chemotherapy, it was reported that peritoneal dissemination was not a significant factor associated with shorter survival time. The difference in survival between patients with and without peritoneal dissemination was not found to be significant, but MST was 2.2 months and 3.9 months, respectively (5). The prognostic value of peritoneal dissemination may thus possibly be enhanced after GEM chemotherapy failure.

CRP was found to be the most significant prognostic factor in this study. CRP is a biomarker of infection, inflammation and malignancy. CRP is produced by the liver and is induced by proinflammatory cytokines, such as interleukin-6 or tumor necrosis factor-α (12), which are involved in cachexia. These cytokines are associated with hypermetabolism, weight loss and anorexia and, as a result, may reflect shortened survival (13–15). The prognostic value of CRP has been reported for patients with metastatic PC receiving systemic chemotherapy, and the cut-off value was set at 5.0 mg/dl (5,10,11). We used this reported cut-off value for CRP in analyzing prognosis in the present study. As a result, the same conclusion was reached regarding the prognostic value of CRP in patients with GEM-refractory PC. CRP level has been reported to be a prognostic factor in many malignancies, including hepatocellular carcinoma and colorectal cancer (16–23).

In this study, serum lactate dehydrogenase (LDH) is not identified as a prognostic factor. LDH is an important marker of tumor bulk and tumor load for different solid tumors and lymphoma. Although different cut-off levels other than 400 IU/l were analyzed, there were no significant differences in univariate and multivariate analyses.

MST in patients with a CRP level of <5.0 mg/dl was 2.4 months (95% CI: 1.82–2.98), which is significantly better than the 1.4 months for patients with CRP levels of ≥5.0 mg/dl. CRP level is not included as a variable in most clinical studies of first-line chemotherapy, but it is an important parameter for selecting appropriate patients for clinical studies and selecting candidates for second-line chemotherapy.

To clarify conditions for effective second-line chemotherapy, we divided patients into two groups according to the prognostic factors: the good prognosis group (patients with PS 0 or 1, no peritoneal dissemination and CRP <5.0 mg/dl) and the poor prognosis group (positive for at least one of the three prognostic factors). MST in the good prognosis group was 3.4 months (with the 95% CI ranging from 2.6 to 4.1 months), whereas MST in the poor prognosis group was 1.5 months. Twenty-nine patients (39.1%) were included in the good prognosis group, the members of which could expect at least more than 2 months survival. We consider that those patients with favorable factors (i.e. those that comprise the good prognosis group) are good candidates for second-line chemotherapy. Candidates for clinical trials of new second-line chemotherapy agents should be selected from this group to allow accurate evaluation of survival time. In this study, the number of patients was too small to conduct a Cox proportional hazards model. Therefore, a prospective trial should be conducted to validate these results.

Recently, several trials of salvage chemotherapy regimens have been conducted for GEM-refractory PC, with response rates ranging from 0 to 24% and MST ranging from 3.1 to 10.3 months (24–34). Among these regimens, oxaliplatin combination regimens have shown promising results. Cantore et al. reported oxaliplatin/irinotecan regimen in which objective response was 10% and MST was 5.9 months (24). Jacobs et al. conducted a randomized trial using rubitecan as compared with the physician's choice. This large study comprised 409 patients and found an MST of

3.6 months in rubitecan-treated patients, and 3.1 months in control patients (25). In these studies, survival after failure of GEM treatment was much better than that in the present study. One of the reasons for this may be that only patients with good PS were enrolled in the studies above. It remains urgent to develop promising second-line chemotherapy to prolong survival in patients with advanced PC with poor PS.

Most of the patients in the present study did not receive other chemotherapy after GEM failure, because no other agent was approved for the treatment of PC in Japan. In the present study, GEM treatment was continued in 14 of the 74 patients after confirmation of progression if the patient still had good PS, had clinical benefit, or had decreased tumor marker levels, even after disease progression was confirmed by imaging (e.g. by CT). In Japan, some anti-cancer agents, such as irinotecan and S-1, have been reported to have promising anti-cancer effects in clinical studies when administered as monotherapies (35,36). We expect that these agents will become available as second-line chemotherapy in many patients in near future.

In conclusion, serum levels of CRP, PS and peritoneal dissemination were identified as important prognostic factors in patients with GEM-refractory PC. These factors should be considered in determining the treatment following first-line chemotherapy in patients with advanced PC.

Conflict of interest statement

None declared.

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8．治療法
2）放射線治療

放射線治療とは

病変の浸潤範囲が広いため切除不能と判断された場合，膵がん病巣の制御を目指して放射線治療が行われます。また切除が行われた場合の補助治療のために行う場合もあります。

放射線治療は照射した部位だけのがんの制御を目指したものであり，治療によるメリットと副作用をよく理解して行う必要があります。

適応

病巣の部位（局所）の制御が目的ですから，遠隔転移があっては適応になりません。また切除ができる状態であれば，切除したほうが治療成績は優れていると考えられますから，放射線治療の適応になりません。したがって，遠隔転移はないが切除するには局所の浸潤が進んでいる状態，すなわち「局所進行がん」が放射線治療の適応になります（表１）。

放射線治療では病巣だけでなく，その周囲の正常組織にも放射線の影響が出るため，様々な副作用が認められます。したがって，放射線治療を安全に行うためにはある程度の体力が必要です。「全く症状がなく日常生活が可能」から「症状はあるが身の回りのことは自分で十分できる」程度の体力があれば問題ありませんが，「自分の身の回りのことに介助が必要な状態」のようだと副作用が強く出てしまい，放射線治療の適応は難しい場合が多いと考えられます。

表１　放射線治療の主な適応

１．がんの進行度
　切除不能局所進行がん：１）と２）を両方満たす状態
　１）画像診断上，他臓器への転移を認めない
　２）主要な血管など周囲の組織への浸潤が高度のため手術で完全に病巣を取り除くことができない
２．全身状態
　「症状がなく日常生活が可能」，あるいは「症状があって正常の活動・労働することは不可能でも自分自身の世話はできる」状態
３．活動性の胃・十二指腸潰瘍がないこと
４．胸水あるいは腹水がないこと
５．心臓，呼吸器，肝臓，腎臓などの機能が十分であること
６．感染症など重篤な合併症がないこと

膵臓は胃や十二指腸の近くに位置しています。したがって，膵がんの放射線治療では胃や十二指腸にも放射線照射の影響が出やすいため，あらかじめ胃潰瘍や十二指腸潰瘍がないことを上部消化管内視鏡で確認しておく必要があります。もし，潰瘍があった場合には，そちらの治療をしてから放射線治療を行うべきと考えられます。

そのほか，安全に放射線治療を行っていくためには，胸水あるいは腹水がないこと，心臓，呼吸器，肝臓，腎臓の機能が十分であること，感染症など重篤な合併症がないことなどを確認しておく必要があります。

方法

体の外から放射線を照射する「体外照射」と，手術により開腹して病巣に放射線を照射する「術中照射」(がんの病巣は切除しません)が一般に行われています。膵がんでは体外照射が主となる放射線治療であり，1回線量 1.8 Gy，総線量 50.4 Gy（週5回，計 28 回の照射）の照射が最も多く行われています。また1回 2.0 ～ 3.0 Gy，総線量 40 ～ 45 Gy の照射も行われています（表2）。

術中照射は局所制御効果の増強を目的として，多くの場合，体外照射の「先」に組み合わせて行われます。また手術により病巣を切除した際，完全に取り切れた場合でもがんが遺残している可能性もあることから，切除に引き続いて術中照射が行われる場合もあります。

放射線治療の適応となる局所進行膵がんであっても，画像診断でとらえられない小さな遠隔転移がすでに生じていることも少なくありません。また，放射線治療によって元の病巣（原発巣）が制御されていても遠隔転移が認められることも多く，膵がんの場合は放射線治療のみでの治療には限界があると考えられています。したがって，放射線治療と化学療法を組み合わせた治療，すなわち放射線化学療法が一般的に行われます。

表2　放射線治療の方法

	体外照射	術中照射
線　源	X線	電子線
手　術	不要	開腹手術
1回照射線量	1.8 ～ 3.0 Gy	15 ～ 25 Gy
回　数	28 ～ 15 回（週5回）	1回
総　線　量	50.4 ～ 45 Gy	15 ～ 25 Gy

化学療法は抗がん剤を用いた治療法であり，放射線治療と同時に行う場合と放射線治療が終了した後に行う場合があります。抗がん剤には放射線の感受性を増加させる効果をもつものもあり，同時に使う場合は放射線増感作用も期待されます。

放射線化学療法で使用される抗がん剤は，5-フルオロウラシル（5-fluorouracil：5-FU）あるいは塩酸ゲムシタビン（ジェムザール®）が主なものです。ジェムザール®は，現在のところ膵がんに対する標準的な抗がん剤であり（次項「進行再発膵がんの化学療法」を参照），体表面積あたり1回1,000 mgが通常の投与量ですが，放射線治療と同時に行う場合，副作用が強く出るため1/4程度の量が用いられています（表3）。

表3　放射線化学療法（同時併用）に用いる主な抗がん剤と投与法

薬　剤	5-フルオロウラシル（5-FU）	塩酸ゲムシタビン
投与法	持続点滴	30分で点滴
投与量	200 mg/m²	250 mg/m²
投与間隔	放射線治療中連日	放射線治療中週1回

mg/m²：体表面積の単位で，身長と体重から計算する，平均は1.5 mg/m²程度。

治療効果

局所制御に対する効果と延命に対する効果が期待されます。「局所進行膵がん」では，がん病巣が膵臓の近くの神経に浸潤するため，腹痛や背部痛など疼痛を伴うことが多いのが特徴です。放射線治療は局所制御により疼痛の改善が80%以上の患者さんに認められると報告されています。原発巣の縮小効果（半分以下になる率）は報告により差がありますが，20～50%程度と考えられます。

局所進行膵がんにおける放射線治療の延命に対する治療効果については，米国で放射線治療単独と化学療法を併用する放射線化学療法との無作為化比較試験が行われています。その結果，放射線化学療法が放射線単独療法に比べ有意に予後が良好であったと報告されており，放射線治療は化学療法と併用して行われるのが標準的治療となっています。これまで様々な照射方法や化学療法の新しい試みが行われてきています。

2年以上の生存も少なくないのですが，まだまだ治療成績は満足できるものではないのが現状です。今後有効な化学療法と同時により効果的な放射線治療の開発が望まれるところです。

副作用

一般的に，消化管粘膜は放射線の影響を強く受けるため，胃潰瘍や十二指腸潰瘍，およびそれによる消化管出血が起こる可能性があります。また全身倦怠や悪心・嘔吐，食欲低下，腹痛などが多くみられます。

放射線治療では化学療法が併用されることが多く，化学療法による副作用にも注意が必要です。主な副作用として悪心・嘔吐，下痢，便秘，口内炎などの消化器症状，骨髄機能の低下(白血球減少，貧血，血小板減少)，発熱，発疹，肝機能異常，間質性肺炎などがあげられます（表４）。

表４　放射線治療（放射線化学療法を含む）の主な副作用

消化器症状（悪心・嘔吐，食欲低下，下痢，便秘，口内炎，腹痛）
胃十二指腸炎，胃十二指腸潰瘍
骨髄機能低下（白血球減少，貧血，血小板減少）
発熱，発疹
肝機能異常
間質性肺炎

これらの副作用の出現やその程度は，特に治療をせずに耐えられ得る程度のものから，薬剤の投与やいろいろな処置を必要とするものまで個人差がみられます。強い副作用が認められた場合には治療を中止する場合もあります。悪心・嘔吐，食欲低下，全身倦怠感などについては，必要に応じて制吐剤（吐き気止め）や栄養剤などの点滴を行います。

放射線照射による胃十二指腸潰瘍は難治性のことが多く，胃潰瘍の治療薬を予防的に内服することがすすめられます。

（古瀬純司）