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Is pancreaticogastrostomy safer than pancreaticojejunostomy?

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Abstract
Background/Purpose. Failure of a pancreatic–enteric anastomosis very frequently leads to morbidity and mortality after pancreaticoduodenectomy. Pancreaticojejunostomy or pancreaticogastrostomy is often used after pancreaticoduodenectomy. The many reports on pancreaticogastrostomy support the low rates of anastomotic leakage and mortality compared with pancreaticojejunostomy.
Methods. Between January 1995 and December 2004, 155 pancreaticojejunostomies and 58 pancreaticogastrostomies were performed after pancreatic resection in the Second Department of Surgery of Nagoya University Hospital. Postoperative morbidity and mortality were analyzed.
Results. The incidence of pancreatic fistula was similar for the pancreaticojejunostomy (12.2%) and pancreaticogastrostomy (20.7%) groups and the mortality rate was 0% in both groups.
Conclusions. This restrospective clinical study suggested no significant difference in the incidence rate of pancreatic fistula and mortality between pancreaticojejunostomy and pancreaticogastrostomy.

Key words Pancreaticogastrostomy · Pancreaticojejunostomy · Morbidity · Mortality · Pancreatic fistula

Introduction

Pancreaticoduodenectomy has become the treatment of choice for benign and malignant diseases of the head of the pancreas and periampullary region. The mortality rate of pancreaticoduodenectomy has decreased in recent years at major surgical centers.[1] However, leakage from the pancreatic–enteric anastomosis still occurs and can be a source of considerable morbidity and can contribute to mortality. Pancreaticojejunostomy is commonly used after pancreaticoduodenectomy. Various modifications of pancreaticojejunal anastomosis have been tested, but no universal agreement has been reached regarding one particular variation of pancreaticojejunostomy being safer, less prone to fistula formation, or both. Pancreaticogastrostomy was first described clinically by Waugh and Clagett in 1946,[2] and it was considered to be safer than pancreaticojejunostomy.[3–11] This article introduces our experience of pancreaticojejunostomy and pancreaticogastrostomy and reviews the published reports on pancreaticogastrostomy.

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Methods

Between January 1995 and December 2004, 213 pancreatectomies with pancreatoenterostomy were performed in our institute. The reasons for pancreatic resection are shown in Table 1: pancreatic duct carcinoma in 90 patients, bile duct carcinoma in 23 patients, ampullary carcinoma in 19 patients, intraductal papillary mucinous neoplasm in 43 patients, chronic pancreatitis in 6 patients, duodenal carcinoma in 5 patients, duodenal carcinoid in 4 patients, islet cell tumor in 4 patients, serous cystadenoma in 3 patients, and other tumors in 16 patients.

Pancreaticojejunostomy was performed in 155 patients and pancreaticogastrostomy was performed in 58 patients (Table 2). Pancreaticojejunostomy was performed in end-to-side fashion using mucosa-to-mucosa anastomosis. Our method of pancreaticogastrostomy is as follows: The pancreatic remnant is freed from the retroperitoneal space for about 3 cm. A stent is inserted into the pancreatic duct and fixed. Posterior gastrostomy of a suitable size for the stump of the pancreatic remnant is done and anterior gastrostomy is performed. The pancreatic stump is inserted into the gastric lumen in posterior gastrostomy. Pancreaticogastrostomy is done in the gastric lumen via anterior gastrostomy

Table 1. Indication for pancreatic resection

	Pancreaticojejunostomy ($n = 155$)	Pancreaticogastrostomy ($n = 58$)
Pancreatic duct carcinoma	86	4
Bile duct carcinoma	22	1
Ampullary carcinoma	17	2
IPMN	7	36
Chronic pancreatitis	6	0
Duodenal carcinoma	5	0
Duodenal carcinoid	0	4
Islet cell tumor	1	3
Serous cystadenoma	1	2
Others	10	6

IPMN, intraductal papillary mucinous neoplasm

Table 2. Comparison of procedures for pancreatic resection

Procedures of pancreatic resection	Pancreaticojejunostomy ($n = 155$)	Pancreaticogastrostomy ($n = 58$)
Pancreaticoduodenectomy	97	0
Pylorus-preserving pancreaticoduodenectomy	56	10
Pancreatic head resection with segmental duodenectomy[12]	0	30
Segmental resection	0	18
Letton and Wilson	2	0

Table 3. Comparison of mean age, mortality, and morbidity

	Pancreaticojejunostomy ($n = 155$)	Pancreaticogastrostomy ($n = 58$)
Age (years)	63.1 + 9.7	60.0 ± 10.4
Sex (male:female)	102:53	37:21
Mortality	0 (0%)	0 (0%)
Leakage	19 (12.2%)	12 (20.7%)
Bleeding	5 (3.2%)	3 (5.2%)
Bleeding caused by leakage	3/19 (15.9%)	1/12 (8.3%)

(Fig. 1). The stent is brought out through the anterior gastric wall and the anterior gastrostomy is closed. Mortality and morbidity rates, especially the anastomotic leakage and postoperative intra-abdominal bleeding, were analyzed.

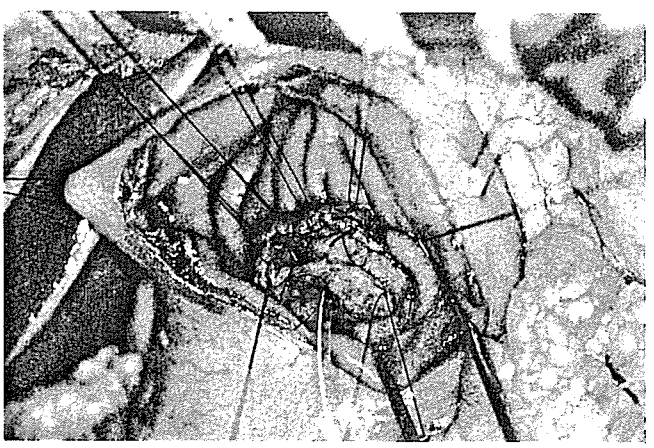

Fig. 1. Pancreaticogastrostomy being performed in our institution

Results

Table 3 compares the mean age, mortality, and morbidity between the pancreaticojejunostomy and pancreaticogastrostomy groups. There were 139 men and 74 women with a mean age of 62 ± 10 years (range 26–83 years). No mortality was observed in either group. The overall incidence of leakage of pancreaticoenterostomy was 14.6% (31/213), which was similar for the pancreaticojejunostomy (12.2%, 19/155) and pancreaticogastrostomy (20.7%, 12/58) groups. Postoperative

Table 4. Pancreaticogastrostomy versus pancreaticojejunostomy

Author	Year	Journal	Cases	Leakage	Hospital deaths	Type of study
Flaunter L et al.[3]	1985	Am J Surg	P–G 27 P–J 28 D–O 30		0 (0%) 3 (10.7%) 4 (13.3%)	Retrospective
Miyagawa S et al.[4]	1992	Hepatogastroenterology	P–G 21 P–J 31	1 (4.8%) 6 (19.4%)	0 3 (9.8%)	Retrospective
Yeo CJ et al.[13]	1995	Ann Surg	P–G 73 P–J 72	9 (12.3%) 8 (11.1%)	0 0	Prospective randomized
Pikarsky AJ et al.[5]	1997	Arch Surg	P–G 28	4 (14.3%)	1 (3.6%)	
Farbe JM et al.[6]	1998	Br J Surg	P–G 160	4 (2.5%)	5 (3%)	Retrospective
Kapur BML et al.[7]	1998	Am J Surg	P–G 125	0 (0%)	6 (4.8%)	Retrospective
Mason GR[8] (review)	1999	World J Surg	P–G 199 (1946–1988) P–G 614 (1990–1997)	2 (1%) 29 (4.7%)	9 (4.5%) 20 (3.3%)	
Takano S et al.[9]	2000	Br J Surg	P–G 73 P–J 69	0 (0%) 9 (13%)	0 (0%) 2 (3%)	Prospective nonrandomized
Schlitt HJ et al.[10]	2002	Br J Surg	P–G 250 P–J 191	7 (2.8%) 24 (12.6%)	17 (4.4%) 24 (12.6%)	Retrospective
Aranha GV et al.[11]	2003	J Gastrointest Surg	P–G 117 P–J 97	19 (16.3%) 18 (18.6%)	0 (0%) 4 (4.1%) 30d. mortality	Retrospective
Watanabe M et al.[14] Japan Pancreas Surgery Group survey	2004	J Hepatobiliary Pancreat Surg	P–G 511 P–J 2483	56 (11%) 330 (13.3%)	5 (0.98%) 45 (1.81%)	Retrospective
Nakao A et al. (this article)	2005	J Hepatobiliary Pancreat Surg	P–G 58 P–J 155	12 (20.7%) 19 (12.2%)	0 (0%) 0 (0%) 30d. mortality	Retrospective

P–J, pancreaticojejunostomy; P–G, pancreaticogastrostomy; D–O, duct occlusion

massive bleeding was observed in 5 of 155 (3.2%) patients undergoing pancreaticojejunostomy and in 3 of 58 (5.2%) patients undergoing pancreaticogastrostomy. Postoperative bleeding caused by leakage from pancreaticoenterostomy occurred in 3 of 19 patients (15.9%) who underwent pancreaticojejunostomy and 1 of 12 patients (8.3%) who underwent pancreaticogastrostomy. Thus, there seems to be no marked difference in mortality and morbidity between the pancreaticojejunostomy and pancreaticogastrostomy groups in our series.

Discussion

Mortality following pancreaticoduodenectomy is attributed mainly to leakage of the pancreaticoenterostomy. Pancreaticojejunostomy is commonly used after pancreaticoduodenectomy in our department. Pancreaticogastrostomy is performed after pancreatic head resection with segmental duodenectomy[12] or segmental resection of the pancreatic body for benign or low-grade-malignancy tumor of the pancreas. There are large differences between the pancreaticojejunostomy and pancreaticogastrostomy groups concerning the background of pancreatic disease and the pancreatic resection procedure in our series. Therefore, it is difficult to compare statistically the mortality and morbidity between the pancreaticojejunostomy and pancreaticogastrostomy groups. However, there were no apparent differences in mortality and morbidity between the pancreaticojejunostomy and pancreaticogastrostomy groups. The incidence of pancreatic fistula in our series was relatively high, but there was no mortality in our department. The relatively high incidence of pancreatic fistula in the pancreaticogastrostomy group may have been caused by the higher incidence of soft and normal pancreatic remnants compared with the pancreaticojejunostomy group in our series, because pancreaticogastrostomy was mainly indicated for intraductal papillary mucinous neoplasm or benign tumor of the pancreas.

Pancreaticogastrostomy has gained favor in recent years as a potential means of reducing the incidence of pancreatic fistula after pancreaticoduodenectomy[3–11] (Table 4). However, these studies were restrospective and nonrandomized. Yeo et al.[13] conducted the first proper prospective randomized study. Their prospective randomized comparison of pancreaticojejunostomy and pancreaticogastrostomy revealed no difference in the incidence of pancreatic fistula and no mortality in either group (Table 4). It is important to note that their study was performed in an institution with a high volume of pancreaticoduodenectomies every year and by a group of surgeons with extensive experience in pancreatic resection. Watanabe et al.[14] published the Japan Pancreas Surgery Group survey of 511 pancreaticogastrostomy patients and 2483 pancreaticojejunostomy patients. There were no significant differences between pancreaticogastrostomy and pancreaticojejunostomy with respect to the incidence rates of intrabdominal hemorrhage and abscess or mortality (Table 4). These two reports indicated no advantage for either pancreaticogastrostomy or pancreaticojejunostomy regarding short-term outcomes, but additional follow-up is needed to evaluate differences in, for example, long-term pancreatic function or patency of the main pancreatic duct.[15]

In conclusion, we could not support the hypothesis that pancreaticogastrostomy was safer than pancreaticojejunostomy. In recent years, the morbidity and mortality rates of both pancreaticojejunostomy and pancreaticogastrostomy have decreased, and there may be no significant differences in morbidity and mortality rates for these procedures in a large-patient-volume institution.

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Clinical Significance of Focal Adhesion Kinase in Resectable Pancreatic Cancer

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Abstract

Focal adhesion kinase (FAK) is a non-receptor, cytoplasmic protein tyrosine kinase that is involved in the regulation of cellular signaling, migration, apoptosis, and cell cycle progression. Previous reports have shown that FAK is expressed in various kinds of cancer tissues and cancer cell lines; however, no information is available about human pancreatic carcinoma specimens. Tissue such specimens were obtained from 50 patients who underwent pancreatic resection for pancreatic invasive ductal carcinoma at our institute from 1996 to 2002. Immunohistochemical analysis of FAK was performed in the resected specimens. Focal adhesion kinase expression in seven human pancreatic cancer cell lines was analyzed by reverse transcription polymerase chain reaction (PCR) analysis and Western blot analysis. Focal adhesion kinase expression was detected in 24 of 50 cases (48%). There was a statistically significant correlation between FAK expression and tumor size ($P = 0.004$), although FAK expression did not significantly correlate with other factors such as tumor histological grade, lymph node metastasis, distant metastasis, histological stage, and overall survival. Reverse transcription PCR analysis and Western blot analysis showed that FAK was expressed in all seven pancreatic cancer cell lines. Focal adhesion kinase expression was not directly related to clinicopathological factors except tumor size in pancreatic carcinoma. Focal adhesion kinase expression may not be a prognostic marker for pancreatic cancer patients.

Pancreatic ductal adenocarcinoma is one of the most aggressive tumors associated with high morbidity and mortality. It is the fourth leading cause of cancer death, accounting for an estimated 30,700 new cases and an estimated 30,000 deaths annually in the United States. This malignancy is highly fatal with an overall 5-year survival rate of less than 5% even after aggressive surgical treatment.

Focal adhesion kinase (FAK) is a non-receptor cytoplasmic protein tyrosine kinase that is localized to cellular focal adhesions; it was originally isolated from v-src–transformed chick embryo fibroblasts.[1] Focal adhesion kinase protein plays physiologically important roles in the regulation of cellular signaling, adhesion, migration, apoptosis, and cell cycle progression.[2–4] In addition, FAK expression is elevated in a number of different tumors including breast, colon, thyroid, head and neck, ovarian, liver, and esophageal cancers;[5–9] however, no information is available on FAK expression in pancreatic cancer. The present study was conducted to determine the relationship between FAK expression and the clinicopathological factors in pancreatic adenocarcinoma.

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MATERIALS AND METHODS

Tissue Samples

Formalin-fixed paraffin-embedded tissue specimens were obtained from 50 patients with pancreatic invasive ductal carcinoma confirmed by histopathologic diagnosis who underwent pancreatic resection at the Department of Surgery and Surgical Basic Science, Kyoto University, between 1996 and 2002. Patients with other pancreatic malignancies such as intraductal papillary mucinous neoplasm, acinar cell carcinoma, or endocrine tumors were excluded. The patients included in this study were 31 men and 19 women, whose ages ranged from 45 to 79 years (64.3 ± 8.3 years [mean ± SD]). Tumor specimens were collected after obtaining the patients' informed consent in accordance with institutional guidelines. Tissue samples were fixed with 4% paraformaldehyde, embedded in paraffin, and cut into 4-μm-thick sections.

Immunohistochemistry

All slides were deparaffinized using xylene, 100% ethanol, and 90% ethanol, followed by a thorough deionized water wash. During heat-induced epitope recovery, sections were kept at 95°C while submerged in Target Retrieval Solution (S3307; DAKO Cytomation, Kyoto, Japan) for 45 minutes, then cooled for 20 minutes at room temperature followed by a twice deionized water wash. To quench endogenous peroxidase activity, samples were blocked in 3% hydrogen peroxide in methanol for 15 minutes at room temperature and then washed in Tris buffered saline buffer containing 0.05% Tween 20 (TBST). Sections were blocked in normal goat serum for 30 minutes, then blown off and incubated at 4°C overnight with mouse antihuman FAK antibody (05-537; Upstate Biotechnology, Waltham, MA) at a dilution of 1:200 in Dako diluent (DAKO Cytomation, Kyoto, Japan). The sections were washed in TBST and then incubated with biotinylated goat anti-mouse IgG at a dilution of 1:300 (DAKO Cytomation) for 60 minutes at room temperature. The slides were washed in TBST, and then horseradish peroxidase-conjugated streptavidin at a 1:300 dilution (DAKO Cytomation) was applied for 20 minutes incubation. The chromogenic reaction was performed with DAB, toned with the DAB + substrate solution (K3468; DAKO Cytomation) for 5 minutes. Slides were counterstained with Mayer hematoxylin for 5 minutes before they were dehydrated and cover-slipped with permanent mounting medium (Richard-Allan Scientific, Kalamazoo, MI). Negative controls were prepared by substituting normal mouse serum for primary antibody, and no detectable staining was evident.

Immunohistochemical Scoring

The expression of FAK was evaluated independently by two investigators (K.F. and R.D.) in blinded fashion. For each tissue, FAK expression was examined on a scoring system that measured intensity (0, none; 1, borderline; 2, weak; 3, moderate; 4, strong) and the proportion of positively stained cells among cancer cells (0 = none; 1 = 1%–49%; 2 = 50%–100%). Scores between investigators were averaged, and a mean scored was calculated for each sample. The staining intensity score was multiplied by the score of positively stained cells to obtain the overall score. The specimens with a staining intensity score greater than 2 were regarded as positive expression of FAK.

Cell Lines

Pancreatic cancer cell lines, AsPC-1, BxPC-3, CFPAC-1, HPAC, MIAPaCa-2, PANC-1, and Suit-2, were cultured as monolayers in the appropriate medium[10] supplemented with 10% fetal bovine serum, 100 U/ml penicillin, and 100 μg/ml streptomycin and maintained in a 5% humidified CO2 atmosphere at 37°C, and the medium was replaced as needed.

Western Blot Analysis

To perform sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and Western blot analysis for FAK expression, cells were plated onto 100-mm dishes and grown to 80% confluence. Cells were harvested by scraping on ice and lysed for 60 minutes in phosphorylation-inhibitory RIPA buffer containing 50 mM Hepes (pH 7.0), 250 mM NaCl, 0.1% Nonidet P-40, 1 mM phenylmethylsulfonyl fluoride (PMSF), and 20 μg/ml gabexate mesilate, and then they were sonicated for 20 seconds. Total extracts were cleaned by centrifugation at 12,000 rpm for 10 minutes at 4°C and the supernatants were collected. Protein concentrations were measured using BCA Protein Assay Reagents (Pierce, Rockford, IL). The lysates were re-suspended in the same volume of the gel loading buffer, which contained 50 mM Tris-HCl (pH 6.7), 4% SDS, 0.02% bromophenol blue, 20% glycerol, and 4% 2-mercaptoethanol, and then boiled at 95°C for 3 minutes. The extracted protein was subjected to

Western blotting, as previously described.[10] In brief, 30-microgram aliquots that were taken from the total quantity of protein were size-fractionated to a single dimension by SDS-PAGE (6% sodium dodecylsulfate gel) and transblotted to 0.45-μm polyvinylidene difluoride membrane (Bio-Rad, Richmond, CA) in a semi-dry electroblot apparatus (Bio-Rad). Membranes were blocked overnight at 4°C in Tris-buffered saline (TBS) containing 5% bovine serum albumin and 0.1% Tween 20. The membrane was probed with anti-FAK monoclonal antibody at 1:1000 dilution (05-537; Upstate Biotechnology, Waltham, MA), anti-FAK rabbit polyclonal phosphospecific antibody at 1:500 dilution (44-624; Biosource, Camarillo, CA) or anti-beta-actin monoclonal antibody at 1:5000 dilution (A5441; Sigma, St. Louis, MO). Anti-beta-actin antibody served as the internal control. The membrane was washed with several changes of medium. The proteins were visualized by enhanced chemiluminescence regents (Amersham, Buckinghamshire, UK) according to the manufacturer's instructions using goat anti-mouse horseradish peroxidase-conjugated IgG at 1:2000 dilution (62-6520; ZYMED, San Francisco, CA) or goat anti-rabbit horseradish peroxidase-conjugated IgG at 1:2000 (62-6120; ZYMED). Membranes were exposed to x-ray film for 20–60 seconds.

Reverse-transcriptional PCR

Total cellular RNA was extracted using TRIZOL Reagent (Life Technologies, Rockville, MD), and cDNA was synthesized by random priming from 1 μg of total RNA using a first-strand cDNA synthesis kit (Pharmacia Biotech, North Peapack, NJ) according to the manufacturer's instructions. Primer sequences used are listed as forward then reverse 5′ to 3′. Focal adhesion kinase primers 5′ aatacggcgatcatactggg3′ and 5′catgccttgcttttcg ctgt3′ amplify a product of 620 base pairs, and beta-actin primers 5′ggcatcgtgatggactccg3′ and 5′gctggaaggt ggacagcg3′ amplify a product of 612 base pairs. The PCR was carried out with a mixture of cDNA (derived from 100 ng of RNA), 0.2 μM each of the sense and antisense primers, 0.2 μM of deoxynucleotide triphosphate, and 2.5 U Taq DNA polymerase in reaction buffer (TaKaRa, Kyoto, Japan) with a final volume of 50 μl. The PCR reactions were performed as follows; 1 cycle of 94°C for 5 minutes; then 40 cycles of 94°C for 30 seconds, 52°C for 30 seconds, 72°C for 30 seconds, and finally 1 cycle of 72°C for 7 minutes in a thermal cycler (Gene Amp PCR system 2400; PE Applied Biosystems, Foster City, CA). Products of amplification were separated on 1% agarose gel and photographed after ethidium bromide staining.

Statistical Analysis

Clinicopathological characteristics were compared with FAK expression (positive and negative) using the chi-squared test or the Fisher's exact probability test. The Kaplan-Meier method was used to calculate the survival curves, and the log-rank test was performed to compare differences in the survival rates of patients. All analyses were done using Stat View software (version J-4.5; Abacus Concepts, Berkeley, CA). A probability value < 0.05 was considered statistically significant.

RESULTS

FAK mRNA Expression and FAK Protein Expression in Pancreatic Cancer Cell Lines

The mRNA expression of FAK in seven pancreatic cancer cell lines (AsPC-1, BxPC-3, CFPAC-1, HPAC, MIAPaCa-2, PANC-1, and Suit-2) derived from human pancreatic adenocarcinoma was tested with reverse-transcriptional PCR analysis. Focal adhesion kinase mRNA was detected in all seven cell lines (Fig. 1).

Focal adhesion kinase protein expression levels in pancreatic cancer cell lines were evaluated by Western blot analysis (Fig. 2). In all seven pancreatic cancer cell lines the FAK protein was detected as a single band corresponding to the molecular size of 125 kDa. The FAK expression at the protein level was similar among seven cell lines.

FAK Phosphorylation at Tyrosin 397 in Pancreatic Cancer Cell Lines

There are six tyrosin phosphorylation sites in the FAK catalytic domain. The major site of autophosphorylation, tyrosin 397, is a docking site for the SH2 domains of a number of proteins, including the Src family of tyrosin kinase[11], phosphatidylinositol 3′-kinase[12], phospholipase C[13], and Grb7[14]. To investigate the catalytic activity of FAK in each cell line, immunoblotting with anti-FAK [pY397] was performed (Fig. 3). The level of FAK phosphorylation at tyrosine 397 was not changed by serum in all cell lines.

Expression of FAK in Pancreatic Cancer and Normal Pancreatic Tissues

Focal adhesion kinase expression in pancreatic tissues was investigated by immunohistochemical analy-

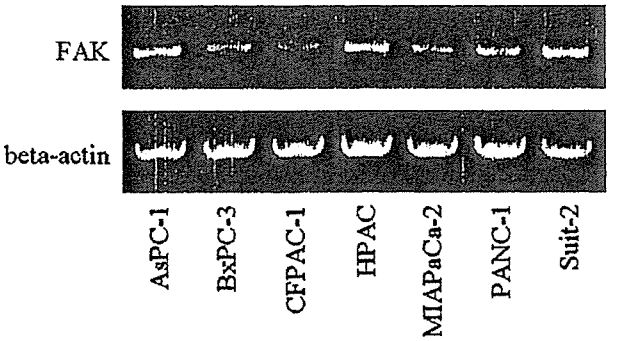

Figure 1. FAK mRNA expression in pancreatic cancer cell lines. Reverse-transcriptional PCR analysis showed the mRNA expression of FAK in seven cell lines derived from pancreatic adenocarcinoma. FAK mRNA expression was detected in all seven cell lines.

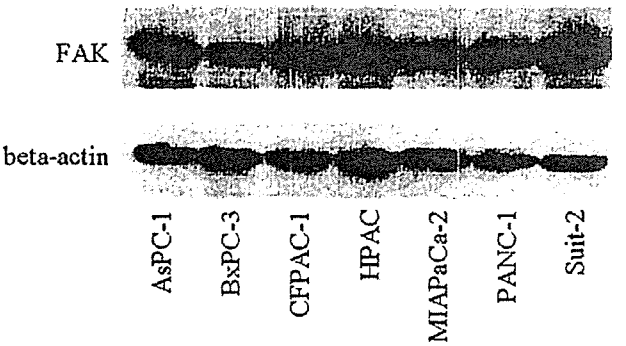

Figure 2. Expression of FAK protein in pancreatic cancer cell lines. FAK was detected in pancreatic cancer cell lines by Western blot. The FAK expression levels were similar among cell lines.

Table 1.
Clinical profile of patients with pancreatic cancer

	FAK-positive n = 24 (48%)	FAK-negative n = 26 (52%)
Age	64.1 ± 8.5	64.4 ± 8.2
Sex	15	16
male	15	16
female	9	10

sis, and FAK staining was identified not only in cancer cells but also in normal ductal cells (Fig. 4). In normal pancreatic tissue, FAK staining was observed strongly in the cytoplasm of ductal cells, faintly in islet cells, but not in acinar cells. In pancreatic cancer tissue, FAK was expressed in the cytoplasm and on the plasma membrane of the cancer cells (Fig. 5). Several sections showed labeling of the majority of cancer cells, whereas in others, only some areas of the tumor were found to be positive for FAK (Fig. 6). As heterogeneous expression of FAK was observed in cancers, FAK expression was evaluated with the criteria described in *Materials and Methods*. Of the 50 invasive ductal adenocarcinomas studied, FAK expression was positive in 24 samples (48%) and negative in 26 samples (52%) (Table 1).

Relationship between FAK Protein Expression and Clinicopathological Features and Survival Rate of the Patients

The relationship between FAK expression and the clinicopathological factors was analyzed (Table 2). There was a statistically significant correlation between FAK expression and tumor size ($P = 0.004$). However, FAK expression did not significantly correlate with other factors such as age, sex, tumor histological grade, lymph node metastasis, distant metastasis, International Union Against Cancer (UICC) stage, portal venous system invasion, nerve invasion, arterial invasion, anterior pancreatic serosal invasion, and retroperitoneal tissue invasion. In terms of the FAK expression status, the survival rate was not statistically different between the two groups (Fig. 7).

DISCUSSION

Focal adhesion kinase has been reported to be strongly expressed by a variety of human tumors including breast, colon, thyroid, head and neck, ovarian, liver, and esophageal cancers, as well as brain, head and neck, thyroid, breast, esophagus, stomach, liver, colon, ovarian, and prostate cancers.[5–9] Several reports on esophageal[9] and hepatocellular carcinomas[15] showed that the survival rate of the patients with FAK-positive cancer was significantly worse than that of the patients with FAK-negative cancer. In addition, it has been reported that FAK expression was stronger in cancer tissues than that in normal tissues.[5,9,15–17] Together with the reports from in vitro experiments,[2–4] FAK has been implicated in the regulation of important cancer cell behaviors such as adhesion, spreading, migration, invasion, metastasis, and apoptosis.

In the present study, we first showed that FAK is upregulated and strongly expressed in all seven pancreatic cancer cell lines at the levels of mRNA, protein, and phosphorylated protein. At the tissue level, we also demonstrated for the first time that FAK was present in 24 of the 50 patients (48%). Therefore, it is speculated that FAK could have some roles in the progression of pancreatic cancer.

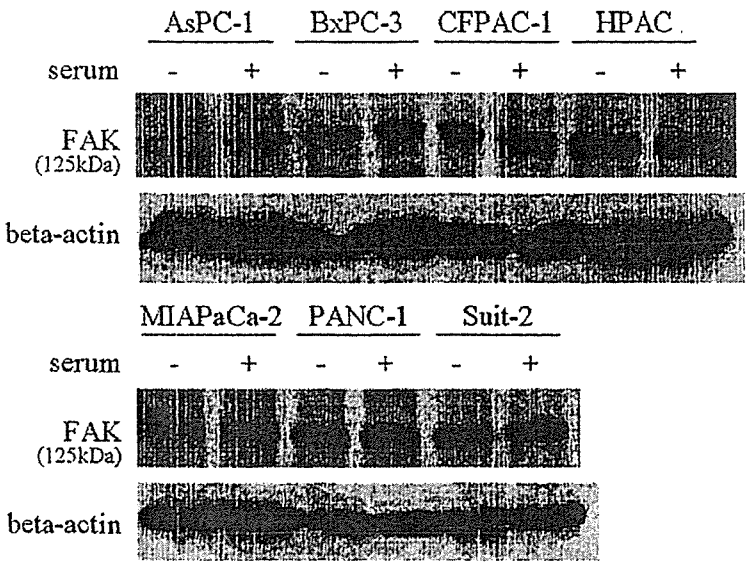

Figure 3. FAK phosphorylation at tyrosin 397 in pancreatic cancer cell lines. The level of FAK phosphorylation at tyrosine 397 was not changed by serum in all cell lines.

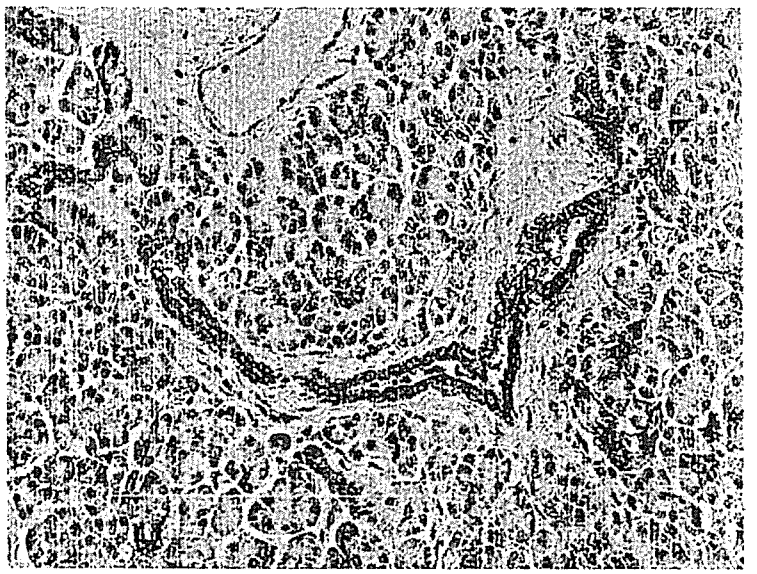

Figure 4. Immunohistochemical detection of FAK in normal pancreatic tissue. In normal pancreatic tissue FAK staining was observed in the cytoplasm of ductal cells and faintly in islet cells, but not in acinar cells. The nuclei are counterstained with Mayer's haematoxylin. The scale bar is 200 μm.

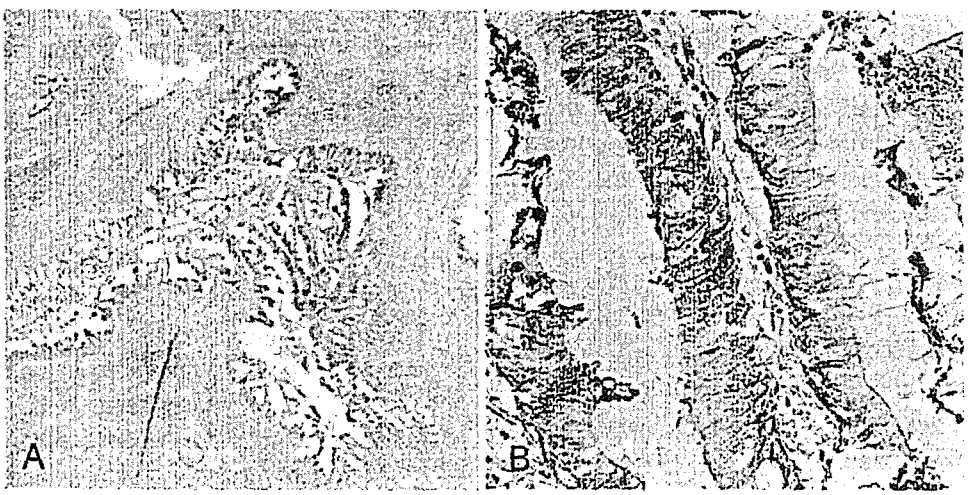

Figure 5. Immunohistochemical detection of FAK in pancreatic adenocarcinoma. In pancreatic cancer tissue, FAK was expressed in the cytoplasm and on the plasma membranes of the cancer cells. Original magnification; x 200 (A): x1000 (B).

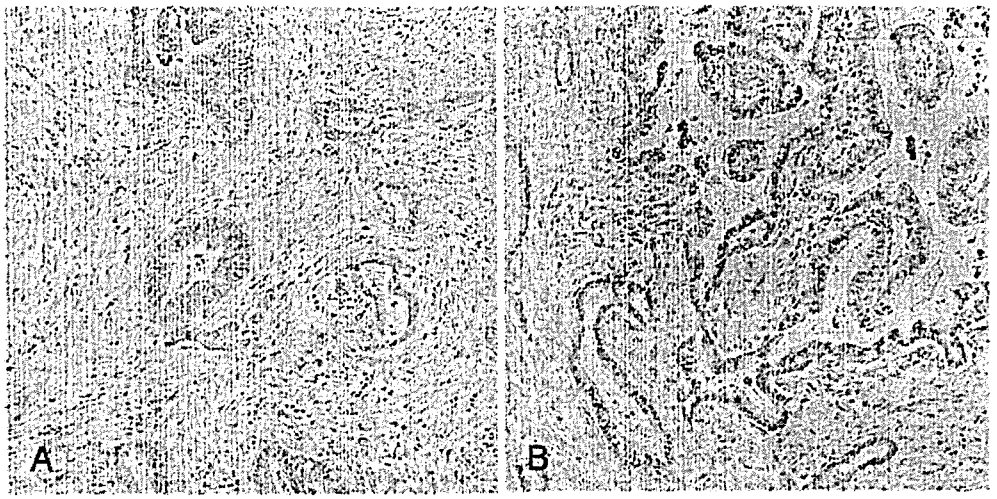

Figure 6. Heterogenous expression of FAK in pancreatic cancer tissues. Several sections showed labeling of the majority of cancer cells (A), whereas in others only a part of tumor area was positive for FAK (B). Original magnification; × 200.

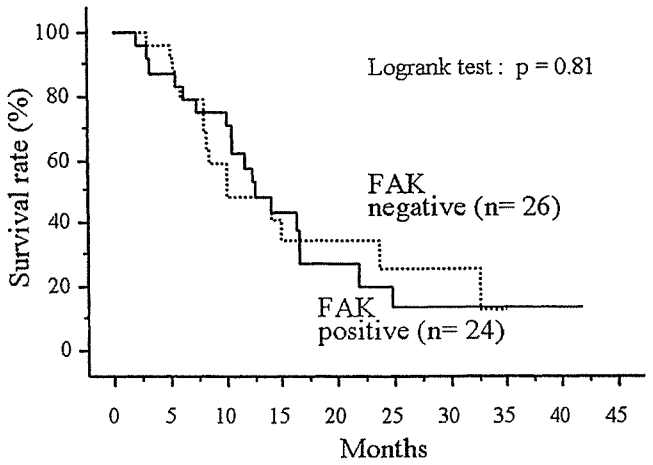

Figure 7. Survival curves of the patients with pancreatic cancer. There was no statistically significant difference in the survival between patients with FAK-positive tumors and patients with FAK-negative tumors ($P = 0.81$).

As a result, we found that there is a significant correlation between FAK expression and tumor size in pancreatic cancer patients. It has been reported that astrocytoma cells expressing FAK formed larger tumors in nude mice than tumor cells derived from the parental cell lines.[18] Further, expression of a hyperactive mutant of FAK, SuperFAK,[19] in the breast cancer cell line resulted in an increase in the size of tumors in nude mice.[3] In addition, the FAK dominant negative, FAK-related nonkinase (FRNK) expression inhibited the growth of human carcinoma cells into tumors in nude mice.[20] These reports are consistent with our results and suggest that greater tumor size might be associated with an increased rate of cell proliferation by FAK expression.

Previous reports on different kinds of cancer have shown that FAK expression correlated with survival rate,[9,15] although FAK was not a prognostic factor by itself in those studies. We showed that the survival curve of FAK-positive and FAK-negative patients showed no significant separation. It is well documented that the most important prognostic factor in completely resected patients is nodal status;[21,22] however, other predictors of a favorable outcome include a tumor size < 3 cm, negative margins, well-differentiated tumors, and intraoperative blood loss of less than 750 ml.[23–25] Focal adhesion kinase expression was significantly associated with tumor size in our study, although it was not a prognostic predictor for survival of the pancreatic cancer patients.

Recent studies have demonstrated that suppression of FAK by small interfering RNA (siRNA) enhanced the chemosensitivity of pancreatic adenocarcinoma to gemcitabine,[26] promoted anoikis, and inhibited metastasis of pancreatic cancer cells in vivo.[27] These observations suggest that FAK might be an important determinant of malignant cellular behavior and could be a rational target for therapeutic intervention in pancreatic cancer. We noted, however, FAK was expressed in the normal pancreatic duct. It is not clear why normal pancreatic ductal cells express FAK, although this might be an obstacle when molecular target therapy for FAK would be conducted in vivo.

In conclusion, this is the first report to show the relationship between FAK expression and the clinicopathological factors in pancreatic cancer. We have revealed that FAK expression was related to tumor size in pancreatic cancer, but it was not related to other clinicopathological factors. Focal adhesion kinase expression may not be a prognostic marker for pancreatic cancer

Table 2.
Comparison between the expression of FAK and clinicopathological features of pancreatic cancer.

Category	FAK-positive (n = 24)	FAK-negative (n = 26)	*P* Value
UICC* classification system (6th edition)			
Histological grade			
Well–moderate	21	25	0.34
Poor	3	1	
pT			
1, 2	4	5	>0.999
3, 4	20	21	
pN			
0	7	6	0.751
1	17	20	
pM			
0	18	23	0.281
1	6	3	
Stage			
1	1	3	0.375
2	12	13	
3	5	9	
4	6	3	
JPS† classification system (5th edition)			
Tumor size			
<4 cm	15	25	0.004
≥4 cm	9	1	
Lymphatic invasion			
–	2	4	0.669
+	22	22	
Portal venous system invasion			
–	5	5	>0.999
+	19	21	
Nerve invasion (intrapancreatic)			
–	2	1	0.602
+	22	25	
Nerve invasion (extrapancreatic)			
–	11	12	>0.999
+	13	14	
Arterial invasion			
–	21	23	>0.999
+	3	3	
Anterior serosal invasion			
–	17	17	0.767
+	7	9	
Retroperitoneal invasion			
–	11	12	>0.999
+	13	14	

*Union Internationale Contra Cancrum (International Union Against Cancer).
†Japan Pancreas Society.

patients, but it could be a molecular target for therapeutic intervention in these patients.

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Phase I/II Trial of Hyperfractionated Accelerated Chemoradiotherapy for Unresectable Advanced Pancreatic Cancer

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Background: We conducted a Phase I/II study to evaluate the local efficacy and toxicity of hyperfractionated accelerated radiotherapy (HART) combined with 5-fluorouracil (5-FU) and cisplatin (CDDP) in patients with unresectable advanced pancreatic cancer.
Methods: Thirty-five patients (15 with Stage 4A and 20 with Stage 4B disease according to TNM classification) were enrolled between August 1997 and August 2001 into this Phase I/II trial. All patients received concurrent HART (1.5 Gy twice daily separated by 6 h for 5 days per week), 5-FU (375 mg/m^2 given as continuous intravenous infusion), and CDDP (2 mg/m^2 given as 30-min infusion just before each fraction of irradiation). In the Phase I trial, the total dose of radiation was escalated from 27 to 45 Gy.
Results: Twenty-one patients were enrolled in the Phase I study and six patients were given the final planned dose (45 Gy) which did not exceed the maximum tolerated dose. Eleven patients (52.4%) suffered from Grade 3 or worse neutropenia. Vomiting and mucositis were observed in 21 (100%) and 12 (57.1%) patients, respectively. An additional 14 patients were entered in the Phase II trial and received a total dose of 45 Gy, which is recommended in Phase I trial. Concerning the local tumor control of 20 patients with the recommended regimen, 7 patients (35%) achieved partial response, 10 (50%) remained stable and local progressive disease occurred in 3 (15%). The median survival time and the overall 1-year survival rate were 11.2 months and 40.0%, respectively, in 20 patients who received the recommended regimen. In Stage 4A patients they were 13.0 months and 70.0%, respectively. The trend of toxicities in patients with the recommended regimen was almost the same as that observed in the Phase I study.
Conclusion: The chosen combined modality treatment was well tolerated, and showed a expected local efficacy for the treatment of unresectable advanced pancreatic cancer.

Key words: pancreatic cancer – radiotherapy – chemotherapy – 5-fluorouracil – cisplatin

INTRODUCTION

Worldwide, over 200 000 people die annually of pancreatic cancer and the overall 5-year survival has remained as low as less than 5% (1). Although surgery is the only curative treatment modality, less than 20% of patients with pancreatic cancer are candidates for resection. Despite the efforts of the past decades, conventional treatment approaches, such as surgery, radiation, chemotherapy, combinations of these have had little impact on the course of this aggressive neoplasm (2). At the time of diagnosis, locally advanced unresectable pancreatic cancer without clinical metastasis represents about 40% of pancreatic cancer (3). External beam irradiation with chemotherapy has been used regularly in patients with locally advanced unresectable pancreatic carcinoma because the results of previous randomized trials by Gastrointestinal Tumor Study Group (GITSG) indicated that concurrent external beam radiation therapy and chemotherapy resulted in a significantly longer survival time th

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radiotherapy (RT) (4) or chemotherapy alone (5). However, the median survival times (MSTs) even of patients treated with chemoradiotherapy (CRT) remain unsatisfactory. Although numerous trials using modified CRT approaches have been conducted in an attempt to improve the efficacy of the treatment, few regimens have demonstrated significant superiority over conventional CRT in randomized controlled trials (2,3). Therefore, there is a clear need to establish more effective CRT for locally advanced pancreatic cancer (LAPC).

Concerning RT, novel fraction schedules have been explored since the 1980s with the aim of improving local tumor control and survival without increasing late morbidity (6). In hyperfractionated radiotherapy (HRT), the dose per fraction is reduced and the total dose increased to give improved tumor control without increased late morbidity (6). By contrast, in accelerated radiotherapy (ART) the overall duration of RT is reduced to overcome repopulation of tumor cells during the course of treatment (6). More recently, hyperfractionated accelerated radiotherapy (HART) was designed to combine both a reduction in dose per fraction and a shortening of the overall time of RT in an effort to gain a therapeutic benefit without increasing the risk of complications. The randomized controlled trials using HART in squamous cell carcinoma of head and neck (SCCHN) and non-small-cell carcinoma of lung (NSCLC) led to encouraging results (7,8). There are several reports which showed the effect of HART with or without concurrent chemotherapy on pancreatic cancer (9–14). Although a few reports are available on these modified fraction schedules, HART with concurrent chemotherapy on pancreatic cancer still remains to be controversial. Recently, several *in vitro* and *in vivo* studies, including a clinical lung cancer study on concurrent CRT using 5-fluorouracil (5-FU) and cisplatin (CDDP), have proved that biochemical modulation effects between 5-FU and cisplatin CDDP are effective, where the maximum radiosensitizing effects are achieved by daily CDDP administration before each fraction of radiation (15–18). In consideration of these data, here we report in the results of a prospective Phase I/II study that was conducted to evaluate the local efficacy and toxicity of the HART combined with continuous 5-FU infusion and low dose of CDDP just before each fraction of irradiation in unresectable advanced pancreatic cancer.

PATIENTS AND METHODS

ELIGIBILITY

Patients with histologically and/or cytologically proven, locally advanced pancreatic carcinoma and/or metastatic disease were enrolled in this study. They were required to have a World Health Organization (WHO) performance status (19) of 0–1, and adequate functions of bone marrow (WBC count >4000/μl, platelet count >100 000/μl, hemoglobin >10 g/μl), renal (serum creatinine concentration <1.5 mg/dl, blood urea nitrogen <20 mg%) and hepatic functions (serum transaminase level <2× of the upper normal range) except hyperbilirubinemia due to obstructive jaundice. All patients had to have a measurable primary tumor that could be assessed by abdominal computed tomography (CT). All patients should be expected to live more than 3 months. Patients were excluded if they had serious or uncontrolled concurrent medical illness, or a history of other malignancies. No prior chemotherapy or radiation therapy was allowed. The local ethics committee approved this study. Informed consent was obtained from all patients according to institutional regulations.

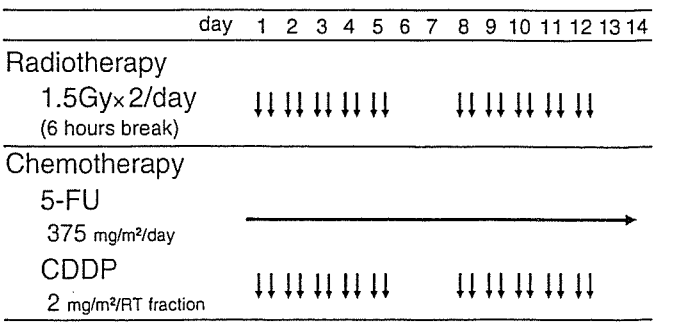
Pretreatment evaluation included a complete medical history, physical examination, complete blood count, differential blood cell count, biochemistry analysis, chest X-ray, electrocardiogram (ECG) and CT of the abdomen.

RADIOTHERAPY

Radiotherapy targeted at primary pancreatic tumors was delivered with X-rays of 10–18 MV from a linear accelerator with 4-field technique. Gross tumor volume (GTV) was defined as the macroscopically abnormal area visualized on each CT image with contrast enhancement. GTV included the tumor as defined on CT image, as well as areas of potential or proven involved regional lymph nodes. Clinical target volume (CTV) was defined as the GTV plus a 10-mm margin in all directions to account for subclinical tumor spread. Radiotherapy was not targeted at distant metastatic lesions. Each treatment field was irradiated twice daily, 6 h apart, 5 days per week at 1.5 Gy per fraction (Fig. 1). In the Phase I trial, the starting radiation dose was 27 Gy in 18 fractions (dose level 1), and the subsequent dose levels were 33, 39 and 45 Gy (dose level 2, 3 and 4, respectively). Dose escalation was achieved by increasing the frequency of radiation by 4 fractions. The final planned dose level of the trial was 45 Gy in 30 fractions. In the Phase II trial, the patients received the fixed dose that was decided in the Phase I trial.

CHEMOTHERAPY

Chemotherapy was administered concurrently with RT, using 5-FU 375 mg/m^2/day given as continuous intravenous infusion, and CDDP 2 mg/m^2 given as 30-min infusion just before each fraction of irradiation (Fig. 1). Sufficient hydration to



5-FU, 5-fluorouracil; CDDP, cisplatin; RT, radiotherapy

Figure 1. The treatment schedule used in this study.

ensure a urinary output of at least 100 ml/h before and 4 h after the infusion of CDDP was required. All patients with liver metastasis were treated with arterial infusion therapy of 5-FU for 5 days, 200 mg/m^2/day by continuous hepatic arterial infusion after the course of HART-based CRT. In patients with only locally advanced disease without liver metastasis, no additional therapy was performed in case of no disease progression. The patients with disease progression received second-line chemotherapy with uracil-tegafur.

Evaluation

Treatment toxicities were evaluated by analyzing the combined data of patients with locally advanced disease (Stage 4A) and those with metastatic disease (Stage 4B). Because RT was targeted only at primary pancreatic tumors and not at distant metastatic lesions in Stage 4B patients, we evaluated the local response rate by analyzing combined data of Stage 4A and 4B patients. The treatment efficacy against metastatic lesions was not evaluated in this study. Survival of Stage 4A and 4B patients were analyzed separately.

Toxicity Evaluation

Toxicity of the therapy was initially to be evaluated with World Health Organization Toxicity Criteria (WHO-TC) (20). After publication of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 (20), toxicity was also evaluated according to it. On completion of the study, all toxicities were reviewed and re-evaluated according to NCI-CTC ver.2. Toxicity grades and frequencies were unchanged under the two criteria. Dose-limiting toxicity (DLT) was defined as Grade 4 neutropenia, Grade > 3 thrombocytopenia, Grade > 3 anemia, Grade > 2 hemorrhage from the gastrointestinal tract or Grade > 3 toxicity in other organ system (except nausea/vomiting and hyperbilirubinemia secondary to biliary obstruction).

Patient cohorts had a minimum of three patients at each dose level. If none of the patients treated at a given dose level had DLT as defined above, patients were entered at the next dose level. If DLT was observed in one out of three patients, three additional patients were entered at that dose level. If one or two out of six patients had a DLT, patients were entered at the next dose level. If three or more of three to six patients had a DLT, the maximum tolerated dose (MTD) was considered to have been exceeded and escalation was discontinued.

Response Evaluation

In this study, only local response of primary pancreatic tumors was analyzed because target lesions of current radiochemotherapy were primary tumors. For response evaluation, CT reassessments were repeated every 4 weeks. A complete response (CR) was defined as a total resolution of all evidence of tumor on two consecutive evaluations 4 weeks apart. A partial response (PR) required a 50% reduction in the maximum perpendicular tumor measurements for at least 4 weeks. Stable disease (SD) was defined as less than 50' reduction and less than 25% increase of measurable tum lesions lasting for at least 8 weeks. Patients were considere to have progressive disease (PD) if the measurable tum lesions increased by greater than 25% according to initi staging within the first 2 months of therapy.

Statistical Methods

This Phase I/II study was designed to evaluate the overa feasibility of, and the toxicity, local tumor response, and ove all survival with, administration of the HART combined wi chemotherapy using 5-FU and CDDP. The sample size for tl Phase II trial was determined as follows. The thresho response rate was defined as 5% and the expected respon rate was set as 25%. This study was regarded to be adequate recruit a total of 20 patients assuming alpha error of 0.05 a beta error of 0.2 based on Simon two-stage Phase II desi (21). Survival was calculated from the date of admission to tl date of death or last follow-up. Survival curves were calculat by the Kaplan–Meier method. Statistical calculations we performed using StatView software (version 5.0).

RESULTS

From August 1997 to August 2001, 35 patients were enroll into this Phase I/II study.

Phase I Study

Patient Characteristics

A total of 21 patients were entered into the Phase I trial in fc cohorts. The number of patients who were entered into the dc level 1, 2, 3 and 4 were 3, 6, 6 and 6, respectively. Th pretreatment characteristics are listed on Table 1. Elev patients were male and 10 were female. Their median a was 64 years with a range of 49–78 years. Nine patie had a WHO performance status of 0, and 12 had a status 1. Eleven patients had cancers located in the head of the p creas, 9 had in the body and one had in the tail. Seven patie had Stage 4A disease and 14 had Stage 4B (12 patients h liver metastasis, one had both lung and distant lymph nc metastasis, and one had distant lymph node metastasis) acco ing to the TNM classification (5th edition) (22). Eight patie had undergone a biliary bypass procedure before treatme seven endoscopic stenting and one cholecyctojejunostomy

Toxicities

Toxicities in Phase I trial are listed on Table 2. No DLT v observed in the first three patients treated at dose level Hematological toxicities meeting the criteria for DLT occur in three patients; Grade 4 neutropenia was observed in of six patients at dose level 3 and 4, and Grade 3 ane was observed in one of six patients at dose level 4. N hematologic toxicities meeting the criteria for DLT occur in six patients, including one of six patients with Grad

Table 1. Patient characteristics in Phase I study

Age (years)	
Mean	64
Range	49–78
Sex	
Male	11
Female	10
WHO PS	
0	9
1	12
Localization	
Head	11
Body	9
Tail	1
Clinical stage	
4A	7
4B	14

WHO, World Health Organization; PS, performance status.

Table 2. Toxicities in Phase I study

Level (Gy)	1 (27)					2 (33)					3 (39)					4 (45)				
n	3					6					6					6				
Grade	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Neutropenia	0	1	2	0	0	0	1	2	3	0	1	0	1	3	1	0	1	1	3	1
Thrombocytopenia	2	1	0	0	0	4	1	1	0	0	5	0	1	0	0	4	2	0	0	0
Anemia	1	2	0	0	0	0	3	3	0	0	1	3	2	0	0	0	3	2	1	0
Vomiting	0	1	2	0	0	0	1	4	1	0	0	2	2	2	0	0	1	3	2	0
Mucositis	1	2	0	0	0	3	1	1	1	0	2	2	2	0	0	2	3	1	0	0

vomiting at dose level 2, two of six patients with Grade 3 vomiting at dose level 3 and 4, and one of six patients with Grade 3 mucositis at dose level 2. In this Phase I study, 45 Gy, the final planned dose, does not exceed the MTD as defined in the protocol. Therefore, patients received 45 Gy irradiation in the subsequent Phase II study.

PHASE II STUDY

PATIENT CHARACTERISTICS

Fourteen patients were enrolled onto the Phase II trial, and all of them received 45 Gy irradiation, which was recommended in Phase I trial. A total of 20 patients including 6 patients entered in the recommended dose level in the Phase I trial were evaluated for toxicities and treatment efficacy. Their pretreatment characteristics are listed on Table 3. Twelve patients were male and eight were female. Their median age was 65 years with a range of 49–78 years. Nine patients had a WHO performance status of 0, and 11 had a status of 1. Eleven patients had cancers located in the head of the pancreas,

Table 3. Patient characteristics in Phase II study

Age (years)	
Mean	65
Range	49–78
Sex	
Male	12
Female	8
WHO PS	
0	9
1	11
Localization	
Head	11
Body	9
Clinical stage	
4A	10
4B	10

WHO, World Health Organization; PS, performance status.

Table 4. Toxicities in Phase II study

	Grade	0	1	2	3	4
Neutropenia	19 (95%)	1	3	6	8	2
Thrombocytopenia	8 (40%)	12	6	2	0	0
Anemia	16 (80%)	4	8	6	2	0
Vomiting	20 (100%)	0	4	9	7	0
Mucositis	12 (57%)	8	7	4	1	0

and nine had them in the body of the pancreas. Ten patients had Stage 4A disease and 10 had Stage 4B (all 10 patients had liver metastasis) according to the TNM classification. Seven patients had undergone a biliary bypass procedure before treatment (six endoscopic stenting and one cholecystojejunostomy). All patients completed the prescribed course of therapy. One patient with Stage 4A disease underwent pancreatoduodenectomy 1.5 years after the end of the treatment.

TOXICITIES

Toxicities in 20 patients who received recommended dose irradiation are listed on Table 4. The results showed almost the same trend as observed in Phase I trial (Table 2). With regard to hematological toxicity, neutropenia was the most common. Granulocyte-colony stimulation factor (G-CSF) was administered to the 10 patients with Grade 3 and 4 neutropenia. Anemia was observed in 80% patients. Only two patients had Grade 3 anemia. For the non-hematological toxicity, vomiting was observed in all 20 patients. Mucositis was observed in 12 patients.

RESPONSE AND SURVIVAL

Twenty patients who received recommended dose irradiation were evaluated for the treatment response. All of the 20 patients were assessable for local response and survival. CA19-9 values are available for all patients. Seven patients showed more than 50% reduction, seven showed a reduction less than 50% and six showed an increase in CA19-9 level. The MST of patients with Stage 4A and 4B were 13.0 and 5.0 months, respectively, according to Kaplan–Meier method. The overall 1-year survival rate was 70.0 and 10.0% in Stage 4A and 4B group, respectively. Figure 2 shows the overall survival curves for these two groups. As to the primary lesion, PR and SD were observed in 7 and 10 patients, respectively. Three patients had PD. All patients who complained of pain before treatment obtained improvement in the symptom during or after treatment.

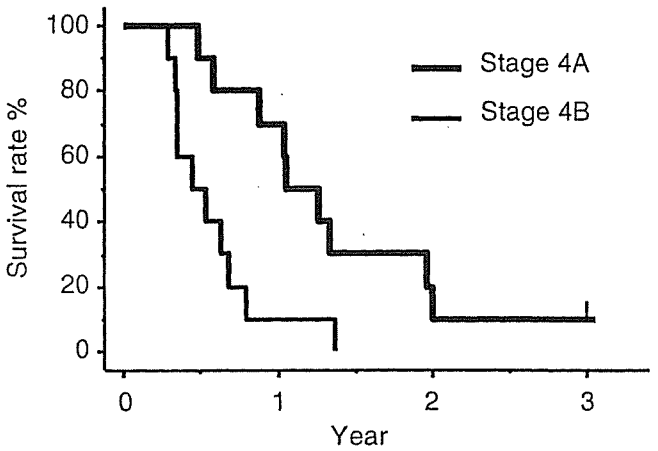


Figure 2. Overall survival rate of 20 patients who received HART with chemotherapy for advanced pancreatic cancer. Ten patients had Stage 4A disease (thick line) and 10 had Stage 4B (thin line). A vertical line indicates a censored case.

DISCUSSION

Several prospective randomized trials have shown a benefit with CRT compared to either RT or chemotherapy alone in the management of LAPC (3). However, improvements are modest and local control remains a significant challenge.

In an attempt to enhance loco-regional control, we chose HART combined with continuous 5-FU and low dose of CDDP just before each fraction of irradiation. The rationale for this protocol are as follows: (i) HART could shorten the treatment duration without increasing the risk of complication (6); (ii) cytotoxic effects by continuous 5-FU administration were superior to bolus 5-FU administration (23); (iii) CDDP enhanced the cytotoxicity of 5-FU (the inhibition of methionine transport by CDDP increasing the formation of covalent ternary complex of thymidylate synthase (TS), dUMP and 5,10-methylene-tetrahydro-folinic-acid coupled with the acceleration of folinic acid metabolism, resulting in the enhancement of 5-FU cytotoxicity by TS inhibition) (15) (iv) 5-FU could act as a radiosensitizer and continuous 5-FU administration with radiation was more effective (24,25); (v) daily low-dose CDDP administration before each fraction of radiation maximized the radiosensitizing effects (16,17).

Several reports showed the results of HART or HRT for LAPC (Table 5). Schuster et al. (9) applied HART (three fractions of 1.0–1.1 Gy, total 69–70 Gy) without chemotherapy for 12 patients and reported no serious acute toxicity. However the local response rate and the MST were 8.3% and 7.9 months respectively. The GISTG reported on HRT (two fractions of 1.2 Gy, total 50.4 Gy) with bolus 5-FU infusion (350 mg/m^2) on the first 3 and last 3 days of RT in 18 patients (10). The MST was 35 weeks and the 1-year survival rate was 39%. During the trial, 67% patients had a Grade 3 or worse toxicity. Prott et al. (11) treated 32 patients by HART (two fractions of 1.6 Gy, total 44.8 Gy) with 5-FU (600 mg/m^2) and folinic acid (300 mg/m^2) on the first 3 days of RT. The MST was 12.7 months. Luderhoff et al. (12) conducted a pilot study

Table 5. Hyperfractionated radiotherapy for advanced pancreatic cancer

Author	Fraction	Total dose	Chemotherapy	Local response rate	MST	1-year survival rate	Re
Schuster et al.	1.0–1.1 Gy ×3	60–70 Gy	—	8.3% (1/12)	7.9 months	8.3%	9
Seydel et al.	1.2 Gy ×2	50.4 Gy	5-FU, streptozotocin, mitomycin C		35 weeks	39%	10
Prott et al.	1.6 Gy ×2	44.8 Gy	5-FU, folinic acid		12.7 months	53.1%	11
Luderhoff et al.	1.1 Gy ×3	45-50 Gy	5-FU	23.1% (3/13)	36 weeks		12
Ashamalla et al.	1.1 Gy ×2	63.8 Gy	Paclitaxel	29.4% (5/17)	10 months	45%	13
Ueno et al.	1.2 Gy ×2	45.6–64.8 Gy	5-FU	20.7% (6/29)	12.2 months	55%	14
Current study	1.5 Gy ×2	45 Gy	5-FU, CDDP	40.0% (4/10)[1] 30.0% (3/10)[2]	13.0 months[1] 5.0 months[2]	70.0%[1] 10.0%[2]	

5-FU, 5-fluorouracil; CDDP, cisplatin; MST, median survival time.
[1]Stage 4A patients; [2]stage 4B patients.