of a small number of randomized controlled trials (RCTs) suggest that concomitant external beam radiotherapy and chemotherapy (radiochemotherapy) are preferable to chemotherapy alone or radiation alone for patients with advanced, nonresectable pancreatic cancer with no distant metastasis.[15,16]

The recent report by the European Study Group for Pancreatic Cancer (ESPAC-1) has shown a worsening of outcome in patients undergoing curative resection followed by adjuvant radiochemotherapy,[17] although another report by the Gastrointestinal Tumor Study Group (GITSG) suggested that adjuvant radiochemotherapy had a survival benefit.[18] However, there is no consensus on the treatment of locally invasive pancreatic cancer with no distant metastasis, since no RCTs exist for this locally advanced stage of pancreatic cancer. An RCT was therefore conducted to establish the treatment strategy for locally invasive pancreatic cancer that extends beyond the pancreatic capsule but does not invade the superior mesenteric artery or the common hepatic artery.

MATERIAL AND METHODS

Eligibility. Our criteria for patient enrollment were (1) patients were between 20 and 75 years of age with a performance status of 0 through 2; (2) the tumor had either invaded the serosal (anterior) or retroperitoneal (posterior) surface of the pancreas, or extended to the intrapancreatic portal vein without complete obstruction (ie, the tumor was either S2, RP2, or PV2 according to the Japanese classification system [JCS]);[19] (3) no adjacent organs were involved except the transverse mesocolon, the duodenum, and the common bile duct; (4) there was no invasion to the superior mesenteric artery or the common hepatic artery, or the peripancreatic nerve plexuses (A0 and PL0); (5) para-aortic lymph node metastases were absent (N0 or N1); (6) the maximal diameter of the tumor was more than 2 cm and less than 6 cm (TS2 or TS3); and (7) there were no liver metastases or peritoneal seeding (H0 and P0). These criteria are consistent with Stage IVa cancer according to the JCS. Tumors that met the entry criteria represent a tumor that extends beyond the pancreas, but without involvement of major arteries (the celiac axis or the superior mesenteric artery). These tumors correspond to T3N0M0 (Stage IIA) or T3N1M0 (Stage IIB) of the American Joint Commission for Cancer (AJCC) staging system (T3, Stage II).

The other exclusion criteria were (1) previous radiation therapy or chemotherapy; (2) abnormal reaction to drugs, including contrast media; (3) presence of serious cardiovascular, pulmonary, renal, or hepatic diseases; (4) coexistence of another active malignant neoplasm; and (5) any conditions that the physician considers should preclude the trial.

Figure 1 shows the protocol for the present study. Once a patient met our eligibility criteria based on preoperative examinations including abdominal computed tomography (CT), angiography, ultrasonography, chest x-rays, and routine laboratory tests, informed consenting patients were registered as potential candidates at the central office of the trial not later than 1 day before the scheduled laparotomy. Eligibility was finally decided according to the operative findings of the laparotomy; eligible patients were randomly assigned to either a resection group or a radiochemotherapy group via a telephone call to our central office.

Treatments. Patients assigned to the resection group underwent pancreatoduodenectomy (PD) or distal pancreatectomy for resection of the main pancreatic cancer with dissection of the regional lymph nodes that were classified as Group 1 (or higher) according to JCS.[19] At least a half circle of the plexus of the root of the superior mesenteric artery was resected. Patients received no postoperative adjuvant therapy unless recurrence was obvious, at which point the doctor in charge was permitted to select another therapy.

In patients assigned to the radiochemotherapy group, the abdomen was closed once a biopsy specimen had been taken to confirm the diagnosis, although the surgeon in charge was free to perform an anastomotic resection such as gastrojejunostomy or biliodigestive anastomosis. The patient received radiation therapy beginning within 1 week after the operation. The radiotherapy was delivered as a single course of a total radiation dose of 5040 cGy in 28 fractions at 180 cGy over 5.5 weeks by using 10 to 14 megavolt photons. The radiation fields covered the primary tumor and a margin of 1 to 3 cm covering the regional lymph nodes, and was directed on the basis of CT images taken 1 or 2 days before treatment. The 3- or 4-field therapy and the dynamic arc conformal technique were recommended, but the 2-field therapy was allowed when necessary based on institutional availability. During the radiotherapy, there was continuous intravenous infusion of 5-fluorouracil (5-FU) at 200 mg/m^2/day. This was followed by weekly intravenous infusion of 5-FU at 500 mg/m^2,

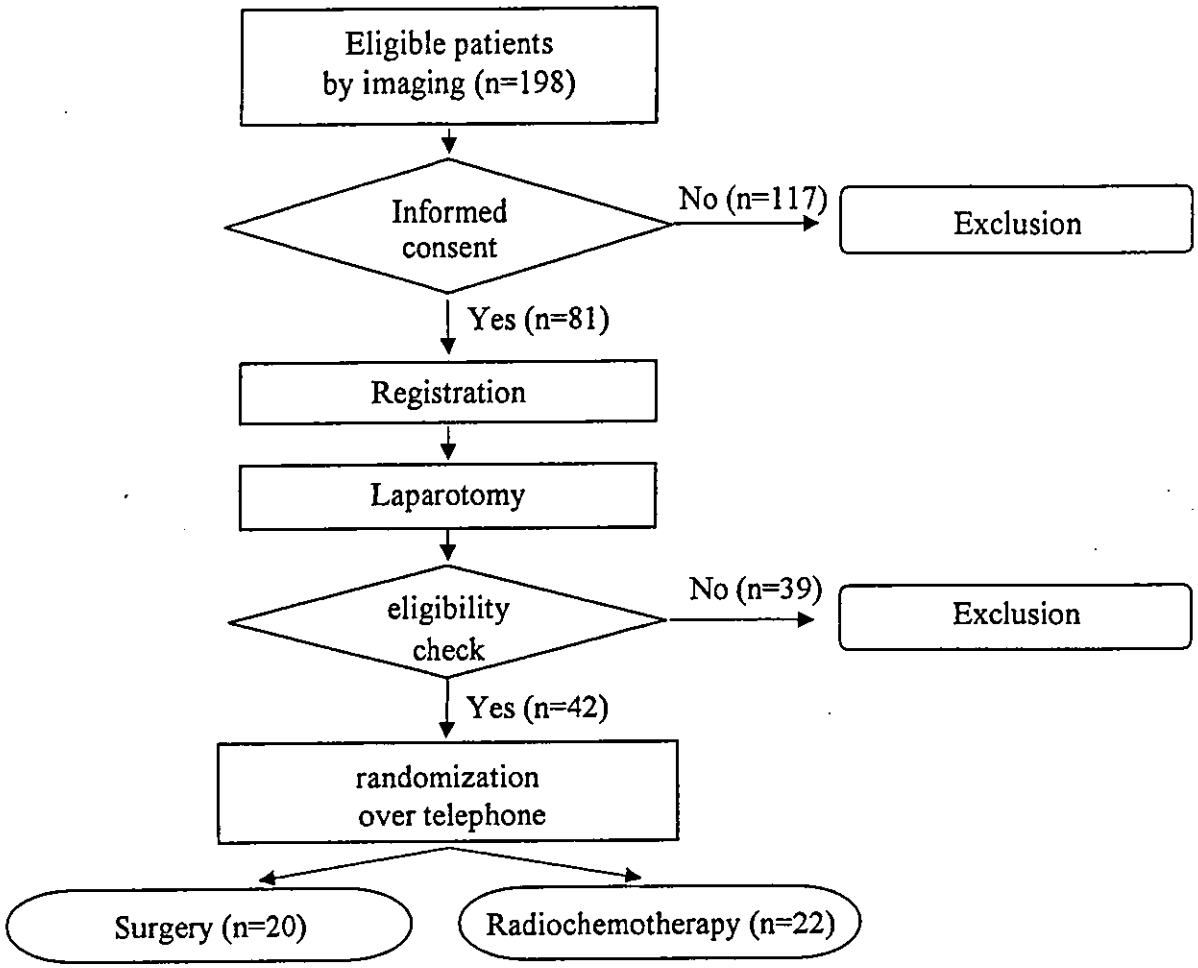

Fig 1. Schema for the study protocol.

starting in most patients within 1 week and always within 4 weeks of completion of radiochemotherapy.

Statistical analysis. The sample size was determined as follows: Supposing that the 1-year survival rate for Stage IVa cancer treated by surgical resection is 60% and that the 1-year survival for locally invasive cancer treated by radiochemotherapy is 40% (median survival of 9 months), 73 patients per group are needed to detect the difference at a 1-sided 5% significance level with 80% power. The target sample size was therefore set at 150 patients. Both treatments involve routine procedures, with unpredictable complications or death considered unlikely. Interim analysis was scheduled when half of the target sample size was reached.

The distributions of the baseline characteristics of the patients were compared between the treatment groups by using the chi-square test for binary variables, the Mann-Whitney *U* test for ordinal variables, and the unpaired *t* test for continuous variables.

Conventional survival statistics, including the hazard ratio (log-rank test) and the 1-year survival rate, were calculated to compare the outcomes between the 2 treatment groups. The mean survival time was also estimated, since it has recently been recognized as a superior measure of survival benefits.[20-22] Mean survival time was calculated as the area under the survival curve,[23] and its standard error was estimated by using the Irwin method[24] with Kaplan-Meier adjustment[25] for the total number of deaths. To assess the prognostic significance of individual variables and to identify independent predictors of survival, Cox regression analysis was used with a stepwise selection procedure.

Postoperative changes in quality-of-life scores[26] (performance status, general well-being, diarrhea, pain) were recorded. The questionnaire covers 4 categories including daily activities, physical

Table I. Reasons for exclusion at laparotomy*

	No. of patients
Peritoneal metastasis	10
Distant lymph node metastasis	9
Anterior organ invasion	7
Liver metastasis	6
Major arterial invasion	4
Retroperitoneal organ invasion	3
Stage III	3†
Portal venous stenosis‡	2
Tumor diameter >6 cm	2
Serous cystadenoma by frozen section	1
Tumor diameter <2 cm	1

*All reasons were counted for each patient.
†Overdiagnosis preoperatively for portal venous invasion.
‡Portal invasion of the tumor with a development of collateral vein.

condition, social activities, and mental and psychologic status. The patients were requested to circle their own status on a scale from 1 to 5. The laboratory data (hemoglobin, total protein, albumin, total cholesterol, log carcinoembryonic antigen [CEA] and log carbohydrate antigen [CA19-9]) were recorded and compared by using repeated measure analysis of variance between the treatment groups. All analyses were run with the use of the Statistical Package for Social Science, version 11 (SPSS Inc, Chicago, Ill).

RESULTS

During this study, 198 patients from the participating institutions were diagnosed with resectable, locally invasive pancreatic cancer that met the chosen criteria. These patients were informed in detail about the study and were asked to register for the clinical trial. Written informed consent was obtained from 81 patients (41%). The remaining 117 patients were not registered in the clinical trial because 91 strongly requested surgical resection, and the remaining 26 requested radiochemotherapy.

The study started in January 1999. The required number of patients was not enrolled in the first 2-year period, and accrual was therefore extended by an additional 2 years. At the end of the second 2-year period, it was estimated that we would need to continue accrual for another 4 years to reach the required number. This finding, together with our ethical concerns and financial difficulty, led to premature termination of the trial. The follow-up data were analyzed at this point when the power was estimated to be 67 percent. So far, a total of 81 potentially eligible patients have been registered and undergone laparotomy. Of these, 39 patients

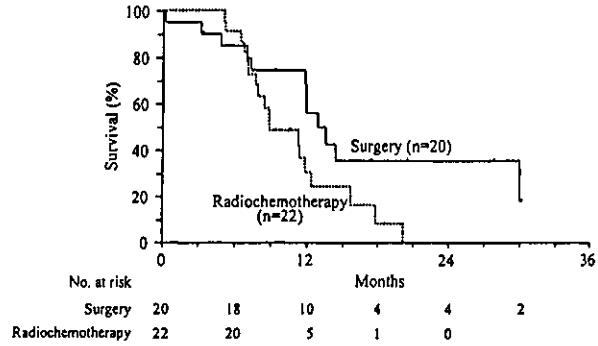

Fig 2. Survival curves of the resection group and radiochemotherapy group.

were excluded based on the operative findings (Table I).

We compared the preoperative evaluation based on imaging modality with the operative findings in our 81 registered patients. Table II shows the diagnostic accuracy for each factor. CT evaluation has a diagnostic accuracy of 65% for anterior capsular invasion, 84% for retroperitoneal invasion, and 86% for portal venous system invasion.

Finally, 42 patients were randomized and were treated as indicated. Twenty patients were assigned to the resection group (12 males and 8 females) with an average age of 65 years old (range, 51-75), and 22 patients were assigned to the radiochemotherapy group (15 males and 7 females) with an average age of 63 (range, 49-72). There were no statistical differences in the patients' backgrounds. The patients in the resection group underwent surgical resection, involving PD in 15 patients (8 PDs and 7 PPPDs) and distal pancreatectomy in 4 patients. One patient in the resection group was found during the operation to have invasion to the superior mesenteric artery, and resection was abandoned by the surgeon in favor of radiochemotherapy. This patient was nevertheless included in the resection group, according to the "intention to treat" principle. Lymph node dissection was completed to group 2 (D2) in 9 patients and to group 1 plus para-aortic lymphnode (D1+α) in 10 patients according to JCS.[19] The pancreatic head plexuses I and II were resected in 16 patients, but were not resected in 3 patients. The entire circle of the superior mesenteric arterial plexus was resected in 4 patients, the half circle of the plexus was resected in 13 patients, and the plexus was not resected in 2 patients. The reconstruction was performed by the Whipple method in 4 patients, by the Child method in 10 patients, and by the Imanaga method in 5 patients.

In the other group, all 22 patients received radiochemotherapy after the laparotomy. In 3

Table II. Accuracy of preoperative evaluation by imaging modality compared to findings at laparotomy

	*Overdiagnosis**	*Underdiagnosis**	*Correct diagnosis** *(diagnostic accuracy, %)*
Anterior capsular invasion (S)	21	7	53 (65)
Retroperitoneal invasion (RP)	10	3	68 (84)
Portal venous system invasion (PV)	9	2	70 (86)
Arterial system invasion (A)	0†	4	77 (95)
Distant lymph node invasion (N)	0†	9	72 (89)
Peritoneal metastasis (P)	0†	10	71 (88)
Liver metastasis (H)	0†	6	75 (93)

*Values are the number of patients.
†Patients who were diagnosed to have these factors by imaging were not enrolled in this study.

patients, however, both radiation and 5-FU were discontinued because of severe colitis in 1 patient, disease progression in 1, and refusal of treatment in the other. The dose of radiation given to these patients (n = 22) was 4518 ± 1420 cGy. The dose of 5-FU was 9805 ± 4429 mg during radiation, and 10114 ± 4766 mg after the radiation therapy. The resection group and the radiochemotherapy group were comparable with respect to the baseline variables of the tumor in terms of localization: invasion to the anterior pancreatic capsule, retroperitoneal tissue, portal venous system, arterial system, distal bile duct, duodenal wall, and extrapancreatic nerve plexus. Lymph node metastases were found in 14 of 20 patients in the resection group (70%) and in 5 of 22 patients in the radiochemotherapy group (23%) ($P < .001$). This difference was related to the differences in the level of lymphadenectomy between the groups.

Morbidity, mortality and survival. By the time of the last follow-up in April 2002, 11 patients in the resection group and 17 patients in the radiochemotherapy group had died of the disease (4 and 9, respectively, from distant metastases, 4 and 4 from locoregional recurrence, and 3 and 4 from both components). The mean follow-up from the entry was 13 months for the resection group and 10 months for the radiochemotherapy group. One additional death occurred in the resection group secondary to liver failure after thrombosis of the superior mesenteric vein and the superior mesenteric artery on the seventh postoperative day. Otherwise there were no serious complications, such as anastomotic leakage, pancreatic fistula, and bleeding.

Figure 2 shows the survival curves for the 2 treatment groups. The resection group had better survival than the radiochemotherapy group (Fig 2, Table III); operative resection increased the survival time by an average of 5.9 months, and the 1-year survival rate by 30%, and halved the hazard ratio. The resulting statistical significance increased further when the operative death was treated as censored (the right 3 columns in Table III). Cox univariate analyses revealed the only variable to be a significant predictor of survival was the treatment ($P = 0.02$) (Table IV). The Cox stepwise procedure also showed that treatment is the only independent predictor ($P = .04$).

Effects of treatment on quality of life scores and other variables. The mean hospital stay of the resection group was shorter than that of the radiochemotherapy group (66 ± 29 days vs 102 ± 57 days; $P = .03$ on 32 df). Under the Japanese insurance system, patients are generally allowed to stay in the hospital until they can live in their homes without professional support. The total costs for the primary hospital stay were $17,500 ± $5120 for resection plus postoperative care, and $28,200 ± $6130 for radiochemotherapy (mean ± SD).

Three months after laparotomy, both treatments were associated with significant decreases in body weight, hemoglobin, albumin, total cholesterol levels and log CA19-9; the patients' average satisfaction had increased significantly in both groups (Fig 3). The extent of these changes did not differ between the 2 groups. A significant difference was found only in the average number of bowel movements per day, which increased after resection but was unchanged after radiochemotherapy.

DISCUSSION

Although the question of whether to perform resection for pancreatic cancer has long been discussed,[11,27] no general consensus has arisen. In our study, we specifically selected patients with a resectable, locally invasive pancreatic cancer that extended beyond the pancreatic capsule but did not invade the superior mesenteric artery or the common hepatic artery. This stage of pancreatic

Table III. Comparison of survival between the treatment groups

	*Resection group**	*Radiochemotherapy group**	*Difference ratio**	P *value**	*Resection group†*	*Difference ratio†*	P *value†*
Mean survival time (months) (95% CI)	16.9‡ (11.9-21.9)	11.0 (8.9-13.1)	5.9 (0.5-11.3)	0.03	17.8‡ (12.8-22.7)	6.8 (1.4-12.1)	.01
Median survival time (95% CI)	13.0 (10.2-15.9)	8.9 (5.0-12.8)	4.1 (-0.7-8.9)	0.10	13.7 (10.8-15.2)	4.7 (-0.1-9.6)	.06
1-year survival (%) (95% CI)	61.8 (39.2-84.4)	30.2 (9.2-51.2)	31.6 (7.4-62.4)	0.05	65 (42.2-87.9)	34.8 (3.8-65.9)	.03
Hazard ratio (95% CI)			0.46 (0.22-0.97)	0.04		0.41 (0.1-0.88)	.02

*All deaths are included.
†Operative death is treated as censored observation.
‡This value (Irwin's restricted mean) is smaller than the true estimate (the areas under the complete survival curve) because the longest survival time is censored; hence, the additional length of life gained by surgery is also underestimated.

Table IV. Prognostic influences of treatment and tumor factors

Variable	*Hazard ratio**	P *value**
Treatment (resection vs radiochemotherapy)	0.41	.02†
Location (heat vs body/tail)	1.01	.91
Tumor size ($\leq$4 cm vs >4 cm)	1.00	1.00
Serosal invasion (present vs absent)	0.89	.78
Retroperitoneal invasion (present vs absent)	0.63	.30
Portal vein invasion (present vs absent)	1.28	.58
Bile duct invasion (present vs absent)	0.68	.36
Duodenal invasion (present vs absent)	0.64	.29
Gender (male vs female)	0.96	.92

*Operative death is treated as censored observation.
†Significant values.

cancer (Stage IVa in JCS,[19] T3 Stage II in AJCC system) includes the largest number of patients, and Japanese surgeons have generally tried to cure the disease by resection with or without postoperative radiochemotherapy. In the United States and other Western countries, however, possibly fewer of these patients would undergo radical surgical resection.[28] Certainly PD has been performed safely worldwide for the past 5 years, with an operative death rate of less than 5 %.[11] Whether the apparently better results of surgical resection compared with nonsurgical treatments is due to selection bias (a majority of prognostically favorable patients undergo resection and the remaining patients receive other treatments) or due to more accurate disease information obtained by laparotomy has yet to be elucidated. To answer this question, we compared operative resection alone with radiochemotherapy alone under otherwise equal conditions (ceteris pallibus).

Our present trial has several unique points. We compared 2 different types of treatments in patients having very similar conditions. Our eligibility criteria were based on operative findings, which are more accurate than preoperative imaging; there were considerable discrepancies between preoperative and operative diagnoses in the extent of the tumor and distant metastases. Our eligibility criteria took into account more than 10 variables to specify the study population closely. These variables included performance status, tumor size, histopathology, nodal involvement, and tumor invasion of contagious structures such as the serosal and retroperitoneal surface of the pancreas, duodenum, common bile duct, portal vein, major arteries, and nerve plexus. As a result, about half of all preregistered patients were excluded from the trial, leaving a subset of patients who were very homogeneous and well matched, and were expected to respond similarly to the treatments.

This study was difficult to conduct in Japan where a majority of people so far have relied on resection for pancreatic cancer because patients with pancreatic cancer rarely survive more than 3 years with any therapies that do not include resection. According to a nationwide survey by

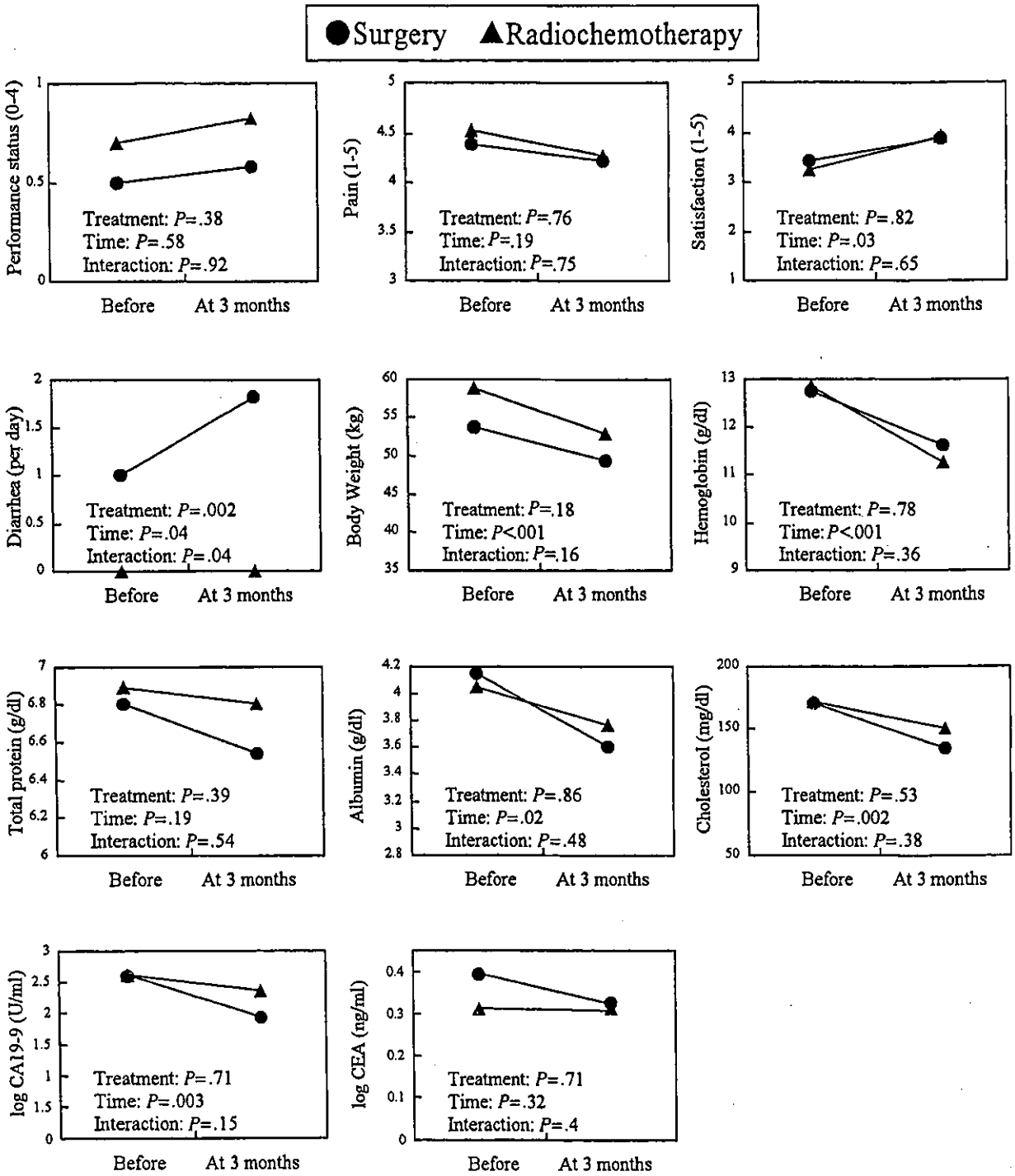

Fig 3. Changes in quality-of-life scores and other variables before and after treatment. *Treatment*: overall difference between the treatment groups. *Time*: overall difference between preoperative time and 3 months after the laparotomy. *Interaction*: interaction between treatment effect and time effect.

the Japanese Pancreas Society, 2005 patients with surgical stage IVa pancreatic ductal cancer, which is almost identical to the stage in this study, underwent resection between 1980 and 1999, with an average 1-year survival of 49%, 5-year survival of 10%, and 10-year survival of 5%.[4] On the other hand, no data were available on the results of radiochemotherapy alone without resection in comparable patients. Our randomized trial, however, revealed that radiochemotherapy administered to comparable patients resulted in significantly shorter survival than resective surgery. Moreover, this difference between the treatment groups was greater than expected and was detected with a much smaller number of patients than estimated at the time of sample size determination. Although statistically there remains the risk of type I error (wrong judgment that resection is better than radiochemotherapy), we concluded that the trial should not be continued and decided in favor of resection for the following reasons: It is highly unlikely that radiochemotherapy would ever achieve a long-term survival rate comparable to that of resection; no major factors could reverse the overall advantage of resection unless the operative mortality and morbidity were high; the hospital stay for the resection group was significantly shorter than that for the radiochemotherapy group; the overall cost for the resection group was lower than that for the radiochemotherapy group.

It has been thought that liver metastases are observed frequently after a radical operation. Nevertheless, the increased number of long-term survivors in Japan after a radical operation suggests the possibility that, at least, a portion of the patients with locally invasive pancreatic cancer might have a limited disease and could enjoy the maximal benefit by surgical resection. It should be taken into account that the current study was performed by a group of specialized institutions focusing on pancreatic diseases because recent reports have shown a distinct association between high patient volume and decreased mortality rates.[11,29-32] The mortality rate of PD for pancreatic cancer has been reported to be 3% to 8%.[11] The current series encountered only 1 in-hospital death after pancreatic resection, which should be a serious drawback to the surgical treatment, although the overall survival was still better in the resection group.

CONCLUSION

Patients with pancreatic cancer without distant metastasis (ie, that extends beyond the pancreatic capsule but does not invade either the superior mesenteric artery or the common hepatic artery) should be treated by surgical resection. The results of the European Study Group for Pancreatic Cancer (ESPAC) trial showed a potential benefit of adjuvant intravenous fluorouracil and folinic acid after surgical resection.[17] Therefore, it would be better for patients meeting our criteria to undergo resection, unless new treatment modalities are expected to achieve substantial long-term survival.

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Acute Pancreatitis in the Early Stages of Pregnancy Associated With a PSTI Gene Mutation

To the Editor:

Acute pancreatitis can be considered one of the causes of abdominal pain during pregnancy. However, the incidence of acute pancreatitis during pregnancy is relatively rare since it has been reported in only 0.03% of pregnant women.[1] On the other hand, the pancreatic secretory trypsin inhibitor (PSTI) gene has recently been identified as being associated with hereditary and idiopathic chronic pancreatitis.[2] PSTI is a potent protease inhibitor that is thought to be an inactivation factor of intrapancreatic trypsin activity.[3] Here we report a case in which a woman with a PSTI gene mutation was thought to have shown acute pancreatitis ignited by pregnancy.

A 29-year-old Japanese woman complained of abdominal pain, nausea, diarrhea, and fever at 13 weeks + 2 days' gestation, February 9, 2001. Because of liver dysfunction and white blood cell count (WBC) elevation, she was admitted to our obstetrics and gynecology ward. These conditions were thought to be early morning sickness. Treatment was initiated with rest, and gradually her liver dysfunction and inflammation were relieved. But on February 14, she was suddenly aware of severe upper abdominal pain and her laboratory data showed an increase in serum pancreatic specific amylase (p-amylase). Therefore, she was admitted to our ward. Both her father and elder sister had a history of acute pancreatitis. She had no life history of smoking or drinking. The patient had Moya-moya disease at the age of 8. Physical examination revealed severe abdominal tenderness. There was neither anemia nor jaundice. The liver and spleen were not palpable. Laboratory studies showed the following values: WBC count was 9.64 × $10^3/\mu L$. p-Amylase was 185 U/L (normal range, 10–65) and lipase was 112 U/L (normal range, 16–51). AST was 30 U/L, and ALT was 39U/L. C-reactive protein (CRP) was 0.1 mg/dL, which was within the normal range. Ultrasonography showed swelling of the pancreatic body and tail, and the margin of the pancreas was indistinct. Dilatation of the main pancreatic duct was not observed. There was no cystic formation. Because of the pregnancy, computed tomography was not done. Taken together, the diagnosis of acute pancreatitis was made.

She started a low-fat diet and was treated with enzymes for 2 weeks, but her response was not favorable. Therefore, at 17 weeks + 1 day's gestation, strict fasting was initiated, and she was treated with vigorous intravenous hydration and gabexate mesylate. Although an elevated serum amylase value continued, her symptoms and pancreatic swelling gradually improved. After 8 days of strict fasting, she started a low-fat diet once more and therapy with camostat mesylate and enzymes. At 21 weeks + 1 day's gestation, she was discharged and treated as an outpatient. The level of serum p-amylase gradually decreased and pancreatic swelling, observed by ultrasonography, disappeared at 33 weeks' gestation. She delivered a healthy female infant via Cesarean section at 37 weeks + 6 days. After childbirth, serum amylase elevation and pancreatic swelling have not been detected. Magnetic resonance cholangiopancreatography (MRCP) showed no anomaly of the pancreatic duct such as pancreatic divisum. Therefore, we suspected that there was a possibility that acute pancreatitis would be caused by hereditary pancreatitis because of her family history. We then investigated her and her family for cationic trypsinogen (CT) gene mutations that have been reported and considered causative factors for hereditary pancreatitis.[2] However, mutations in CT genes were not observed. Therefore, we checked for PSTI gene mutations (Fig. 1A). An A to G transition resulting in a substitution of asparagine

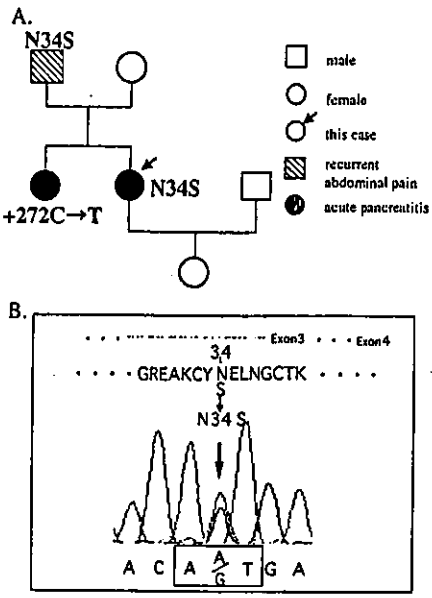

FIGURE 1. A, Pedigree of this family. This patient has a PSTI mutation (N34S) (arrow). The father has the same mutation, and the sister showed another PSTI polymorphism. B, The PSTI gene mutation in exon 3 of this patient.

by serine at codon 34 in exon3 (N34S) (Fig. 1B) was revealed for both the patient and her father. It was heterozygous for this mutation. Her sister showed another PSTI polymorphism, +272 C>T in 3'UTR. It was an intronic sequence variant. Her mother had neither CT nor PSTI gene mutations.

Acute pancreatitis during pregnancy is rare, occurring in <1 in 3000 pregnant women.[1] The most common cause of pancreatitis during pregnancy is gallstones (68%),[1] followed in frequency by trauma, alcohol ingestion, viral infection, biliary abnormalities, and finally hyperlipidemia.[4,5] However, in this case, the basic diseases described above considered to be the causes of acute pancreatitis during pregnancy were not observed. Therefore, we determined the mutation of CT and PSTI because the pedigree analysis indicated the possibility of hereditary pancreatitis. As a result, this patient was found to have PSTI gene mutation (N34S).

Recently, several genes have been identified as being associated with he-

reditary and idiopathic chronic pancreatitis, ie, cationic trypsinogen (PRSS1), cystic fibrosis transmembrane conductance regulator (CFTR) and PSTI.[2,6,7] PSTI is synthesized in pancreatic acinar cells as a 79-amino-acid premature peptide. When PSTI is secreted into pancreatic juice as a protease inhibitor having a 56-amino-acid mature peptide, it is thought that it protects the pancreas from trypsin activation.[3,8] PSTI mutations decrease inhibiting trypsin activity and result in autodigesting the pancreas. Since PSTI has the capacity to inhibit about 20% of total potential trypsin activity within the pancreas,[8] it is thought that only PSTI mutations are not potential disease-causing mutations.

It is known that there are many mutations and polymorphisms in the PSTI gene, ie, N34S, P55S (163C>T in exon 3), M1T(2T>C in exon1), IVS3+2T>C and 272C>T.[3,8,9] Pfützer et al[8] reported that mutation of N34S was observed in 25% of patients with familial pancreatitis and idiopathic chronic pancreatitis. Furthermore, N34S heterozygous mutations are observed in approximately 1% of the general population,[2] whereas the rate of incidence of idiopathic chronic pancreatitis is rare (a prevalence of 0.0066% in the same population).[8] Therefore, it is not considered that only PSTI mutations necessarily cause pancreatitis. It is possible that PSTI gene mutations effect pancreatitis brought on by environmental factors.

In this case, we suggested that PSTI gene mutation ignited by pregnancy could induce pancreatitis.

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Hyperamylasemia and Acidemia: Is There an Association?

To the Editor:

Numerous studies have shown a high incidence of hyperamylasemia in patients with diabetic ketoacidosis (DKA) without clinical or autopsy examination evidence of pancreatitis.[1–7] The mechanism of this association is unclear: the largest and most recent report on the issue revealed correlations between amylase and both hyperosmolarity and acidemia,[7] although other studies have failed to show an association between amylase and pH.[1,3,4] One study[8] also showed a correlation between hyperamylasemia and acidemia in patients without DKA or clinical evidence of pancreatitis. In this study, 12 of 33 patients were found to have hyperamylasemia, 5 of whom had values 2 times or more the upper limit of normal range. Nine of the 12 had only elevated total amylase with normal pancreatic isoamylase, and only 1 had an elevated lipase. Weaknesses of the study include the lack of serial amylase values to determine whether hyperamylasemia resolved with resolution of the acidemia, obtaining amylase too long after pH determination, no characterization of the severity of illness, and a control group that may not have had similar severity of illness. Moreover, no mechanism for the findings was elicited.

Hence, we carried out a study to (1) validate or refute the association of hyperamylasemia and acidemia not due to DKA using a superior study design and (2) to investigate a possible mechanism of such a finding. We recruited nonconsecutive adult patients with APACHE II[9] scores (AII) >5 and arterial pH values of <7.32 (acidemic group) or AII scores >5 and pH in the range of 7.36–7.44 (control group) from a university hospital's intensive care unit (ICU). The control, high AII group was to detect any effects of severe illness per se (in the absence of acidemia) on amylase and lipase. We excluded patients with the following characteristics known to result in elevated amylase levels: diagnosis of pancreatitis by the primary team, DKA, renal failure (defined as creatinine clearance <35 mL/min or serum creatinine increase >0.5 mg/dL in the previous 48 hours), acidemia after cardiopulmonary resuscitation, perforated viscus, or bowel ischemia. All patients had serum analyzed for amylase, lipase, and osmolarity within 2 hours of their qualifying arterial blood gas. Patients with acidemia had repeat serum analysis at least daily until the acide-

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原著

膵癌骨転移合併例の臨床的特徴およびその対策

井口東郎　安田幹彦　松尾　亨
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要旨：近年，膵癌においても骨転移合併例に遭遇する機会が増加しており，その臨床的特徴について検討し，対策について考察を加えた．膵癌骨転移は膵体尾部癌で多く，肝転移をともなう症例が多かった．骨転移の型は溶骨型で，骨代謝マーカーで溶骨を反映する血清1CTPの上昇が認められた．骨転移成立には破骨細胞の活性化が重要な過程であるが，膵癌骨転移症例では破骨細胞活性化作用を有するPTHrP，IL-6，VEGFの血中レベルが上昇していた．膵癌で骨転移合併後の生存期間は長くないが，診断および治療開始の遅れからQOL低下を招いている．膵癌の経過観察では，骨転移を念頭におくことと，1CTPの定期的な測定が早期診断にとって重要と考えられる．

索引用語：膵癌，骨転移，骨代謝マーカー，サイトカイン

はじめに

膵癌は最も予後不良の癌で，以前は骨転移が問題になることは皆無に近かったが，近年の治療の進歩により，僅かではあるが生存期間の延長がみられ，それによって臨床上問題となる骨転移合併例に遭遇する機会が増加している．骨転移は生命予後を規定することは少ないが，疼痛，病的骨折，神経症状などでQOLを著しく低下させるため，たとえその後の生存期間が短期であっても，その対策は重要である．今回，われわれは，膵癌に骨転移を合併した自験例の臨床的特徴について検討を行い，膵癌診療における骨転移対策について考察を加えた．

I　対象および方法

2000～2003年に九州がんセンターで入院治療を行った通常型膵癌は179例（男性113例，女性66例；40～93歳）で，このうち骨転移を合併した13例を対象とした．通常型膵癌の診断は組織学的所見あるいは画像所見および腫瘍マーカーから行った．骨転移は骨シンチでスクリーニングを行い，異常集積を認めた部位をX線写真，MRIあるいはCTで確認した．

対象例において，臨床的特徴として膵癌占拠部位，臨床病期，骨転移部位，膵癌診断から骨転移出現までの期間，骨転移出現後の生存期間ならびに骨以外の遠隔転移について検討した．また，膵癌に合併する骨転移の診断に骨代謝マーカーが有用であるかを検討するために，対象例の骨転移診断時における骨代謝マーカー（血清C-terminal telopeptide（1CTP），尿N-terminal telopeptide（NTx），血清骨型アルカリフォスファターゼ（BAL））を測定した．骨転移成立には破骨細胞活性化による骨吸収亢進が重要であるため[1]，膵癌骨転移に関わるサイトカインを探る目的で，破骨細胞活性化作用を有するサイトカインとしてPTH関連蛋白（PTHrP），IL-6およびvascular endothelial growth factor（VEGF）の血中濃度をELISAで測定した．なお，血清VEGFレベルは腫瘍由来VEGFに加えて血小板由来VEGFも反映されるため[2]，本項においては血小板VEGFの影響を除外する目的で，VEGFの測定値（pg/ml）を血小板数（10^4/ml）で補正した値で表示した．

II　結　果

1．膵癌骨転移の臨床的特徴（Table 1）

膵癌骨転移症例の男女比は男性8例，女性5例で，膵癌診断時の臨床病期は1例がII，残る12

1）九州がんセンター消化器内科

Table 1. 膵癌骨転移合併例（n＝13）の臨床的特徴

症例	年齢	性	臨床病期	占拠部位	骨転移部位	骨転移の型	膵癌診断から骨転移出現までの時期（月）	骨転移に対する治療	骨転移出現後の生存期間（日）	骨以外の遠隔転移
#1	59	女	II	ph	腰椎	溶骨	26	NSAIDs	83	肺
#2	79	男	IVb	pb-pt	胸-腰椎，肋骨	混合	5	モルヒネ，BP†	87	肺，肝
#3	71	女	IVb	pb-pt	胸-腰椎，肋骨，骨盤	溶骨	7	モルヒネ，BP	83	肺，肝
#4	54	男	IVa	pt	肋骨	溶骨	6	放治‡，モルヒネ	244	肝
#5	65	男	IVa	pt	肩甲骨	溶骨	4	放治，NSAIDs	73	腹膜
#6	50	男	IVb	pb-pt	胸-腰椎，肋骨	溶骨	0（同時）	放治，モルヒネ，BP	77	肝，副腎，皮膚，筋肉
#7	52	男	IVa	ph	胸-腰椎	混合	19	モルヒネ	58	腹膜
#8	62	女	IVb	pt	胸椎	溶骨	0（同時）	なし	19	肝，腹膜
#9	74	女	IVb	pt	胸椎，骨盤	溶骨	0（同時）	BP	84	肺，肝
#10	55	男	IVb	pt	胸椎，肋骨	混合	29	放治，モルヒネ，BP	82	肝
#11	46	女	IVb	ph	腰椎	溶骨	0（同時）	放治，モルヒネ，BP	60（生存中）	皮膚，筋肉
#12	68	男	IVb	pt	胸-腰椎，肋骨	溶骨	12	放治，モルヒネ，BP	31	肝，腹膜
#13	71	男	IVb	pt	腰椎，頬骨	溶骨	10	放治，モルヒネ，BP	36	肝

† BP，ビスフォスフォネート製剤；‡放治，放射線治療

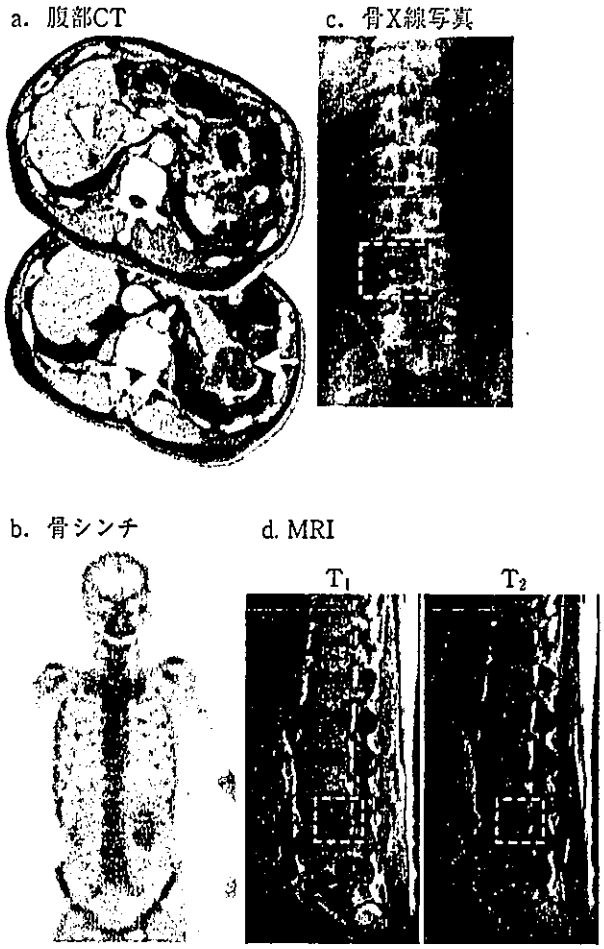

Figure 1. 膵癌骨転移典型例（Table 1 の #13）の画像所見　a：腹部 CT；膵尾部の腫瘤（膵癌，↑）および肝転移（△）　b：骨シンチ；腰椎（L_4）および左頬骨に hot spot　c：骨 X 線写真；腰椎（L_4）に骨破壊像（⬚）　d：MRI；腰椎（L_4）に T_1 強調像で低信号，T_2 強調像で等信号の転移巣（⬚）

例が IV（IV a 3 例，IV b 9 例）であった．膵癌に対する治療の内訳は，臨床病期が II（Table 1 の #1）と IV a（Table 1 の #7）の各 1 例で手術を施行し，臨床病期が IV a，IV b の 10 例では gemcitabine (GEM) を主とした化学療法あるいは放射線化学療法を施行，残る IV b の 1 例（Table 1 の #6）では対症療法のみを施行した．なお，手術を施行した 2 例の術後の臨床病期は #1 が III（根治度 A）ならびに #7 が IV a（根治度 C）であった．

Table 1 に骨転移合併例の臨床的特徴をまとめた．この 20 年間の本邦における膵癌の占拠部位別頻度をみると，膵頭部癌 6084 例に対して膵体尾部癌 1721 例と膵頭部癌が多いのに対して[3]，膵癌骨

転移合併例は頭部の3例に対して体尾部が10例であり，膵体尾部癌に骨転移の合併が多かった．骨転移部位としては脊椎（胸，腰椎）が11例と最も多く，以下，肋骨6例，骨盤2例，肩甲骨および頬骨が各1例と続き，骨転移の型としては溶骨型が10例と多く，残る3例は溶骨と造骨が混じった混合型であった．Figure 1に膵癌骨転移典型例（Table 1の#13）の画像所見を呈示する．本症例は膵尾部癌で肝転移を合併しており（Figure 1a），下肢しびれ感が出現して骨転移と診断された症例である．骨シンチで腰椎（L_4）および左頬骨に異常集積がみられ（Figure 1b），X線写真でL_4の溶骨像が確認された（Figure 1c）．MRIでもT_1強調像で低信号，T_2強調像で等信号の病変がL_4にみられ（Figure 1d），溶骨性病変に一致する所見であった．

膵癌の診断が下されてから骨転移の診断までの期間については，膵癌診断時の臨床病期や治療法が各症例で異なるため，一概には論じられないが，手術を施行した2例で26カ月および19カ月，また，膵癌診断時の臨床病期はIVbであったが，5-fluorouracil（5-FU）を用いた放射線化学療法およびそれに続いてGEMによる化学療法を施行した1例で19カ月と，その期間が長かった．一方，残る10例では，4例で膵癌診断と同時に骨転移が診断されており，また，6例では膵癌診断から4～12カ月と比較的短期間に骨転移の診断がなされていた．

骨転移合併後の生存期間については，GEMを用いた放射線化学療法を施行した1例で244日と比較的長期生存が得られたが，11例で19～87日（平均65日）と骨転移合併後の生存期間は短かかった．なお，1例は骨転移と診断されてから60日であるが，現在，生存中である．

骨以外の遠隔転移については，肝転移が9例と最も多く，以下肺転移が4例，腹膜播種が3例，皮膚転移が2例，筋肉転移が2例および副腎転移が1例であった．

2. 骨代謝マーカー（Figure 2）

骨代謝マーカーとしてはそれぞれ，溶骨および造骨を反映するマーカーがあり，今回われわれは

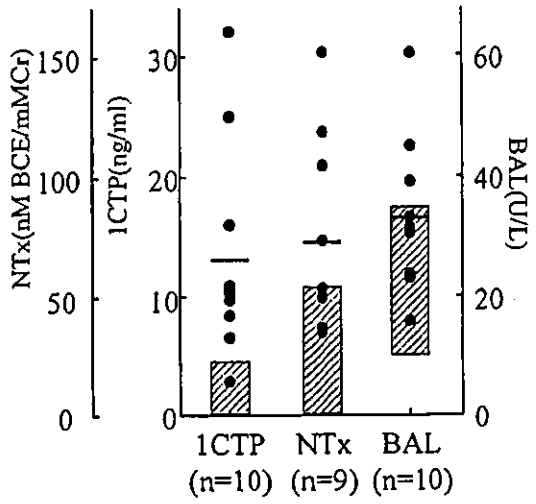

Figure 2. 膵癌骨転移合併例における骨代謝マーカーの血中（1CTP，BAL）および尿中レベル（NTx）（▨は正常域）

溶骨マーカーとして血清1CTPおよび尿NTx，また造骨マーカーとしてBALをELISAにて測定した．

膵癌骨転移合併例における各マーカーの血中あるいは尿中レベル（平均値±SE）は，1CTP 13.3±2.8ng/ml（n=10）（正常<4.5），NTx 75.1±13.6 nMBCE/mMCr（n=9）（正常<55），BAL 33.2±3.9 U/L（n=10）（正常10～35）で，溶骨マーカーが上昇を示した．これらマーカーの上昇を症例別に検討してみると，1CTPは10例中9例（90%）とほとんどの症例で上昇していたが，NTxは9例中4例（44%）でしか上昇がみられなかった．一方，BALは3例で上昇がみられたが，そのうち2例は僅かの上昇であり，60U/Lと中等度上昇を示した1例で造骨病変が顕著であった．

3. 破骨細胞活性化作用を有するサイトカイン

破骨細胞活性化を有するサイトカインとしてPTHrP，IL-6，VEGFの血中レベルを測定し，その結果をFigure 3に示した．

膵癌骨転移合併例におけるPTHrP，IL-6およびVEGFの血中レベル（平均値±SE）はそれぞれ61.7±17.7pmol/L（正常13.8～55.3），19.6±12.3 pg/ml（正常<4.0）および33.2±3.0VEGF/Platelet（pg/10^4）（正常6.7～10.7）で，これら平均値はいずれもが上昇していたが，特にIL-6および

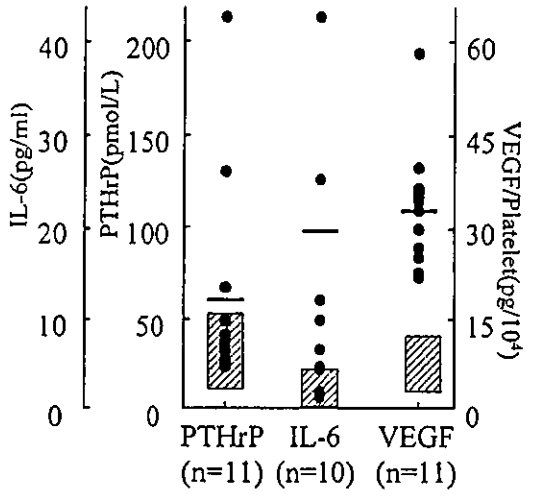

Figure 3. 膵癌骨転移合併例における破骨細胞活性化作用を有するサイトカイン（PTHrP, IL-6, VEGF）の血中レベル（▨は正常域）

VEGFが高値であった．これらサイトカインを症例別に検討してみると，PTHrPは11例中3例(27%)，IL-6は10例中7例(70%)で上昇を示しており，また，VEGFは11例全例で上昇していた．

4. 骨転移の症状およびその治療

骨転移に基づく症状としては当然，疼痛が最も多く，その中で骨転移部位の頻度からも"腰痛"を訴えるケースが多かったが，この他，脊髄圧迫による下肢しびれ感あるいは下肢麻痺を来したケースが4例みられた．

骨転移の治療としては疼痛対策が中心であり，痛みの程度に応じてNSAIDs，モルヒネ，放射線治療あるいはビスフォスフォネート製剤を適宜，組み合わせて施行した(Table 1)．また，脊髄圧迫症状を来したケースでは手術も考えられたが，その後の生存期間を考慮して侵襲の少ない治療法を選択した．

III 考　察

膵癌は本邦で増加傾向にあるが，未だ診断や治療における"breakthrough"がみられず，ほとんどは進行膵癌としてみつかるため，その予後は依然として悲惨であるといわざるを得ない．しかしながら，近年の癌化学療法の進歩には目を見張るものがあり，膵癌においてもGEMの導入後，僅かではあるが生存期間の延長がみられるようになり[4]，われわれの成績においても，臨床病期IVbで化学療法を施行した症例では，以前の5-FUを主とした治療群に比較してGEM群で約4カ月の生存期間の延長が認められた．一方，膵癌骨転移については，森脇ら[5]が剖検における膵癌の骨転移合併頻度を21.3%と報告しているが，実際に臨床の現場において骨転移と診断されるケースは以前は極めてまれであった．ところが最近では，膵癌においても骨転移合併例に遭遇する機会が増加しており，われわれの施設ではこの4年間（2000～2003年)に13例の膵癌骨転移合併例を経験し，この数値は自験膵癌症例の7.3%となる．この成績は膵癌における臨床上問題となる骨転移合併例の増加を示しており，GEM導入による生存期間の延長がその一因と考えられる．

膵癌骨転移は占拠部位別では体尾部癌に多く，また肝転移を有する症例に多いという臨床的特徴が認められた．膵癌占拠部位によって骨転移合併頻度が異なる理由は不明であるが，脊椎（胸，腰椎）への転移が高頻度であることを考え合わせると，大循環を介したいわゆる経動脈性転移に加えて，門脈から脊椎静脈叢を介する経静脈性の転移も関与している可能性がある．こういった見地から膵癌の門脈浸潤について考えてみると，膵頭部癌は上腸間膜静脈に浸潤するのに対して膵体尾部癌では脾静脈へ浸潤し，このような癌の占拠部位による浸潤する脈管の違いが骨転移頻度の違いとして現れたのかもしれない．骨転移部位としては脊椎，特に腰椎が最も多く，症状として疼痛，すなわち腰痛を訴える場合が多かった．この成績は肝転移を有した膵体尾部癌で腰痛を訴える場合は，骨転移の可能性が高いことを念頭において検索を進めていかねばならないことを示唆している．

骨転移成立には癌細胞で産生されるサイトカインによる破骨細胞活性化およびそれによる骨吸収亢進過程が重要であり[6]，肺癌や乳癌骨転移ではPTHrPがその役割を担っていることが*in vivo*の骨転移動物モデルにおいて明らかにされた[6][7]．実際の各種癌症例の骨転移に関わるサイトカインに

ついては，乳癌骨転移でPTHrPの発現頻度が高いとする報告や[8]，肝細胞癌骨転移とVEGFの関連を示唆する報告[9]がみられるが，不明な点が多いのが現況である．膵癌骨転移における破骨細胞活性化に関わるサイトカインについては不明であるが，われわれはそういったサイトカインとしてPTHrP，IL-6およびVEGFについて，膵癌骨転移合併例における血中レベルを検討した．その結果，IL-6とVEGFが高値を示し，PTHrPも頻度は低いながら一部の症例で上昇しており，直接的なエビデンスではないが，これらサイトカインが膵癌の骨転移成立に関与している可能性が示唆された．膵癌の骨転移は，他の消化器癌の骨転移と同様[10]，溶骨型が大部分で，実際，溶骨を反映する骨代謝マーカーのうち1CTPの血中レベル上昇が認められた．ただ，骨吸収マーカーの上昇は溶骨型骨転移に限ったものではなく，混合型や造骨型骨転移においても観察され[11]，これらすべての型の骨転移において破骨細胞活性化による骨吸収亢進が関与していることを反映した結果と考えられる．

膵癌骨転移については，"膵癌で骨転移は少ない"といった先入観があり，疼痛を訴えているにもかかわらず骨転移を思いつかないがためにその診断が遅れ，QOLの低下を招いている場合が多いようである．そこで，その対策として，まずは"膵癌においても骨転移が増加している"ことを念頭におき，疼痛を訴える場合には骨転移の可能性を考え，速やかに骨シンチを施行し，骨転移の診断につなげねばならない．今回，われわれは膵癌骨転移合併例で血清1CTP値が上昇していることを明らかにした．膵癌骨転移の高危険群は，現時点では設定されていないが，われわれの成績からは膵体尾部癌で肝転移を有する症例で骨転移の合併頻度が高かった．よって，こういった症例においては，外来での経過観察における1CTPの測定が骨シンチへの拾い上げを促し，より早期の骨転移の診断につながることが期待される．これによってその後の治療も早期に開始することが可能となり，QOLの低下防止につながるものと考えられる．膵癌骨転移の治療は疼痛対策が主となり，その後の生存期間を考慮し保存的治療が選択される場合が多いと思われる．近年，強力な破骨細胞機能抑制作用を有するビスフォスフォネート製剤が登場し[12]，骨転移の治療においても疼痛軽減や癌増殖抑制に効果をあげている[13]．われわれも放射線治療，モルヒネ，NSAIDsといった従来の保存的治療法に加えてビスフォスフォネート製剤を積極的に使用しているが，現在のところは骨転移と診断されるのが遅く，その後の生存期間も短いため，その効果が確認できていないというのが現況である．今後，膵癌骨転移がより早期に診断されるならば，従来の治療法に加えてビスフォスフォネート製剤を適宜，組み合わせることにより，QOLの低下防止につながることが期待される．

おわりに

以上，膵癌骨転移の自験症例より，その臨床的特徴をまとめてみた．今後も膵癌において骨転移が増加するであろうし，そのことに留意して，骨転移をより早期に診断し，また早期に治療を施すことにより患者QOLの低下を防止せねばならない．

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Clinical features and management of pancreatic cancer with bone metastases

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Prognosis of pancreatic cancer is one of the worst among various cancers, however, incidence of bone metastasis has been increased even in pancreatic cancer in recent years. Therefore, we examined clinical features of pancreatic cancer presenting bone metastases who were treated in our cancer center, and propose how to manage these patients.

We experienced 13 patients (7.3%) with pancreatic cancer with bone metastases during 2000-2003. Among these patients, pancreatic cancer was located at pancreatic body to tail in 10 cases, while it was located at pancreatic head in 3 cases. Liver metastasis was noted in 7 of 13 cases with bone metastases. Radiographical imagings of bone lesions revealed osteolytic bone destruction, and serum levels of bone resorption marker, 1 CTP, were elevated in these patients. Stimulation of osteoclastic bone resorption is a critical step for bone metastasis, thus, serum levels of cytokines (PTHrP, IL-6, VEGF), which exert a promotive effect on bone resorption, were measured. Serum levels of IL-6 and VEGF were elevated in most of these patients, while elevation of serum PTHrP levels was found in 3 of 13 patients with bone metastases. Survival periods of pancreatic cancer patients with bone metastases was not long, however, treatment for bone metastases is important in terms of quality of life (QOL). An earlier diagnosis is essential to prevent deterioration in the QOL of pancreatic cancer patients presenting bone metastases. Periodical measurement of serum 1CTP in addition to bone scintigraphy is helpful for the earlier diagnosis for bone metastases.

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〔原　著〕

Stage IV膵癌に対する放射線化学療法とgemcitabineによる化学療法の成績

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要　旨：1991年から2002年に放射線化学療法（CRT）を完遂した自験膵癌52例（stage IVa 27例：A群，IVb 25例：B群，その亜分類N_3（+）7例：B1群，M（+）18例：B2群）とgemcitabine（GEM）での化学療法22例（C群）を対象に，各群の治療成績を累積生存曲線で比較検討した．CRTはcisplatinあるいは5-fluorouracil（5-FU）を増感剤とし，総線量50.4 Gy照射後，5-FUまたはGEMを投与した．A，B，C群の50%生存期間（median survival time, MST）はそれぞれ366日，196日，256日で生存曲線ではB，C群に比しA群で有意な延長を認めた（$p<0.001$，$p<0.05$）．各群間の生存曲線の比較では，B2群（n=18，MST；158日）に比べ，A+B1群（n=34，MST；341日），B1群（n=7，MST；249日）も有意な延長を示した（$p<0.0001$，$p<0.005$）．C群はB2群より有意の延長を認め（$p<0.05$），B1群と有意差はなかった．維持化学療法の薬剤に関し，GEMを用いた群（GEM群，n=8）のMSTは434日，5-FUを用いた群（5-FU群，n=43）のMSTは218日で，前者の生存曲線が有意に延長していた（$p<0.05$）．以上より，遠隔転移例にはCRTではなくGEM投与を行うべきで，遠隔転移がないIVb例もGEM投与を検討する余地が示唆された．CRT後の化学療法は，5-FUよりもGEMの投与が推奨される．また，GEMを増感剤として使用したCRTの成績の検討も重要であると思われた．

索引用語：進行膵癌　放射線化学療法　化学療法　gemcitabine　累積生存曲線

背景と目的

Burrisらの報告[1]以来，stage IVの膵癌の治療法は，遠隔転移が存在する場合は，gemcitabine（GEM）を用いた化学療法が第一選択であることは一般に認知され，筆者らが行った多施設における進行膵癌に対するGEMの成績[2]でも平均生存期間は約7.5カ月で当科における従来の化学療法の成績調査[3]に比べ良好であった．一方，遠隔転移のないstage IVaのいわゆる局所進行膵癌に対する治療法は，外科的療法か，内科的療法かは長い間議論の的であった．我々は，以前から積極的に放射線化学療法（CRT：chemoradiation）を施行してその治療成績を報告してきた[4]が，今後CRTにもGEMが使用されることが十分考えられる．そこで今回，進行膵癌の標準的治療方針の決定に向けて検討すべき課題は何であるかを整理するため，筆者らの施設において行われてきたstage IVの膵癌に対する治療成績を顧みた．

対象と方法

1991年から2002年に当施設で，CRTが完遂できたstage IVの膵癌52例，およびGEMでの化学療法を施行した遠隔転移を有した22例を対象とした．CRTはcisplatin　6 mg/m²あるいは5-fluorouracil（5-FU）250 mg/m²を増感剤として放

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射線照射直前に点滴静注し，総線量50.4 Gy (1.8 Gy/回，28回)の照射を行った．その後は5-FU(1例は経過中に5-FUからGEMに変更，8例はGEM)を用いた維持化学療法を行った．原則として5-FUは500 mg/m²を週1回，GEMは1,000 mg/m²を週1回の割合で外来で投与した．なお，CRTの完遂率は86.7% (52/60例)で，中止理由は全身倦怠感が多かった．Stagingは膵癌取扱い規約第5版[5]の分類を用いて，CT，血管造影の所見を主体に行った．CRT症例をA群：IVa 27例，B群：IVb 25例，その亜分類としてB1群：N_3(+)でその他の遠隔転移のないIVb 7例，B2群：遠隔転移を有するIVb 18例とした．CRT施行前の画像検査では明らかな肝転移を指摘できずに，CRT直後に肝転移を認めた6症例はB2群とした．また，GEMでの治療群22例(IVb)をC群とした．対象の背景をTable 1に示した．各群の性，年齢に差は認めないが，GEM群は遠隔転移を伴うstage IVb症例が主体なので，発見が遅れる傾向にある体尾部癌が他の2群に比べ多かった．以上の各群の累積生存曲線（以下生存曲線）をKaplan-Meier法にて評価し，log-rank検定で比較検討した．

Table 1　Subjects

therapy	chemoradiation		gemcitabine
stage	IVa	IVb*	IVb
No. of patients	27 cases	25 cases	22 cases
male	16 cases	16 cases	13 cases
famale	11 cases	9 cases	9 cases
age (years) (M±SD)	64.7±9.0	66.6±11.0	61.1±11.7
localization			
head	20 cases	15 cases	4 cases
head/body			1 case
body/tail	7 cases	10 cases	15 cases
whole			1 case
unknown			1 case

* Twenty-five patients with stage IVb disease received chemoradiotherapy. They included 7 patients who bad N_3 lymph node metastasis but lacked liver metastasis. Six patients classified as stage IVb disease because liver metastases appeared soon after chemoradiotherapy.

成　績

まず，A，B，C群の50%生存期間（median survival time, MST）はそれぞれ366日，196日，256日で，生存曲線はB，C群に比しA群で有意な延長を認めた(p＝0.0008, p＝0.0247) (Fig. 1)．A＋B1群の生存曲線は(n＝34，MST；341日)，B2群の生存曲線と比較すると有意の延長を認めた(p＜0.0001) (Fig. 2)．B1とB2群のMSTはそれぞれ249日，158日で，生存曲線はB1群にお

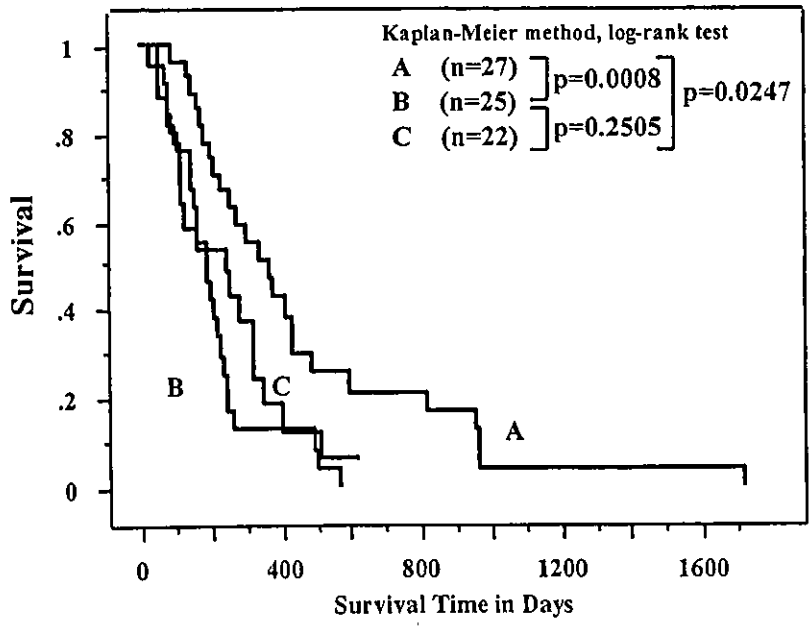

Fig. 1　Survival of patients according to treatment and stage of disease

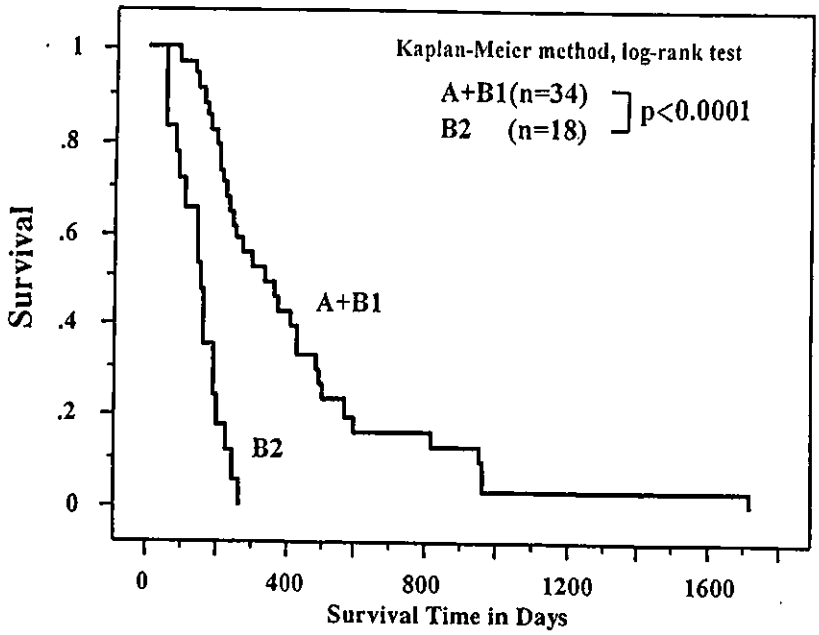

Fig. 2 Survival of patients who received chemoradiotherapy according to distant metastasis

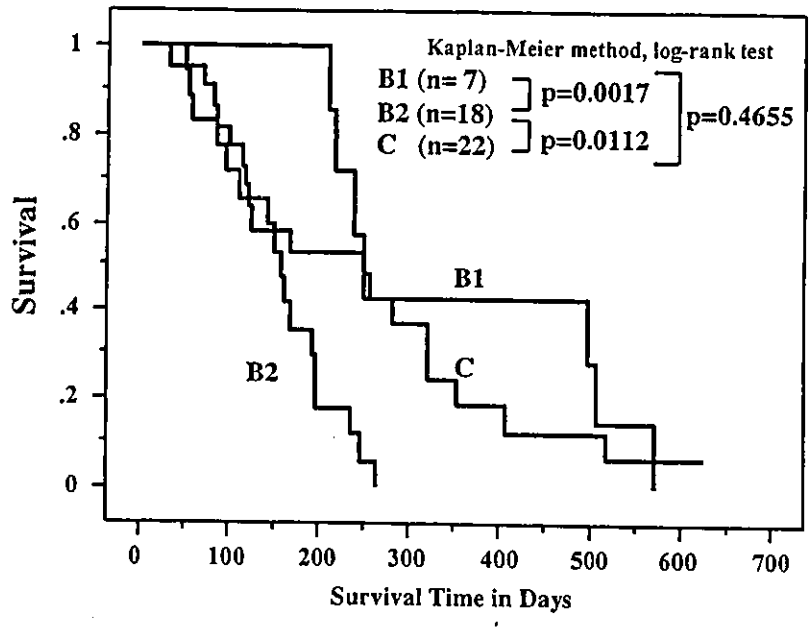

Fig. 3 Survival of patients with stage IVb disease according to treatment and distant metastasis

いて有意の延長を認めた（p=0.0017）．AとB1群間の生存曲線に有意の差は認めず（p=0.5756），B2とC群の生存曲線ではC群の有意の延長を認めた（p=0.0112）．B1とC群間の生存曲線でも有意の差は認めなかった（p=0.4655）(Fig. 3)．以上の各群別のMSTと平均生存期間を，Table 2にまとめて示した．

次に，A+B1群(n=34)，すなわち，遠隔転移のないstage IV症例の治療成績について検討を加えた(Table 3)．腫瘍占拠部位別では頭部(n=26, MST；279日)，体尾部(n=8, MST；366日)で，生存曲線に有意な差は認めなかった．腫瘍マーカーの推移が判定できた26例について，50%以上の低下群（n=9），不変群（n=8），上昇群（n=9）の3群で比較すると，MSTはそれぞれ571日，279日，211日で上昇群，不変群，低下群の順に延長する傾向を認めたが，生存曲線では各群間に有意の差は認めなかった．また，抗腫瘍効果については，PR群(n=5)，NC群(n=21)，PD群(n=4)では，MSTはそれぞれ599日，377日，201日