reported urging the accurate diagnosis of the PV invasion before and/or during the operation. It is important to differentiate true PV invasion from inflammatory adhesion during the operation since cancer cell dissemination is a significant risk when the tumor is in contact with the PV which can be clearly seen by IPEUS. The wall of PV is too thin to be visualized by conventional imaging techniques such as CT or angiography (36). Recently, multidetector 3D-CT has been reported to be a reliable tool in assessing vessel encasement in patients with pancreatic cancer (37). In case of the finding of a tumor contiguous with the PV by CT or angiography, subtle cancer invasion cannot be differentiated from compression. Arterial or direct portography has limited value over this issue too. Ishikawa *et al.* reported that the prognosis of the patients with portal vein invasion could be predicted by arterial portography (30). They described bilateral portal vein stenosis or portal invasion more than 1.2cm (1.4cm on the film) long in length by arterial portography could not expect long-term survival even if radical operation was done. However their report included 14 false-negative cases among 35 patients of subject. Therefore, it can be easily concluded that arterial portography is very limited to diagnose subtle portal vein invasion. To overcome these limitations, we have introduced and used IPEUS over years with high overall accuracy rate. As previously reported, IPEUS provided good diagnostic accuracy of 96% which was superior to other conventional diagnostic modalities. In the current study, overall accuracy was 96.1% (25/26) with one false-positive case.

Recently, we have started to use IPEUS with a mechanical autopull-back device with constant speed, which enables us to determine PV/SMV invasion quantitatively. Furthermore, using these recorded images, it is now possible to create a longitudinal cutopen image constructed by volume rendering in which the invasion area is depicted as a defect of the PV/SMV wall (38,39). According to the results of present study, the patients with PV/SMV invasion more than 18mm measured by IPEUS are not expected to have long-term survival because all patients died within 18 months, indicating the lack of survival benefit from radical resection. For the patients with PV/SMV invasion less than 18mm, however, the expectancy for long-term survival is still dismal but 50% survival term was 17 months. In cumulative survival rate, this group of patients was not statistically worse than those without PV/SMV invasion, but not statistically better than the patients with invasion more than 18mm ($p=0.77$ and $p=0.10$, respectively).

The patients without PV/SMV invasion are expected to have long-term survival as 2- and 3-year survival rates were 54% and 36%, respectively, which were much better than that of the patients with PV/SMV invasion **(Table 1)**. On the other hand, the patients with PV/SMV invasion ≤18mm achieved a 28% 2-year survival rate whereas no patients with >18mm PV/SMV invasion survived longer than 17 months. Even with radical operation, the long-term survival is still dismal for the patients with PV/SMV invasion >18mm according to the results of preliminary IPEUS study.

In this study, most of the cases (11 of 12) in Group II and III were in Stage IV suggesting that involvement of PV/SMV by pancreatic carcinoma seems to be related to the extent of the disease. Extent of PV/SMV invasion (>18 *vs.* ≤18mm) was significantly associated with tumor-positive margin and this may explain the poor prognosis in these patients even after radical surgery. At present, the number of the patients is small and more patients are necessary to clarify the role of radical operation for the patients with PV/SMV invasion, particularly >18mm invasion.

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IMAGES OF INTEREST

Hepatobiliary and pancreatic: Aberrant left gastric vein

The left and right gastric veins usually enter the portal vein trunk, the splenic vein or the confluence of the two. Entry of gastric veins into other sites in the portal venous system is rare (<1%) and such veins are often called aberrant gastric veins. The images shown in this report were from a 66-year-old man who was admitted to hospital with cancer of the body of the pancreas. An enhanced computed tomography (CT) scan showed that the tumor had invaded the portal vein, splenic vein and celiac artery. The splenic vein was completely occluded and, because of this, a more prominent left gastric vein could be seen in the hepatogastric ligament. This vein entered the left portal vein close to the bifurcation of the portal trunk into left and right portal veins (Fig. 1, arrows). This was diagnosed as an aberrant left gastric vein. A CT scan during arterial portography (CTAP) demonstrated small portal perfusion defects in segment II corresponding to the area of perfusion of the aberrant left gastric vein (Fig. 2, arrowheads).

Various pseudolesions have been reported after CTAP. Some of these have been attributed to venous drainage to the liver that bypasses the portal venous blood. This may arise from veins such as an aberrant right gastric vein, cholecystic vein and epigastric/paraumbilical vein, but has rarely been associated with an aberrant left gastric vein. In the case described above, the aberrant left gastric vein became more prominent as a result of left-sided portal hypertension caused by splenic vein obstruction. Preservation of gastric veins to prevent gastric congestion can be relevant to major pancreatic surgery when distal pancreatectomy is accompanied by resection of the celiac trunk and portal vein. In this setting, preservation of veins can be facilitated by the presence of aberrant gastric veins.

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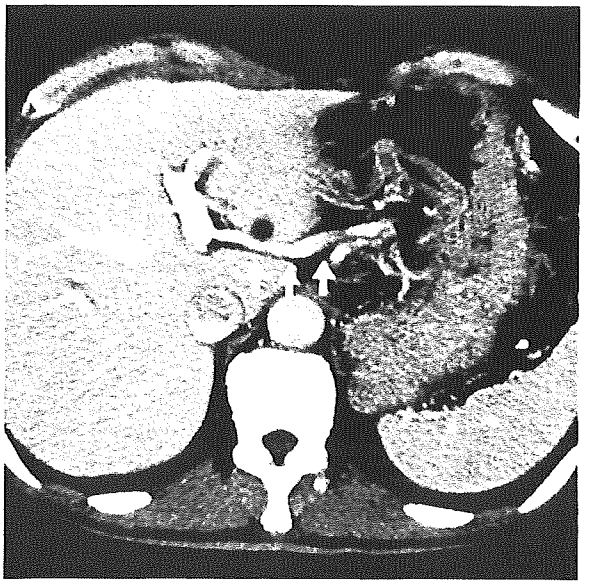

Figure 1

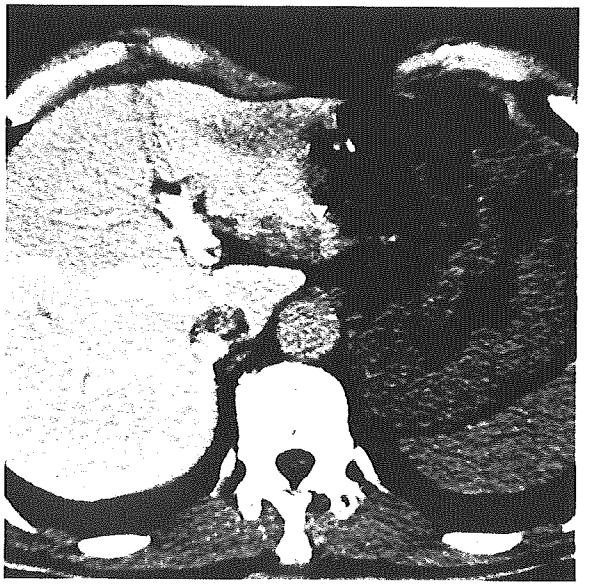

Figure 2

Contributions to the Images of Interest Section are welcomed and should be submitted to Professor IC Roberts-Thomson, Department of Gastroenterology, The Queen Elizabeth Hospital, Woodville South, South Australia 5011, Australia.

Dual-phase ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography as a prognostic parameter in patients with pancreatic cancer

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Abstract. *Purpose:* Recently, dual-phase ^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) was shown to be useful in the differentiation between malignant and benign pancreatic lesions. The aim of this prospective study was to evaluate the value of dual-phase FDG-PET as a prognostic parameter in patients with pancreatic cancer. *Methods:* Sixty-five consecutive patients with pancreatic cancer underwent dual-phase FDG-PET. Standardised uptake values at 1 h (SUV1) and 2 h (SUV2) following the injection of FDG were determined, and the retention index (RI) was calculated by dividing the difference between SUV2 and SUV1 by SUV1. The prognostic value of SUV1, SUV2 and RI was analysed, along with the various clinical and biochemical parameters. *Results:* Multivariate analysis showed that only three factors had an independent association with longer patient survival: female gender ($p<0.01$), TNM stage I–III ($p<0.05$) and RI>10% ($p<0.01$). Neither SUV1 nor SUV2 showed any prognostic significance. Combination of tumour stage and RI allowed more accurate prognostic evaluation. Patients at stage I–III with RI>10% survived longer than did patients at the same stage with RI<10% (15.3 vs 11.5 months, $p<0.01$). Patients at stage IV with RI>10% had an intermediate prognosis, with a median survival of 9.5 months; patients at stage IV with RI<10% showed the worst prognosis, with a median survival of 4.9 months ($p<0.05$). *Conclusion:* RI calculated with dual-phase FDG-PET can be used not only as a tool for initial diagnosis and staging of pancreatic cancer but also as a strong independent prognostic parameter that can allow accurate identification of those patients who will benefit from intensive anticancer treatment at different stages of the disease.

Keywords: Pancreatic cancer – Prognosis – Dual-phase – ^{18}F-FDG – Positron emission tomography

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Introduction

Pancreatic cancer remains a highly lethal disease in spite of new developments in early diagnosis, improvements in surgical morbidity and mortality, and the introduction of promising adjuvant and neoadjuvant therapies [1]. In Japan, pancreatic cancer is the fifth most frequent cause of cancer death, with an estimated annual incidence in 2003 of around 20,000 cases [2]. In the United States, pancreatic cancer is the fourth most frequent cause of cancer death. An estimated 30,700 patients were diagnosed with pancreatic cancer in 2003, and the majority of them presented with locally advanced or metastatic disease that precludes potentially curative surgical therapy [3]. In the minority of patients who present with disease limited to the pancreas, peri-ampullary region and peripancreatic lymph nodes, surgical resection (pancreaticoduodenectomy or distal pancreatectomy) has the potential to improve symptoms, quality of life and survival [4]. However, indications for surgical treatment and adjuvant chemotherapy should be carefully evaluated because of the high risk of procedure-related complications and side-effects. Therefore, prognostic factors permitting identification of those patients who will benefit from such treatment would be clinically useful [5, 6].

^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) is a useful modality that can assist in the diagnosis of pancreatic cancer, pre-operative staging, evaluation of treatment response and detection of recurrence [7]. Recently, dual-phase and multiphase FDG-PET using a combination of early and delayed images was shown to be useful in differentiating benign from malignant pancreatic lesions [8]. However, the role of a delayed FDG-PET scan in prognostic evaluation in pancreatic cancer has never been evaluated previously. The aim of this prospective study was to assess the prognostic value of dual-phase FDG-PET in patients with pancreatic cancer.

Materials and methods

Patients

A total of 65 consecutive patients with pancreatic cancer were examined between December 1997 and February 2003. Before enrolment in this study, each patient gave written informed consent, as required by the Kyoto University Human Study Committee. In all cases, conventional diagnostic methods, such as contrast-enhanced computed tomography (CT) and abdominal ultrasound (US) had previously revealed a mass lesion in the pancreas. The mean age of the patients in our study was 63.2±9.3 years (range 40–83 years; 42 males and 23 females). Histopathological proof of pancreatic cancer was obtained where possible. If histopathological confirmation was absent, the diagnosis was made on the basis of clinical and imaging findings. Patients with doubtful clinical diagnosis were not included in this study. Cancer staging was based on the results of physical examination, CT, magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS) and/or endoscopic retrograde cholangiopancreatography (ERCP). Results of surgery and histopathological examination (if performed) were also used in cancer staging. The main characteristics of the patients included in the study are summarised in Table 1. Anticancer treatments including surgical resection or palliation, radiation treatment and/or chemotherapy were performed within 2 weeks after the dual-phase FDG-PET.

Table 1. Patient characteristics

Patient characteristics	*n*	%
Age (mean ± SD, years)	63.4±9.3	
Sex		
Female	23	35.4
Male	42	64.6
Tumour location		
Head and body	55	84.6
Tail	10	15.4
Tumour size (geometric mean ± SD, cm)	4.0±1.9	
Regional LN		
N0	31	47.7
N1	34	52.3
TNM stage		
Ia	3	4.6
Ib	3	4.6
IIa	10	15.4
IIb	6	9.2
III	2	3.1
IV	41	63.1
Tumour differentiation		
Well	7	15.9
Moderately	22	50.0
Poor	15	34.1
Treatment		
Surgical resection	28	43.1
Palliative surgery or supportive treatment	37	56.9
Total bilirubin (mean ± SD, mg/dl)	2.0±4.4	
Direct bilirubin (mean ± SD, mg/dl)	1.3±3.2	
Glucose (mean ± SD, mg/dl)	96.4±18.1	
Amylase (mean ± SD, IU/l)	92.4±86.2	
CA 19-9 (geometric mean ± SD, U/ml)	248.0±3921.1	
CEA (geometric mean ± SD, ng/ml)	2.6±8.1	
SUV1 (geometric mean ± SD)	6.1±3.5	
SUV2 (geometric mean ± SD)	7.5±4.7	
RI (mean ± SD, %)	23.6±17.0	

Clinical and biochemical data

The following clinical and biochemical data were recorded and analysed for all patients: age and gender, tumour size and intrapancreatic location, tumour differentiation, resectability and stage (AJCC/UICC TNM, 6th edition) [9]. Serum levels of tumour markers, such as carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) were also evaluated.

PET imaging

Fluorine-18 was synthesised by the nucleophilic substitution method [10] with an ^{18}F-FDG-synthesising instrument, F-100 (Sumitomo Heavy Industries, Co. Ltd, Tokyo, Japan) and a cyclotron, CYPRIS-325R (Sumitomo Heavy Industries, Co. Ltd, Tokyo, Japan). In 24 patients, examined between 1997 and 1999, PET was performed using a PCT3600W camera (Hitachi Medico, Tokyo, Japan). In the other 41 cases, examined between 1999 and 2003, PET was performed using a GE Advance camera (General Electric, Milwaukee, WI, USA). The former camera had eight rings, which provided 15 tomographic sections at 7-mm intervals, and an effective resolution of approximately 10 mm. The latter had 18 rings, which provided 35 tomographic sections at 4.25-mm intervals, and an effective resolution of approximately 4.2 mm. There was no statistically significant difference in clinico-pathological characteristics, treatment methods or patient survival between the groups examined with different PET scanners.

The patients fasted for at least 5 h before the PET examination. For the former PET camera, each patient underwent a transmission scan for attenuation correction for 11 min before the injection of FDG, then 12 min static scan was performed. Image reconstruction with attenuation correction was performed by filtered back-projection. For the latter PET camera, each patient underwent a transmission scan for attenuation correction for 1–2 min after the

3–4 min static scan, and image reconstruction with segmented attenuation correction was performed by ordered subsets expectation maximisation. Approximately 370 MBq (10 mCi) of FDG was administered intravenously, and static scanning was performed 1 h and 2 h later. Serum levels of glucose were examined before the FDG injection.

Primary and delayed PET images were compared with corresponding CT images for accurate identification of the tumour using anatomical landmarks (upper pole of the kidney, shape of the liver and the gallbladder bed). After tumour had been identified, the standardised uptake value (SUV) of tumour-related FDG accumulation on 1-h (SUV1) and 2-h (SUV2) images after FDG injection was calculated as follows:

$$SUV = \frac{PET\ count \times calibration\ factor\ (mCi/g)}{injection\ dose\ (mCi)/body\ weight\ (g)} \quad (1)$$

A region of interest (ROI) for SUV calculation on primary PET scans was placed over the area of maximal metabolic activity on the transaxial slice showing tumour-related increased uptake. On delayed PET scans, ROIs were placed in identical positions using predefined anatomical landmarks. Final voxel dimensions were 10 mm for the formerly used PET camera and 4 mm for the recently used one. In the event of absence of accumulation, ROI placement was determined on the basis of the CT examination. The retention index (RI) was calculated as follows:

$$RI = \frac{SUV2 - SUV1}{SUV1} \times 100\% \quad (2)$$

Taking into account the difference in final voxel dimensions between the former and recent PET scanners, absolute values of SUV acquired by the former PET scanner were excluded from survival analysis. However, RI was calculated for all patients regardless of the PET scanner used.

Other imaging modalities

CT was performed using a Hi-Speed Advantage (GE Medical Systems; Milwaukee, WI, USA) or a CT-W3000 (Hitachi Medico; Tokyo, Japan) scanner. Pre-contrast and early and delayed post-contrast images were obtained and analysed in all patients. EUS was performed with an ultrasonographic video-endoscope GIF-UM20 (Olympus; Tokyo, Japan) equipped with 7.5- and 12-MHz sector scan transducers at the tip of a forward-viewing-type video-endoscope system in the left lateral decubitus and supine positions. ERCP was performed with a video-endoscope EVIS JF type230 (Olympus; Tokyo, Japan). MRCP was performed with a 1.5-T superconducting unit (Magnetom Symphony; Siemens, Erlangen, Germany or Sigma Horizon; GE Medical System, Milwaukee, WI, USA) using single-shot rapid acquisition with relaxation enhancement in single and multislice modes.

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normality of data distribution. Quantitative variables were compared using paired Student's t test or Mann-Whitney test if their distribution were abnormal. Qualitative variables were compared using the χ^2 test. Correlation analysis was performed using Spearman's rank correlation test. Patient's survival was determined from the date of the FDG-PET examination to the last follow-up examination at Kyoto University Hospital or patient death. Median survival curves were plotted using the Kaplan-Meier method. In univariate analysis, differences in survival were calculated with the log rank test. For quantitative variables, the different threshold levels were tested to find the one that could reveal the most significant difference in patient survival. In multivariate analysis, the associations between different variables and overall survival were estimated using the Cox proportional hazard regression model. Quantitative data with normal distribution are presented as means ± SD; quantitative data with abnormal distribution are presented as geometric means ± SD. Significance was defined as $p<0.05$. Statistical analyses were performed by using a statistical software package StatView, version 5.0 (SAS Institute, Cary, NC).

Results

Patient characteristics

A diagnosis of pancreatic malignancy was histologically confirmed in 44 patients (67.7%). In the other 21 patients (32.3%), the final diagnosis was made on the basis of the clinical evaluation, including complete history, physical examination and radiological findings. Systemic chemotherapy was performed in 34 patients (52.3%), external radiation therapy in 22 patients (33.9%) and intraoperative radiation therapy (IORT) in nine patients (13.8%).

Overall median survival in the patients included in our study was 13.1 months (range 2.6–52.4 months) with the 3-, 6-, 12- and 24-month survival being 89.2%, 68.0%, 40.0% and 15.4%, respectively. Survival of patients older than 60 years was significantly shorter than that of younger patients (8.9 vs 15.0 months, $p<0.01$). The median survival of the male patients was shorter than that of the female patients (9.4 vs 14.1 months, $p<0.05$).

Tumour characteristics

The mean size of the pancreatic tumours measured on CT images or during histopathological examination of surgically resected specimens (if available) was 4.0±1.9 cm (range 0.9–11 cm). Patients with tumours <3 cm survived longer than those with larger lesions (13.0 vs 9.5 months, $p<0.05$). Tumour was located in the head of the pancreas in 35 patients (53.8%), in the body in 20 (30.8%) and in the tail in ten (15.4%). Location of the tumour in the head/body of the pancreas was also associated with a longer survival. The median survival time for patients with a tumour located in the pancreatic head or body was 11.5 months, compared with 6.3 months in patients with a tumour located in the pancreatic tail ($p<0.05$).

Regional lymph node involvement was diagnosed in 34 patients (52.3%). Neither univariate nor multivariate analysis showed a significant influence of lymph node involvement on patient survival. In contrast to these findings, presence of distant metastasis, diagnosed in 41 patients (63.1%), was strongly associated with short patient survival. The median survival time for patients

without distant metastasis (TNM stage I–III) was 14.2 months, while in patients who had distant metastasis (TNM stage IV) it was only 7.4 months ($p<0.01$). Resectability of the tumour was also associated with better survival. In 28 patients (43.7%) who underwent surgical resection the median survival was 13.0 months, while in patients who received palliative surgery or supportive treatment only, it was 8.3 months ($p<0.01$).

Tumour markers

The serum level of tumour marker CA 19-9 was elevated in the majority of the patients (93.8%). However, its level had no influence on patient survival. In contrast, a high serum level of CEA was strongly associated with shorter patient survival. The median survival of patients with CEA >2.5 ng/ml was 8.4 months, compared with 12.8 months in patients with normal CEA levels ($p<0.05$).

FDG-PET

There were no cases of hyperglycaemia (>150 mg/dl) in the present study. Patients examined with the formerly used PET scanner had an average SUV1 of 4.8±2.1 (range 1.8–10.8) and an SUV2 of 5.4±2.6 (range 2.4–12.7), while patients examined with the recent PET scanner had an average SUV1 of 6.1±3.5 (range 1.6–18.9) and an SUV2 of 7.5±4.7 (range 1.5–23.2). When SUV2 and SUV1 values were compared, an increase in SUV at 2 h after injection was revealed in 58 patients (89.2%), with a decrease in the remaining seven patients (10.8%).

Mean RI in all patients was 23.6%±17.0% (range −24.9 to 52.9). Correlation analysis showed a positive relation between the values of SUV1 and RI ($r=0.38$, $p<0.01$) [(Fig. 1)]. Both SUV1 and SUV2 were positively correlated with tumour stage ($r=0.38$, $p<0.01$ and $r=0.34$, $p<0.01$, respectively) (Fig. 2) and had no significant correlation with length of patient survival ($r=-0.15$, $p=0.2$ and $r=-0.08$, $p=0.5$, respectively). In contrast, RI did not show any statistically significant dependence on the stage of disease ($r=0.06$, $p=0.62$) (Fig. 3) and had a strong positive correlation with the length of patient survival ($r=0.31$, $p<0.01$).

Univariate analysis performed for the patients examined with the recent PET scanner showed that neither the mean value of SUV1 (6.1) nor that of SUV2 (7.5), nor the other cut-off values tested, could predict patient survival. When the prognostic value of RI was analysed, we

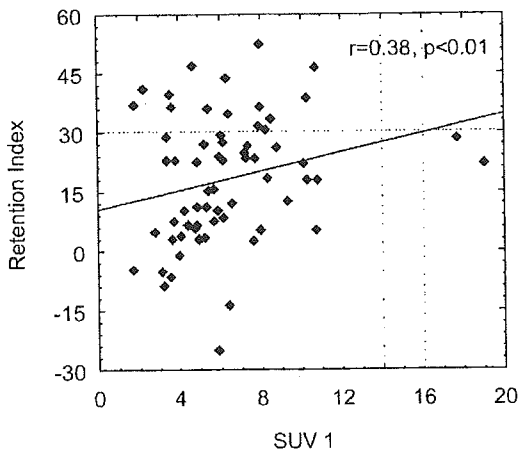

Fig. 1. Correlation of SUV1 and RI

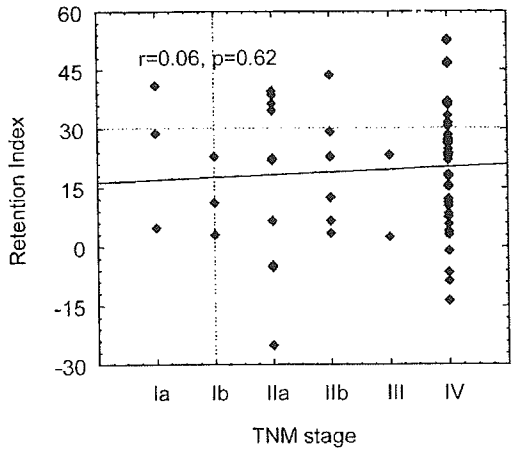

Fig. 3. Correlation of RI and TNM tumour stage

Fig. 2. Correlation of **a** SUV1 and **b** SUV2 and TNM tumour stage

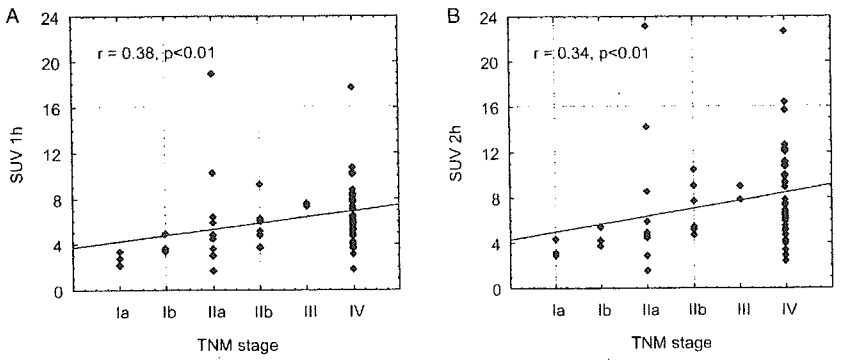

Table 2. Median survival in patients with pancreatic cancer

Prognostic factor	*n*	Survival (months)	*p*-value, univariate	*p*-value, multivariate
Age				
<60 years	23	15.0	$p<0.01$	n.s.
>60 years	42	8.9		
Sex				
Female	23	14.1	$p<0.05$	$p<0.01$
Male	42	9.4		
Tumour location in pancreas				
Head and body	55	11.5	$p<0.05$	n.s.
Tail	10	6.3		
Tumour size				
<3 cm	21	13.0	$p<0.05$	n.s.
>3 cm	44	9.5		
Regional LN				
N0	31	11.3	n.s.	–
N1	34	9.9		
TNM stage				
I–III	24	14.2	$p<0.01$	$p<0.05$
IV	41	7.4		
Tumour differentiation				
Well or moderately	50	11.4	n.s.	–
Poor	15	10.1		
Treatment				
Surgical resection	28	13.0	$p<0.01$	n.s.
Palliative surgery or supportive treatment	37	8.3		
CA 19-9				
<300 U/ml	33	10.4	n.s.	–
>300 U/ml	31	10.1		
CEA				
<2.5 ng/ml	37	12.8	$p<0.05$	n.s.
>2.5 ng/ml	27	8.4		
SUV1				
<6.0	16	13.0	n.s.	n.s.
>6.0	26	9.9		
SUV2				
<7.5	19	11.3	n.s.	–
>7.5	23	10.5		
RI				
<10%	20	7.5	$p<0.01$	$p<0.01$
>10%	45	12.5		

n.s. Non-significant

found that thresholds of RI=10%, 15% and 20% could reveal a significant difference in prognosis. Of all the thresholds, RI=10% was the strongest prognostic indicator: median survival in patients with RI>10% was 12.5 months, which was much longer than that in patients with RI<10% (7.5 months, $p<0.01$).

Multivariate analysis

All eight prognostic factors that showed prognostic significance in the univariate analysis were included in the multivariate model (Table 2). These variables were age and gender of the patient, tumour size, location, stage

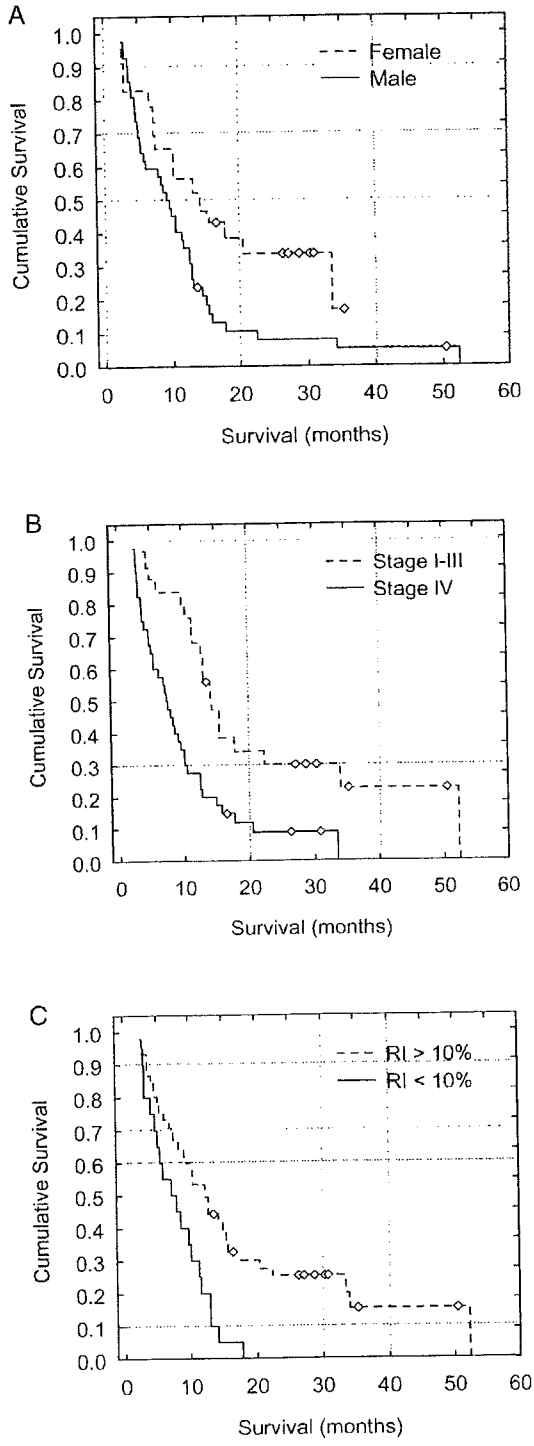

Fig. 4. Cumulative survival for: **a** male (n=42) and female (n=23) patients (p<0.01), **b** patients with TNM stage I–III (n=24) and stage IV (n=41) [(p<0.05)], and **c** patients with RI<10% (n=20) and RI>10% (n=45) [(p<0.01)]

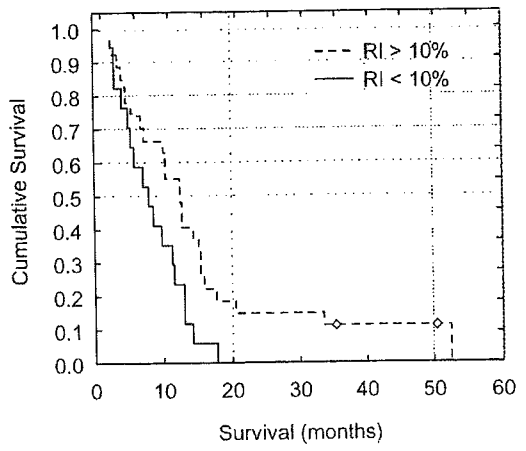

Fig. 5. Cumulative survival for histopathologically confirmed pancreatic cancer patients with RI<10% (n=17) and RI>10% (n=27) [(p>0.05)]

and resectability, CEA level and RI. Only three factors showed an independent association with better patient survival: female gender (p<0.01), TNM stage I–III (p<0.05) and RI>10% (p<0.01) [(Fig. 4)].

Similar findings of prolonged survival in the patients with RI>10% were found in the subgroup of patients (n=44) with histopathologically confirmed pancreatic cancer (Fig. 5). When the two factors stage of disease and RI were combined (Fig. 6), we found that patients diagnosed at stage I–III with RI>10% showed the most favourable prognosis, with a median survival of 15.3 months. Patients diagnosed at stage I–III but with RI<10% had a less favourable prognosis, with a median survival of 11.5 months (p<0.01). Patients diagnosed at stage IV with RI>10% had an intermediate prognosis, with a median survival of 9.5 months; patients diagnosed at stage IV with RI<10 showed the worst prognosis, with a median survival of 4.9 months (p<0.05).

Discussion

In general, patients with pancreatic cancer have a very poor prognosis. Fewer than 1% survive more than 5 years from diagnosis [11]. With such a background, it seems clinically important to identify subgroups of patients who may or may not benefit from aggressive therapy given in an attempt to improve survival [12]. A variety of clinical and pathological factors have been reported to be associated with favourable prognosis in patients with pancreatic cancer, such as young age, small tumour size, tumour location in the head/body of the pancreas, surgical resection with negative resection margins, negative lymph node status, well/moderate tumour differentiation, diploid tumour DNA content, low serum levels of tumour markers (CA242, CA19-9 and MUC-1) and treatment with adjuvant chemoradiation [13–15].

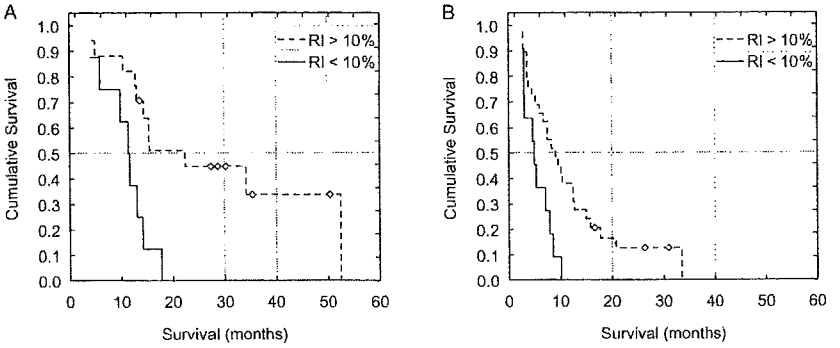

Fig. 6. Cumulative survival for: **a** patients diagnosed at stage I–III with RI<10% (n=8) and RI>10% (n=16) [(p<0.01)]; **b** patients diagnosed at stage IV with RI<10% (n=12) and RI>10% (n=29) [(p<0.05)]

However, there is still controversy over which factors can be used as independent predictors of prognosis and the significance of their influence on patient survival [13].

Univariate analysis of our data showed numerous factors to be significantly related to better survival: patient age <60 years, female gender, tumour size <3 cm, tumour location in the head/body of the pancreas, tumour stage I–III, surgical resection and normal levels of CEA. Multivariate analysis showed that, of these clinicopathological factors, only female gender and disease stage I–III were associated with better patient survival, a finding consistent with other published studies [16, 17].

On the other hand, some factors, such as tumour differentiation, showed no significant influence on patient survival in our study. Although we found a positive relationship between tumour differentiation and prognosis, it was not statistically significant, probably due to the small number of patients with poorly differentiated carcinomas in our group. The fact that we could not prove any significant influence of metastatic lymph node involvement on patient survival is not compatible with some previous reports [13]. This may be explained by the fact that surgical resection and histological evaluation of regional lymph nodes was performed in only 44 (67.7%) of our patients. Moreover, histological evaluation of lymph node metastases in our study might have been inaccurate because of the known limitations of routine haematoxylin-eosin staining for the identification of micrometastases of pancreatic cancer to lymph nodes [18].

In this study we also evaluated the prognostic value of FDG-PET in patients with pancreatic cancer. FDG-PET is diagnostic imaging tool to examine glucose metabolism in living tissues [19]. Various factors, such as increased aerobic and anaerobic glycolysis in tumour cells, changes in the levels of glucose transporter proteins and up-regulation of hexokinase, have been reported to be possible causes of increased FDG uptake in cancers [20, 21]. FDG-PET has been successfully used in the management of patients with pancreatic cancer for initial diagnosis, pretreatment staging, detection of distant metastases, evaluation of treatment response and detection of recurrence [22–24].

Prognostic value of the SUV of FDG at 1 h after injection has recently been reported in breast, head and neck and lung cancers, suggesting that a high tumour SUV is associated with poor survival [25–27]. Prognostic value of standardised uptake of FDG at 1 h after injection in pancreatic cancer has also been reported by several authors [28–31]. However, there is disagreement over the prognostic significance of this method in different groups of pancreatic cancer patients and over the cut-off SUV that can distinguish patients with a good prognosis from those with a poor prognosis. In some studies, the mean SUV in the examined group of patients with pancreatic cancer was used as a cut-off value for prognostic evaluation. However, such results are hardly comparable because of differences in the method of image acquisition, reconstruction and SUV measurements between institutions. For example, the mean value of SUV1 in our patients with pancreatic cancer was 6.1, which was much higher than the values in papers by Nakata et al. [29] and Sperti et al. [31], and SUV1 showed no influence on patient survival in our study.

Use of SUV for prognostic assessment has some serious limitations. First, in the present study we found that both SUV1 and SUV2 showed significant positive correlations with tumour stage. This means that higher SUV values may represent a larger tumour size. Absolute values of SUV can also be influenced by several institution-dependent factors, such as method of reconstruction and the size and shape of the ROI. Thus, Keyes et al. suggested that most of the currently published findings on SUV in tumours are of little or no value for investigators outside the laboratory where the investigations were conducted [32]. High variability of absolute SUV values was also confirmed in a recent study by Higashi et al., who reported that at different institutions the average SUVs of pancreatic cancer vary from 3.0 to 7.3 [7].

A possible solution to these problems is the use of relative values, such as the retention index, or RI. Our study showed that the RI is one of the strongest predictors of patient survival. The combination of two independent prognostic factors, tumour stage and RI, both accurately assessed by FDG-PET, allowed more accurate prognostic evaluation. Thus, as reported in the Results section, there were significant differences between (a)

patients diagnosed at stage I–III with RI<10% and patients diagnosed at the same stage but with RI>10% ($p<0.01$) and (b) patients diagnosed at stage IV with RI<10% and patients diagnosed at the same stage but with RI>10% ($p<0.05$).

These findings may suggest that FDG-PET with the use of RI has an important role in planning of the treatment strategy in patients with pancreatic cancer. Patients with early-stage disease and a high RI may maximally benefit from standard treatment, while those with a low RI may require more aggressive chemotherapy or radiation treatment. As patients with stage IV and a high RI may survive longer, they may benefit from adjuvant chemotherapy. In patients with stage IV and low RI, it seems questionable whether adjuvant chemotherapy is useful or influences survival.

The exact mechanism underlying the substantial difference in RI values in patients with different prognoses remains unknown. This may be because FDG uptake in cancer lesions corresponds not exclusively to cancer cells, but also to non-neoplastic inflammatory elements such as activated macrophages and lymphocytes, which appear in association with growth or necrosis of tumour cells [33]. However, the kinetics of FDG in pancreatic inflammatory lesions may significantly depend on the type of inflammatory response (common or autoimmune). Recent multiphase PET studies by Nakamoto et al. showed a significant difference in FDG kinetics between patients with chronic and patients with autoimmune pancreatitis. In chronic pancreatitis, in which the inflammatory response is supposed not to be very active, the SUV at 1 h after injection was significantly higher than the SUV at 2 h. On the other hand, in three cases of autoimmune pancreatitis, with an active inflammatory response characterised by massive tissue infiltration by activated lymphocytes, FDG uptake increased continuously up to 2 h after injection, resulting in a high RI [7, 34]. Thus, pancreatic cancers showing a high RI may represent tumours with a more efficient antitumour immune response that results in prolonged patient survival. However, future studies may be required to evaluate the pathological, immunological and molecular mechanisms responsible for the difference in FDG kinetics in pancreatic cancers with different prognoses.

Conclusion

Our results suggest that the RI calculated with dual-phase FDG-PET can be used not only as a tool for initial diagnosis and staging of pancreatic cancer but also as a strong independent prognostic parameter that can allow accurate identification of those patients who will benefit from intensive anticancer treatment at different stages of the disease.

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New Pancreas-preserving Total Duodenectomy Technique

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Abstract. Pancreas-preserving total duodenectomy (PPTD) was first described by Chung et al. in 1994. Since then, several surgeons have used PPTD to treat diseases that involve the duodenum diffusely but not the head of the pancreas, mostly familial adenomatous polyposis (FAP). The PPTD method has been changed in each report and seems to have improved over time. We performed PPTD on three patients with different diseases—one with intestinal hemorrhage due to small intestinal amyloidosis; another with numerous duodenal gastrinomas in a patient with multiple endocrine neoplasia type 1 (MEN-1) and Zollinger-Ellison syndrome (ZES); and the third with numerous duodenal polyposis and FAP—using a new method that is simpler and safer than those previously reported. When resecting the whole duodenum, we performed mucosectomy of the major papillar portion and saved the structure of the major papilla. After an approximately 8 mm long sphincteropapillotomy, the opened major papilla was anastomosed to an incisional opening of the small intestine. The orifice of the main pancreatic duct (MPD) was stented by a catheter, and the MPD was kept intact under direct vision during the operative procedures. The head of the pancreas was fixed with the small intestine by interrupted 4-0 silk sutures. Reconstruction of the alimentary tract was performed after either the Billroth I or the Billroth II method. This is the first report of PPTD in which the entire MPD was preserved to simplify the biliopancreatic-ductal reconstruction.

Pancreas-preserving total duodenectomy (PPTD) has occasionally been reported as a surgical technique for familial adenomatous polyposis (FAP) [1–4]. PPTD can be thought of as a counterpart to the duodenum-preserving pancreatectomy (DPP), which has usually been applied for benign or low malignant diseases of the head of the pancreas [5]. PPTD is useful for diffuse duodenal diseases that do not involve the head of the pancreas. The first patient on whom we performed PPTD was a patient with diffuse intestinal hemorrhage due to intestinal amyloidosis that involved the entire jejunum and duodenum. We used a new PPTD technique that preserves the structure of the major papilla and the entire main pancreatic duct. This technique was subsequently used in two other patients with a good postoperative course. We describe here our new technique precisely, as well as the indications for, and the merit of, this technique.

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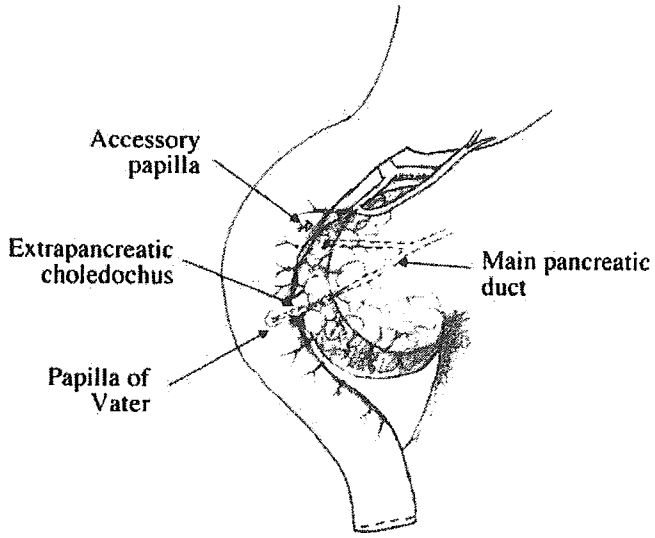


Fig. 1. New pancreas-preserving total duodenectomy (PPTD) method. During surgery the head of the pancreas is preserved, and the duodenum is totally resected. When necessary, part of the stomach is also resected. The structures around the major ampulla are not cut at the line between the duodenum and the head of the pancreas, and only the mucosa over the ampulla is removed. Hence the submucosal structure of the major papilla is saved, as shown in Figure 2a. Thus, the whole tract of the main pancreatic duct (MPD) is preserved.

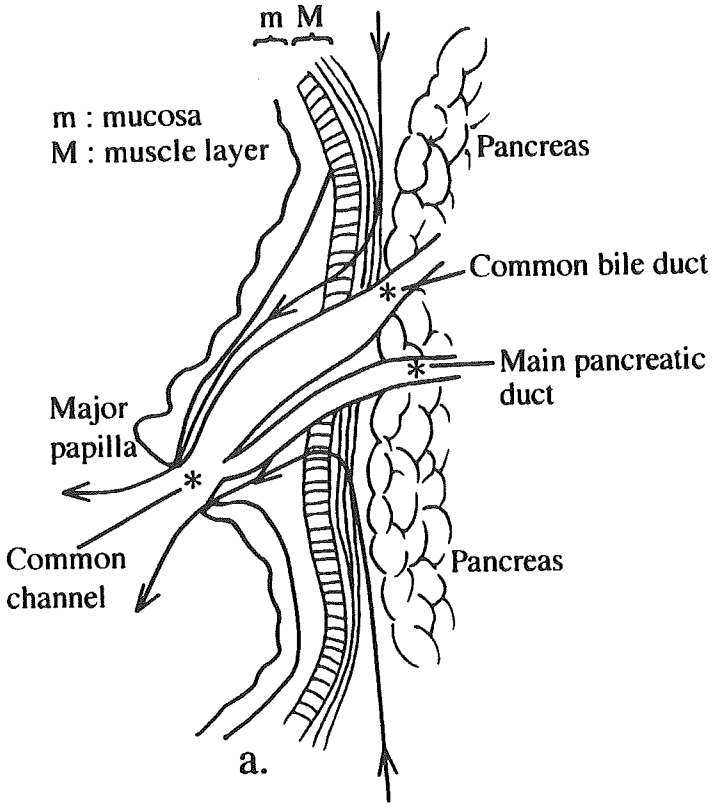
Patients and Methods

Patients

Three patients underwent PPTD with a new technique for the treatment of three different diffuse duodenal diseases: (1) duodenal bleeding due to hemorrhagic diffuse intestinal amyloidosis; (2) numerous duodenal gastrinomas in a patient with multiple endocrine neoplasic type/(MEN-1) and Zollingen-Ellison syndrome (ZES); and (3) multiple polyposis in a patient with FAP.

Surgical Technique

After mobilizing the whole duodenum from the retroperitoneum by Kocher's maneuver, we perform a cholecystectomy and insert a



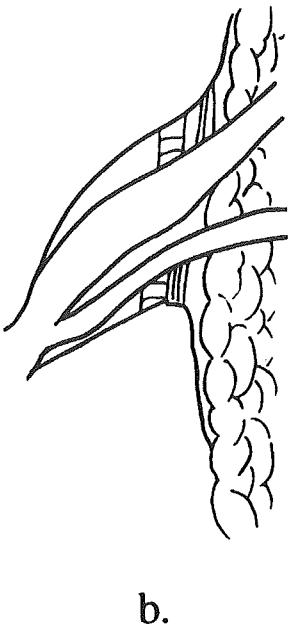


Fig. 2. These figures were originally drawn by Suda et al., and the resection line of our operative method was added. The duodenal mucosa is resected as indicated by the two arrowed lines to keep the orifice of the MPD intact (**a**). **b.** The major papilla after PPTD. (Courtesy of Suda et al.)

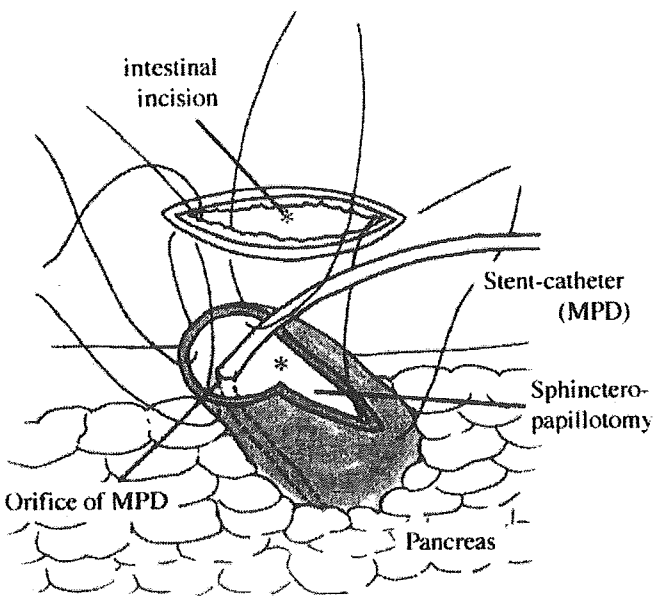


Fig. 3. Anatomists of the major papilla to the intestine after sphincteropapillotomy. A stent catheter was inserted into the MPD to maintain its patency during the anastomotic procedure.

catheter into the cut end of the cystic duct to pass it through the common bile duct into the duodenum. By palpating a catheter in the duodenum, we can easily identify the location of the major papilla. Then, the lower half of the duodenum is separated from the head of the pancreas at the level of the major papilla by dissecting the branches of the pancreaticoduodenal vessels using a Ligasure LAP (Valleylab, Boulder, Co, USA). The stomach is then transected at a line 5 cm to the oral side from the pylorus or on the line juxta-pylorus depending on the extension of the disease. Lifting up the cut stomach, the first part of the duodenum, or both, we carefully separate the upper half of the second part of the duodenum from the head of the pancreas with the Ligasure LAP. During these procedures, the duct of Santorini is identified and ligated twice, with 3-0 silk and 4-0 nylon. Several authors have reported that there was a dense adhesion between the upper half of the duodenum and the head of the pancreas [2, 6]. In such patients, however, we did not encounter any difficulty freeing this part of the duodenum (Fig. 1). The proximal jejunum is then cut, and the lower half of the duodenum is separated from the pancreas.

As the last step of the duodenal resection, we strip off the mucosal layer of the major papilla while palpating a catheter in the distal common bile duct. Thus, a part of the submucosal connective tissue and the muscular layer of the major papilla are saved. These procedures are shown (with the resection line superimposed) in figures that were drawn by Suda et al. and are used by courtesy of those authors (Fig. 2).

Reconstruction of the alimentary tract is performed after either the Billroth I or the Billroth II method. Anastomosis is started by the papillojejunostomy, which is the most important anastomosis in this operation (Fig. 3). Using a knife the major papilla is cut about 8 mm in length on the opposite wall of the orifice of the MPD. A catheter is inserted into the main pancreatic duct to prevent creating a stricture or kinking the MPD during the anastomosis procedures. Then the cut edge of the major papilla is anastomosed to a small incisional opening on the jejunum with about ten 5-0 interrupted absorbable sutures. During the anas-

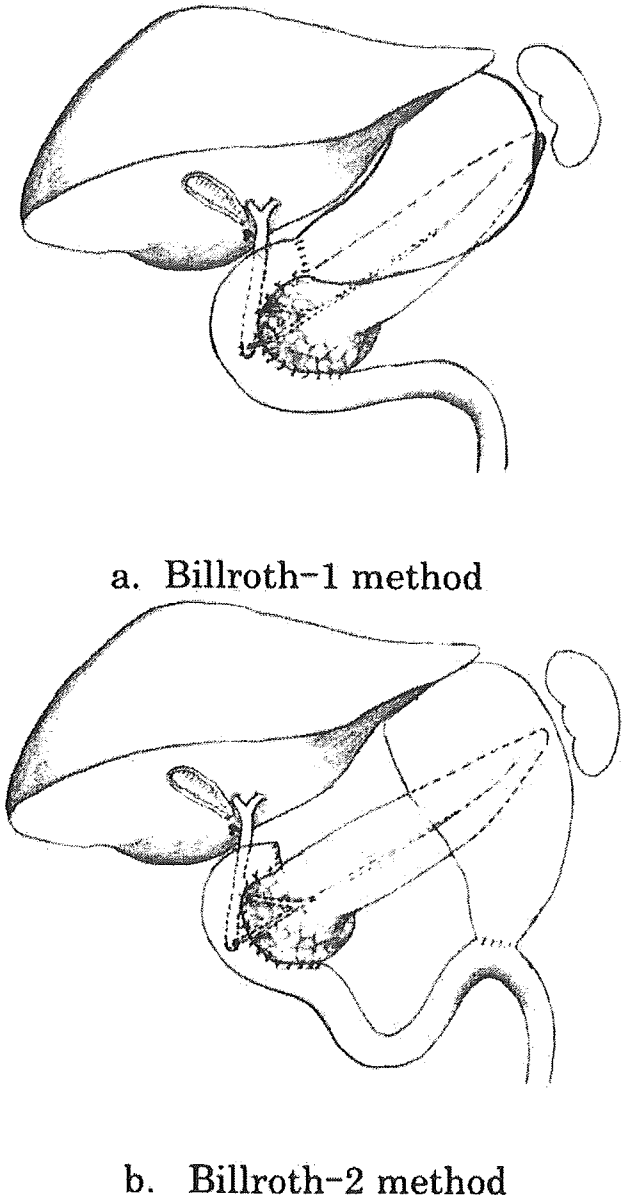


Fig. 4. Alimentary tract is reconstructed by the Billroth I method or the Billroth II method. With the Billroth I method, the stomach is anastomosed to the jejunum about 10 cm oral from the papillojejunostomy (**a**). With the Billroth II method, the stomach is anastomosed to the retrocolically shifted jejunum about 30 cm anal from the papillojejunostomy (**b**).

tomotic procedures the patency of the MPD is kept intact by palpating the stenting catheter in it (Fig. 3). The head of the pancreas, which had been attached to the duodenum, is covered with the small intestine using about 20 interrupted seromuscular sutures of 4-0 silk.

Finally, the stomach is anastomosed to the jejunum in a fashion similar to either the Billroth I or Billoth II method. With the Billroth I method, the stomach is anastomosed to the jejunum about 10 cm oral from the papillojejunostomy. With the Billroth II method, the stomach is anastomosed to the retrocolically shifted jejunum about 30 cm anal from a papillojejunostomy (Fig. 4).

Results

Case 1

A 65-year-old man was admitted with an acute abdomen on October 20, 2002. Emergency laparotomy revealed extensive necrosis of the jejunum including the duodenum. The jejunum was totally resected to stop jejunal bleeding, but the duodenum was left unresected and a side-to-side duodenoileostomy was performed. Pathology examination of the resected jejunum revealed diffuse hemorrhagic enteritis due to severe intestinal amyloidosis. Postoperatively, duodenal bleeding continued because of intestinal amyloidosis. Therefore PPTD was performed with the technique described above on November 22, 2002. Laparotomy was done through an upper midline incision, and the ileoduodenal anastomosis was identified. The ileum was then transected 5 cm from the anastomosis to mobilize the whole duodenum from the retroperitoneum. After total separation of the duodenum from the head of the pancreas, the whole duodenum was resected with part of the gastric antrum and an anastomotic part of the ileum. Reconstruction was performed as described above. The opened ampulla of Vater was anastomosed to an incisional opening of the ileum, and the stomach was anastomosed to the ileum after the Billroth II method. The patient's postoperative course was uneventful, and he has been well without any gastrointestinal bleeding for 18 months postoperatively.

Case 2

A 52-year-old woman with MEN-1 was admitted to our department complaining of hypergastrinemia with duodenal ulcers. It is well known that in patients with MEN-1 and ZES gastrinomas are located in the duodenum. As they are often multiple, recurrence of ZES has not been rare [7, 8]. In this patient, preoperative duodenoscopy revealed more than five mucosal duodenal tumors and multiple ulcer scar-like lesions in the duodenum. Therefore we thought that PPTD was indicated. PPTD was performed using our method on November 6, 2003. The duodenum was totally resected with part of the gastric antrum, and a gastroenteric reconstruction was performed after the Billroth II method. Pathology examination of the resected specimen revealed numerous mucosal gastrinomas in the duodenum. Postoperatively, her serum gastrin levels normalized, evidence that all the gastrinomas were resected. She has been well without any sign of recurrence of gastrinomas for 7 months postoperatively.

Case 3

A 40-year-old man with FAP underwent the same PPTD method for duodenal polyposis on November 11, 2003. This time, to save the stomach and the pylorus, the oral cut line of the alimentary tract was juxtasubpyloric. After resecting the whole duodenum, gastroenteric reconstruction was performed after the Billroth I method (i.e., an end-to-end pylorojejunostomy) because we thought that this reconstruction would make it easier for him to undergo endoscopic surveillance of the intestinal polyps postoperatively. He has been well for 8 months since the operation.

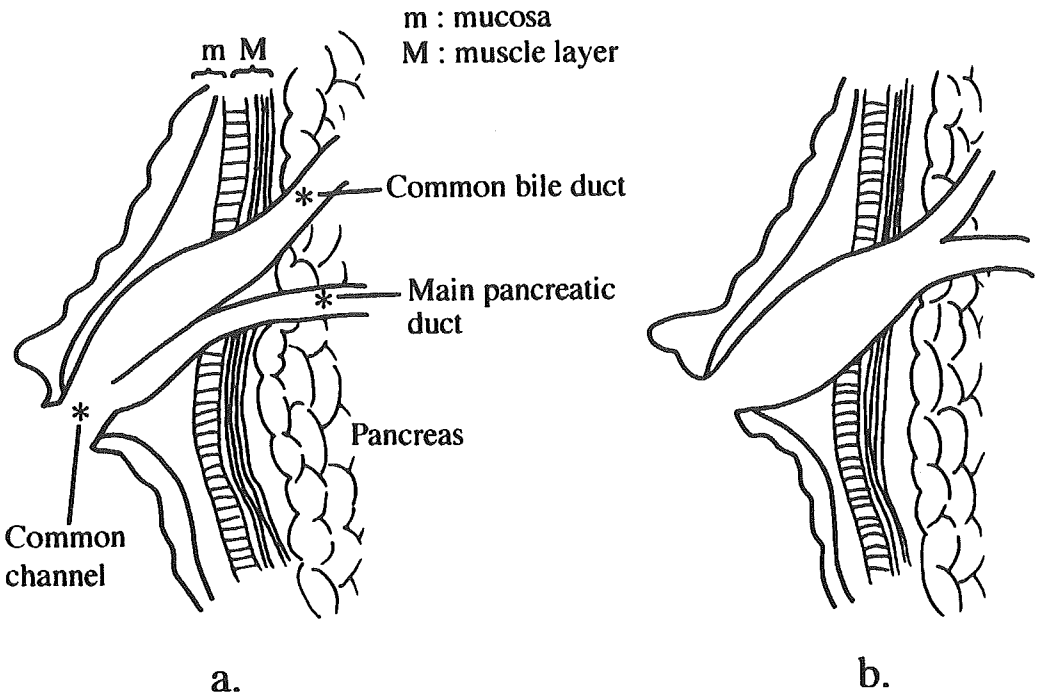


Fig. 5. Suda et al. examined the anatomy of the choledochopancreatic junction in 130 Japanese adults and classified it into three patterns according to Tokuyama [9]. They found that in only four patients (3.1%) did the MPD have an orifice separate from that of the common bile duct (CBD) (type 1). In 19 patients (14.6%), the MPD and the CBD ran into the duodenum together without forming a common channel (type 2). In all of the other 107 patients (82.3%) a common channel existed (type 3), and the choledochopancreatic junction was located in the mucosa or submucosa (type 3a) (**a**). Only in patients with biliary atresia or a choledochal cyst was the choledochopancreatic junction located below the muscular layer of the duodenum (type 3b) (**b**). Thus in most patients without an abnormal biliopancreatic anastomosis, the MPD opens into the mucosal or submucosal layer of the duodenum.

Discussion

We described here a new operative technique for PPTD that has been successfully performed on three patients for the treatment of three duodenal diseases: duodenal bleeding due to hemorrhagic intestinal amyloidosis; numerous duodenal gastrinomas in a patient with MEN-1 and ZES; and multiple polyposis in a patient with FAP. This is the first report that a patient with MEN-1 and ZES underwent a curative resection of multiple duodenal gastrinomas with PPTD.

PPPD is simpler and less invasive that Whipple's operation because it avoids unnecessary resection of the head of the pancreas [2]. In previous reports on PPTD, the distal choledochus was cut on the line between the duodenum and the pancreas. Accordingly, the MPD has been cut because it usually opens close to the orifice of the major papilla (Fig. 2) [9]. Suda et al. [9] examined the anatomy of the choledochopancreatic junction in 130 Japanese adults and classified it into three patterns according to Tokuyama [7]. They found that in only four patients (3.1%) did the MPD have an orifice separate from that of the common bile duct (CBD) (type 1). In 19 patients (14.6%), the MPD and the CBD run into the duodenum together without forming a common channel (type 2). In all of the other 107 patients (82.3%) a common channel existed (type 3), and the choledochopancreatic junction was located in the mucosa or submucosa (type 3a) (Fig. 5a). Only in patients with biliary atresia or a choledochal cyst was the choledochopancreatic junction located below the muscular layer of the duodenum (type 3b) (Fig. 5b). Thus, in most patients without an abnormal biliopancreatic anastomosis, the MPD opens into the mucosal or submucosal layer of the duodenum.

To preserve the orifice of the MPD, we resected the duodenal wall around the major papilla, as shown in Fig. 2a. This was easily achieved by palpating a catheter inserted into the distal CBD. Some of the submucosal connective tissue around the choledochopancreatic junction was saved, as was part of the sphincter of the major papilla (Fig. 2b). The biliopancreatic duct was reconstructed after a sharp papillotomy about 8 mm in length on the opposite wall of the MPD opening. A catheter was inserted into the MPD to prevent kinking or stenosis during the anastomotic procedure, and the cut edge of the major papilla was anastomosed to the small opening in the ileum using 5-0 interrupted absorbable sutures. This is a simple, safe method that avoids anastomosing a nondilated MPD to the jejunum.

Regarding invasion of pancreatic tissue into the upper half of the second part of the duodenum [6], we examined 10 cadavers and found invasion of pancreatic tissue in 7 of them. These results were compatible with the report of Kimura et al. [6]. In these 10 cadavers the length of the common channel was 2.9 $\pm$ 1.9 mm, which was also compatible with the results of Suda et al. [9].

It is well known that in patients with MEN-1 and ZES duodenal gastrinomas cause ZES [7, 8, 10]. Based on our observations and others, these duodenal gastrinomas are often multiple and recur even after extirpation of multiple duodenal gastrinomas [7, 8]. In case 2, the postoperative pathology study revealed numerous mucosal gastrinomas in the duodenum, although fewer gastrinomas had been diagnosed preoperatively. She has been well without any sign of recurrence after PPTD. We think that PPTD

might become a standard method for the curative resection of multiple duodenal gastrinomas in patients with MEN-1 and ZES.

In conclusion, PPTD with our new method seems to be a safe, useful technique for patients with various diffuse duodenal diseases.

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Analysis of E-, N-Cadherin, α-, β-, and γ-Catenin Expression in Human Pancreatic Carcinoma Cell Lines

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Objectives: Cadherins are cell surface glycoproteins that mediate Ca^{2+}-dependent, homophilic cell-cell adhesion. The classic cadherins interact with either β-catenin or γ-catenin, which is bound to α-catenin that links the complex to the actin cytoskeleton. It has been reported that alteration in cadherins/catenins function or expression is found in the neoplastic process as a step in metastasis. The aim of this study was to analyze the expressions of E- and N-cadherins and catenins in human pancreatic cancer cell lines.

Methods: We examined the expression of cadherins and catenins in 7 human pancreatic cancer cells by RT-PCR, Western blotting, and immunocytochemistry. The interactions between cadherins and β-catenin were assessed by immunoprecipitation.

Results: E-cadherin was expressed in all cell lines except for MIAPaCa-2, whereas N-cadherin was expressed in Capan-2, CFPAC-1, BxPC-3, and PANC-1. The α-, β-, and γ-catenins were expressed and cadherins/β-catenin interactions were detected in all cadherin-expressing cells. Immunocytochemical analysis showed membranous expression of cadherins and catenins.

Conclusion: The decreased or loss of cadherins and catenins expression could be involved in the tumor progression and metastasis, although these events may occur in in vivo conditions by interaction between cancer cells and extracellular matrices.

Key Words: pancreatic cancer, cadherin, catenin

(*Pancreas* 2005;30:168–173)

Invasion and metastasis can be facilitated by proteins that stimulate tumor cell attachment to host cellular or extracellular matrix determinants, tumor cell proteolysis of host barriers, such as the basement membrane, tumor cell locomotion, and tumor cell colony formation in the target organ for metastasis.[1] It is known that cadherins are major cell-cell adhesion molecules in tumors as well as in normal tissues. The perturbation of cadherin function causes temporal or permanent disaggregation of tumor cells and may thus promote the invasion and metastasis of such cells.[2]

E-cadherin is a member of a family of Ca^{2+}-dependent integral membrane cell-cell adhesion receptors.[3] E-cadherin is localized at the zonula adherens junction between epithelial cells[4] and is associated with peripheral basal-lateral actin filaments in a multiprotein complex with kinases, phosphatases, and catenins.[5] The cytoplasmic complex, which anchors E-cadherin to the actin cytoskeleton,[6] includes the intracellular proteins α-catenin, which has homology to vinculin,[7] and the armadillo family members β-catenin and γ-catenin.[8] After cell-cell contact, adhesion of the E-cadherin/catenin complex functions to establish epithelial cellular architecture by initiating formation of desmosomes, tight junctions, and gap junctions.[9]

Alteration in E-cadherin/catenin function or expression is found in the neoplastic process as a step in metastasis.[10] The loss of E-cadherin/catenin function results, in part, in a transformation from the normal epithelioid morphology toward an invasive and less differentiated mesenchymal phenotype.[11] Immunohistochemical analysis of highly invasive tumors (breast, melanoma, prostate, non-small cell lung carcinomas) indicates that these tissues have decreased E-cadherin levels, suggesting a decreased function for E-cadherin in organization of tissue structure.[12]

Interestingly, recent studies have reported that N-cadherin, one of the mesenchymal cadherins, enhances tumor cell motility and migration,[13,14] thus showing an opposite effect as compared with E-cadherin. N-cadherin–induced tumor cell invasion can even overcome E-cadherin–mediated cell-cell adhesion.[13,15] Furthermore, N-cadherin is expressed in human tumors that have lost E-cadherin expression.[16,17]

As for the pancreatic cancer cells, the loss of membranous E-cadherin expression is associated with high grade and advanced stage in pancreatic cancer.[18] However, it is not known whether the aforementioned "cadherin switch" is involved in the neoplastic and invasive progression of pancreatic cancer cells. The current study was conducted to investigate the full spectrum of the cadherin/catenin expression in human pancreatic cancer cell lines at the level of messenger RNAs and proteins.

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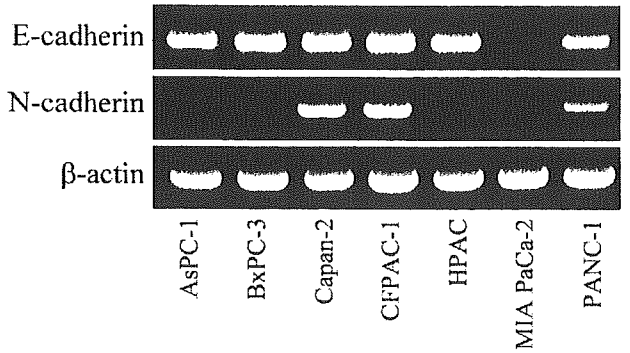

FIGURE 1. E- and N-cadherin mRNA expression in human pancreatic cancer cells. E-cadherin mRNA was detected in all cell lines except for MIAPaCa-2. N-cadherin m-RNA was detected in BxPC-3, Capan-2, CFPAC-1, and PANC-1.

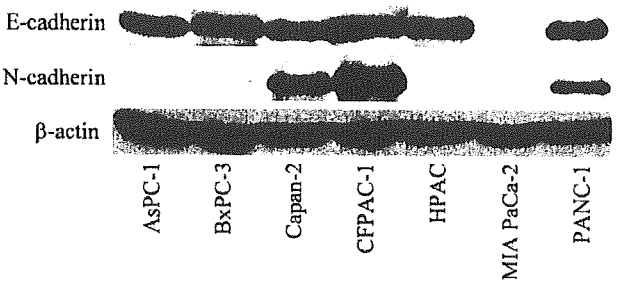

FIGURE 2. E- and N-cadherin protein expression in human pancreatic cancer cells. E-cadherin protein was detected in all cell lines except for MIAPaCa-2. N-cadherin protein was detected in BxPC-3, Capan-2, CFPAC-1, and PANC-1.

METHODS

Cell Line and Culture Conditions

Human pancreatic cancer cell lines (AsPC-1, BxPC-3, Capan-2, CFPAC-1, HPAC, MIAPaCa-2, and PANC-1) were maintained in the following media at 37°C in a humid atmosphere of 5% CO_2/95% air. AsPC-1 cells, BxPC-1 cells, and HPAC cells were cultured in RPMI 1640 medium (Gibco-BRL, Grand Island, NY) with 10% fetal bovine serum (FBS) (ICN Biomedicals, Aurora, OH). CAPAN-2 cells, CFPAC-1 cells, MIAPaCa-2 cells, and PANC-1 cells were cultured in medium recommended by American Type Culture Collection. Each medium contained 100 U/mL penicillin and 0.1 mg/mL streptomycin (Gibco-BRL).

Antibodies

The mouse monoclonal anti-N-cadherin antibody and mouse monoclonal anti-β-catenin antibody were purchased from Zymed Laboratories Inc. (South San Francisco, CA). The mouse monoclonal anti–α-catenin antibody and mouse monoclonal anti–γ-catenin antibody were purchased from Transduction Laboratories (Lexington, KY). The mouse monoclonal anti–β-actin antibody (clone AC-15) was purchased from Sigma (St. Louis, MO). The biotinylated secondary antibody (goat anti-mouse IgG) used immunocytochemistry procedures was purchased from Jackson Immuno Research Laboratories (West Grove, PA). For immunoblotting, the horseradish peroxidase–conjugated antibody was HRP-gout anti-mouse IgG (Zymed Laboratories).

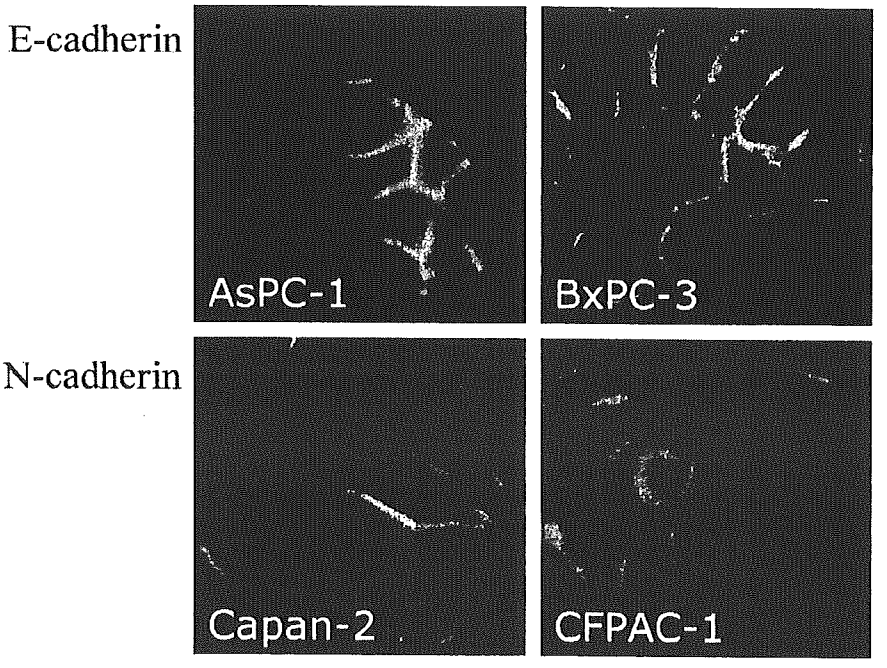

FIGURE 3. Immunocytochemical detection of E- and N-cadherins. Typical staining of E-cadherin and N-cadherin shows a membranous expression.

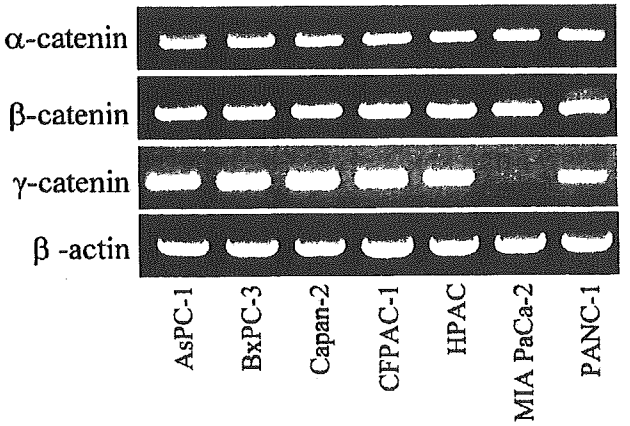

FIGURE 4. α-, β-, and γ-catenin mRNA expression in human pancreatic cancer cells. The mRNA expression of α-, β-, and γ-catenins was detected in all cell lines. However, the expression of γ-catenin in MIAPaCa-2 is extremely low.

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)

Total cellular RNA was prepared using TRIZOL Reagent (Life Technologies, Rockville, MD) and cDNA was prepared 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. Five microliters of first-strand cDNA solution was subjected to PCR with synthetic oligonucleotide primers (NIPPON EGT, Toyama, Japan). The sequences for the primers used in this study are as follows:

E-cadherin upstream: 5′-TCCATTTCTTGGTCTACGCC-3′,
downstream: 5′-CACCTTCAGCCATCCTGTTT-3′
N-cadherin upstream: 5′-GTGCCATTAGCCAAGGGAATT-CAGC-3′,
downstream: 5′-GCGTTCCTGTTCCACTCATAGGAGG-3′
α-catenin upstream: 5′-GTCATTCACGTAGTCACCTCA-3′,
downstream: 5′-TTCTGACATCAAAATCTTCTGTC-3′
β-catenin upstream: 5′-AAGGTCTGAGGAGCAGCTTC-3′,
downstream: 5′-TGGACCATAACTGCAGCCTT-3′
γ-catenin upstream: 5′-ATGGAGGTGATGAACCTGATGG-3′,
downstream: 5′-CCTGACACACCAGGGCACAT-3′
β-actin upstream: 5′-GGCATCGTGATGGACTCCG-3′,
downstream: 5′-GCTGGAAGGTGGACAGCGA-3′

The products were 361, 369, 301, 668, 284, and 613 base pairs, respectively.

The reproducibility of the technique and quality of the total RNA were confirmed using β-actin primers. Specific sequences were amplified by 30 cycles (30 seconds of denaturation at 94°C, 30 seconds annealing at 60°C, and 1 minute extension at 72°C), followed by a final incubation at 72°C for 10 minutes. PCR products were analyzed on a 2% agarose gel.[19]

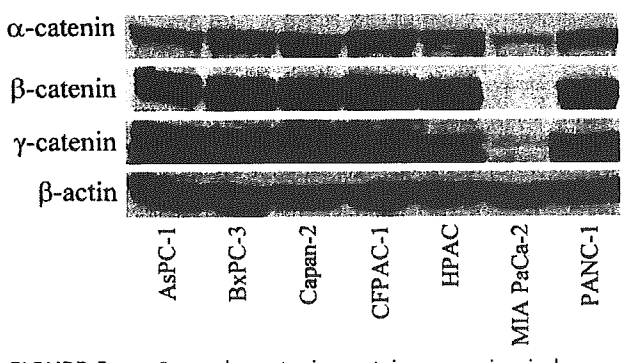

FIGURE 5. α-, β-, and γ-catenin protein expression in human pancreatic cancer cells. α-, β-, and γ-catenin protein was detected in these cells except MIAPaCa-2. No protein expression of β-catenin was found in MIAPaCa-2.

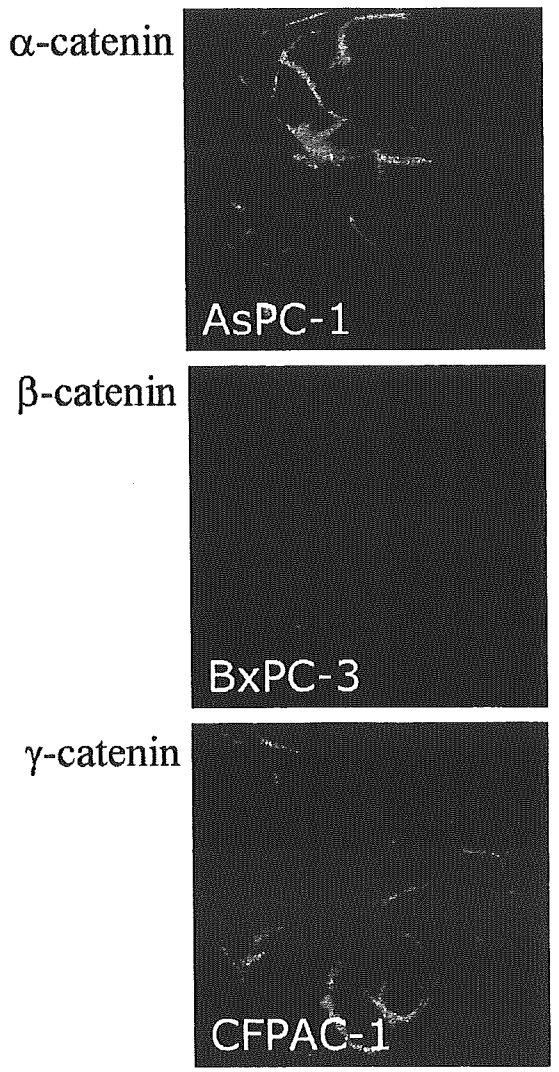

FIGURE 6. Immunocytochemical detection of α-, β-, and γ-catenins. Typical staining of α-, β-, and γ-catenins shows a membranous expression.