Monitoring fibrosis of the pancreatic remnant after a pancreaticoduodenectomy with dynamic MR imaging

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Running title: Remnant pancreatic fibrosis after PD

Abstract

Background: The time-signal intensity curve (TIC) of the pancreas obtained from dynamic contrast-enhanced magnetic resonance imaging (MRI) closely reflects the histological degree of pancreatic fibrosis.

Materials and Methods: Seventy-six patients who had undergone a pancreatic TIC analysis prior to receiving a pancreaticoduodenectomy for various reasons were subjected to a yearly monitoring with pancreatic TIC for the pancreatic remnants. The pancreatic TIC profiles were classified into 3 types: type I, indicating a normal pancreas without fibrosis; and types II and III indicating fibrotic pancreas.

Results: The preoperative pancreatic TICs were type-I in 51 patients, type-II in 20, and type-III in 5, and the corresponding pancreatic fibrosis ratios were proved histologically to be 4.1%, 13.3%, and 21.2%, respectively. The mean postoperative follow-up period was 40.2 months. A type-I changed to type-II in 16 patients, by 32.3 months after surgery. In these patients, the exocrine remnant pancreatic function was preserved at the time of TIC conversion, but it significantly deteriorated thereafter. Pancreatic anastomotic leakage was found to be a significant risk factor predisposing a patient to undergo postoperative TIC conversion. In contrast, a preoperative type-II or III showed a postoperative conversion to type-I or II in 6 patients. In this group, the exocrine pancreatic function was noted to show a good recovery. In 35 patients who had a type-I TIC throughout the study, the remnant pancreatic function was well maintained

Conclusions: Pancreatic TIC analysis has the ab ility to detect an early fibrotic change that precedes a functional deterior ation of the pancreatic remnan t after a pancreaticoduodenectomy. Following a panc reaticoduodenectomy, some patients show an im provement in pancreatic fi brosis, but they may also experience remnant pancreatic fibrosis when pancr eatic anastomotic leakage occurs after surgery.

Key words: pancreatic fibrosis, pancreat ic function; rem nant pancreas; pancreaticoduodenectomy; dynamic magnetic resonance imaging; time-signal intensity curve

Introduction

A pancreaticoduodenectomy is now a safe operation with a low hospital mortality in specialized units. [1-3] However, some patients develop exocrine and endocrine pancreatic insufficiency along with atrophy of the pancreatic remnant and controversy still remains regarding the optimal surgical procedure to preserve the remnant pancreatic function in the long-term course following a pancreaticoduodenectomy.[4-6] A dysfunction of the pancreatic remnant greatly influences the postoperative quality of life, and it is therefore important to maintain and monitor the remnant pancreatic function following a pancreaticoduodenectomy.

In various types of chronically damaged pancreas, the development and progression of fibrosis plays a critical role in the destruction of exocrine and endocrine pancreatic function, by replacing pancreatic acinar parenchyma and islets with dense fibrous tissue.[7-9] The degree of pancreatic fibrosis could thus be a useful indicator for evaluating the pathological conditions of the pancreas, even the pancreatic remnant following a pancreaticoduodenectomy. The authors previously demonstrated a time-signal intensity curve (TIC) of the pancreas obtained from dynamic contrast-enhanced magnetic resonance imaging (MRI) to be a reliable and non-invasive monitoring technique for a precise evaluation of the histological degree of pancreatic fibrosis. [10] We now report on a long-term follow-up study of 76 cases who underwent a pancreaticoduodenectomy, focusing on the significance of monitoring the dynamic changes in fibrosis and

the functional capacity of the pancreatic remnant by utilizing the pancreatic TIC analysis.

Patients and Methods

Between March 1999 and January 2008, 115 patients underwent a pancreatic TIC analysis with dynamic MRI prior to undergoing a pancreaticoduodenectomy for various indications. Of these, 76 patients were successfully monitored yearly with pancreatic TIC for the pancreatic remnants and were included in the study. The patients who were referred to another hospital after the pancreaticoduodenectomy (n=12), less than 12 months of postoperative follow-up (n=13), or dropped from the follow-up within 12 months after surgery due to a recurrence of the disease (n=11) were excluded. The subjects consisted of 48 men and 28 women, including the 26 patients reported in our previous study,[10] with a mean age 65 (range 43-81) years. The pancreaticoduodenectomy was performed for carcinoma of the distal bile duct in 21 patients, papilla of Vater in 17, head of the pancreas in 16, the gallbladder in 4, and the stomach in 2, or for an intraductal papillary-mucinous neoplasm of the pancreas in 10 and alcoholic chronic pancreatitis in 6. After the pancreaticoduodenectomy, an end-to-side pancreaticojejunostomy was performed according to Child's modified procedure for reconstruction of the digestive tract.[11] The histology of the pancreatic stump was free from cancer cells in all patients with malignancy. No patients underwent any radiation

therapy.

Analyses of Pancreatic TIC and Fibrosis

The pancreatic MRI was conducted by using the 1.5-T superconducting system (SIGNA Horizon LXTM; GE Medical Systems, Milwaukee, WI). We used a fat-suppressed three-dimensional fast spoiled gradient re-called echo sequence with the following imaging parameters: TR/TE, 6.0-6.1/1.3-1.4 msec; flip angle, 20°; section thickness, 6-8 mm; no intersection gap; matrix, 256 x 160; 1 excitation; field of view, 32-36 cm. The dynamic series comprised 5 individual dynamic images, obtained before and 25 s and 1, 2 and 3 min after the rapid bolus injection of 0.1 mmol of meglumine gadopentetate (Magnevist®; Schering, Berlin, Germany) /kg of body weight. [10] The contrast medium was administered intravenously at 3 ml/s using an automated injector. The original MRI data were then loaded onto a work station and radiologists positioned the regions of interest (ROI) in the pancreas, in which the first ROI was placed at the pancreatic parenchyma anterior to the superior mesenteric artery, as for the presumed transection line of the pancreas, and the second ROI was at the body of the pancreas to compare with the postoperative follow-up in each patient. The pancreatic TIC was then generated as a percentage increase in the signal intensity (SI), according to the following enhancement formula: (SIpost-SIpre)/SIpre × 100, where SIpre and SIpost represent the pre- and post-contrast SIs, respectively. The patterns of pancreatic TIC were classified into 3 types (**Figure 1**): type-I, characterized by a rapid rise to a peak (25 s after

injection of contrast material) followed by a rapid decline; type-II, with a slow rise to a peak (1 min after administration of contrast material) followed by a slow decline; and type-III, with an even slower rise to a peak (2 min after the administration of contrast material) followed by a slow decline or plateau.

Postoperatively, the histology and histological degree of pancreatic fibrosis at the cut end of the pancreas were examined. Pancreatic fibrosis was assessed quantitatively by the Picrosirius-polarization method.[12] In brief, paraffin-embedded tissue sections obtained from the pancreatic transection line were treated with 0.5 % papain (Wako Pure Chemical Industries, Osaka, Japan) at 37 °C for 90 min. The slides were then stained for 1 h in 0.1 % Sirius Red F3BA (Direct Red 80TM; Aldrich Chemical, Milwaukee, Wisconsin, USA) in saturated aqueous picric acid. To identify the collagen in the Picrosirius-stained material, the samples were photographed under a polarization microscopy and the fibrosis ratios (area of pancreas stained for collagen as a percentage of the total area) were measured by using the freeware image analysis program NIH Image (written by Wayne Rasband at the National Institutes of Health, Bethesda, Maryland, USA) without any knowledge of the MRI findings. The fibrosis ratio was then compared with the pancreatic TIC profile of the first ROI in each patient.

Postoperative dynamic MRI studies of the remnant pancreas were repeatedly carried out at intervals of 12 months, starting 12 months after surgery. A ROI was located on the body of the remnant pancreas and the TIC was obtained as described above.

Detailed Clinical Data Recorded

The morphologic and functional assessment of the pancreas was done at the same time the pancreatic TIC analysis was performed in all patients. The morphologic assessment of the pancreas included the diameter of the main pancreatic duct and the actual thickness of the pancreatic parenchyma (calculated by subtracting the diameter of the main pancreatic duct from the total pancreatic gland thickness). These morphologic data were measured at the pancreas anterior to the superior mesenteric artery preoperatively and at the body of the remnant pancreas postoperatively, by using contrast-enhanced computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP). A BT-PABA test was used to assess the exocrine function of the pancreas. For the evaluation of endocrine pancreatic function, hemoglobin A1c (HbA1c) level was measured. A 75-g oral glucose tolerance test (OGTT) was performed before surgery. An abnormal glycemic response to the OGTT was defined according to the criteria proposed by the World Health Organization study group on diabetes mellitus.[13]

Additional preoperative data analyzed were the age, gender, pathology of pancreatic and periampullary diseases, the serum levels of albumin and total bilirubin, and creatinine clearance. Regarding the intraoperative parameters, texture of the pancreas, type of pancreaticojejunostomy, the extent of the lymphadenectomy, operative time, intraoperative blood loss, and blood transfusion were examined. The history of the pancreaticojejunal anastomotic

leakage was enrolled as a postoperative parameter. Pancreatic leakage was defined according to the criteria established by the International Study Group on Pancreatic Fistula (ISGPF).[14]

Statistical Analyses

The results of the parametric data were expressed as the means ± SD. The Mann-Whitney *U*–test, Kruskal-Wallis test, two-tailed Fisher's exact test, and chi-square test were used for statistical analysis. The correlation of postoperative conversion of pancreatic TIC profile with time was assessed by using the Kaplan-Meier method, and then compared by means of the log-rank test. Values of $p<0.05$ were considered to be statistically significant.

Results

The patterns of preoperative pancreatic TIC of 76 patients examined at the pancreatic parenchyma anterior to the superior mesenteric artery (the first ROI) were type-I in 51 cases, type-II in 20, and type-III in 5 (**Table 1**). The TIC type of the first ROI was identical to that of the second ROI examined at the body of the pancreas in each individual patient. Most patients with a type-I TIC had a soft pancreas with a normal pancreatic duct in size, while the patients with type-II or III frequently demonstrated a hardened atrophied pancreas with a markedly dilated pancreatic duct. Both exocrine and endocrine pancreatic functions were significantly diminished in patients with type-II or III TIC. The

preoperative pancreatic TIC profi les correlated well with the histology and histological extent of the fibrosis of the pancreas. The 51 pancreatic regions with a type-I TIC were histologically norm al, except for 3, with a mean fibrosis ratio of 4.1±1.4% (range 1.8-8.2), while the 20 regions with a type-II TIC were found to be chronic pancreatitis of duct-obstructing process in 16 and alcoholic chronic pancreatitis in 4, with a m ean fibrosis ratio of 13.3 ±4.1% (range 7.5-20.2). Moreover, the 5 regions with a type-III TIC were proved to be obstructive chronic pancreatitis in 3 and alcoholic ch ronic pancreatitis in 2, with a mean fibrosis ratio of 21.2±3.2% (range 17.8-25.5).

The postoperative follow-up period of the 76 patients after the pancreaticoduodenectomy ranged from 12 to 96 months, wit h a m ean of 40.2 months. Of the 51 patients with a pr eoperative type-I TIC, the pancreatic remnant remained a type-I throughout t he study i n 35 patients, while a type-I had converted to type-II in 16 patients w ith a mean postoperative period of 32.3 months (**Table 2**). The TIC conversion occurred wi thin 12 months after surgery in 6 patients, 24 months i n 4, 36 m onths in 3, 60 m onths in one, and by 84 months in 2. Moreover , the type-II TIC had converted to type-III in 3 patients after an additional follow-up of 12 to 36 months. Among the 20 patient s with a preoperative type-II TIC, in contrast, a type-II had reversed to type-I in 5 patients, by 12 m onths after sur gery in 4 and by 24 m onths in one. The pancreatic histology of these patients was obstructive chronic pancreatitis due to pancreatic ductal carcin oma in 4 and an intra ductal papillary-mucinous carcinoma of the pancreas in one, with a mean fibrosis ratio of 12.1±4.4%

(range 8.5-15.7). In addition, a case of alcoholic chronic pancreatitis with a preoperative type-III TIC had demonstrated a type-II 12 months after surgery. The remaining 19 patients with a preoperative type-II or III TIC showed no change in the pancreatic TIC at follow-up. A representative case with a postoperative reversal of pancreatic TIC from type-II to type-I is demonstrated in **Figures 2 and 3**.

The postoperative remnant pancreatic function was well maintained in 35 patients who had a type-I TIC throughout the study (**Table 2**). However, postoperative duct dilatation and parenchymal atrophy of the remnant pancreas were significantly observed in 16 patients who demonstrated a postoperative conversion of pancreatic TIC from type-I to type-II, or III. In these patients, the exocrine pancreatic function assessed with the BT-PABA test was preserved at the time of TIC conversion (mean 63.2%), but significantly dropped after an additional follow-up of 12.7 months (mean 53.1%). In contrast, the mean BT-PABA test results was significantly increased postoperatively from 45.5% to 64.3% in 5 patients who demonstrated a postoperative reversal of pancreatic TIC from type-II to type-I. There were no remarkable changes in the HbA1c value during this follow-up study, irrespective of postoperative TIC conversion.

Among the various clinical parameters, the presence of pancreatic anastomotic leakage was identified as the only notable risk factor predisposing to the postoperative conversion of pancreatic TIC from type-I to type-II, or III ($p=0.002$). The incidence of TIC conversion from type-I to type-II, or III was 61.5% (8 of 13 cases) in patients with pancreatic anastomotic leakage, while

21.1% (8 of 38 cases) in patients without pancreatic leakage. The pathology of the disease, preoperative pancreatic duct size, pancreatic texture, pancreatic anastomotic technique, or fibrosis ratio of the pancreas at surgery had little impact on the postoperative TIC conversion.

Discussion

The reliability of pancreatic TICs obtained from dynamic contrast-enhanced MRI was first evaluated as an indicator of pancreatic fibrosis in this study. The results demonstrated that pancreatic TICs showed a significant correlation with the histological degree of pancreatic fibrosis, confirming the results obtained in our previous study.[10] The fibrotic pancreas due to either obstructive or alcoholic process exhibited a TIC with a slow rise to a peak followed by a slow decline or plateau (types-II and III), and was significantly different from the pattern of a normal pancreas without fibrosis (type-I). Fibrosis diminishes the amount of aqueous protein in the pancreatic acini and the capillary network of the pancreas that may underlie both the loss of signal intensity in the pancreas on fat-suppressed T1-weighted images and the diminished enhancement on dynamic contrast-enhanced images,[15-17] thus displaying a type-II, or III pancreatic TIC on dynamic contrast-enhanced MRI. It is also reasonable that preoperative pancreatic TIC well reflected both pancreatic morphology and function, including pancreatic duct dilatation, parenchymal atrophy, and pancreatic exocrine and endocrine dysfunction, because such pathological

conditions progress simultaneously with the advance of pancreatic fibrosis.

Although no remarkable changes in the endocrine function of the pancreatic remnants were observed in this study during the postoperative follow-up of 40.2 months, the exocrine function showed a drastic change. In patients who showed a postoperative TIC conversion from type-I to type-II, or III, the exocrine remnant pancreatic function was notably diminished, together with the dilation of the pancreatic duct and the atrophy of the pancreatic parenchyma. Interestingly, in these cases the exocrine function was well preserved at the time of TIC conversion and it thereafter decreased with an approximate one-year time lag. These results indicated that the pancreatic TIC analysis has the ability to identify an early fibrotic change in the pancreatic remnants that precedes deterioration of exocrine pancreatic function following a pancreaticoduodenectomy. Because the islets of the pancreas are later affected in the course of chronic pancreatitis, and the resultant endocrine insufficiency is delayed in comparison to the development of exocrine insufficiency,[18-20] the patients who demonstrated a fibrotic TIC, i.e., type II or III, after surgery would therefore be candidates to develop not only exocrine but also endocrine remnant pancreatic insufficiency.

Pancreatic anastomotic leakage was found to be the only significant risk factor predisposing a patient to undergo postoperative conversion of pancreatic TIC from type-I to type-II, or III, indicating that pancreatic anastomotic leakage promotes the development and progression of fibrosis in the pancreatic remnant and eventually pancreatic functional deficiency. Pancreatic juice outflow

obstruction due to stenosis of the panc reaticojejunal anastomosis might occur after pancreatic anastom otic leakage. Mean while, 8 of 38 patients without pancreatic leakage demonstrated a fi brotic TIC after sur gery as well. Unfortunately, since there is no gold standard method to pre vent the pancreatic anastomotic leakage or to preserve rem nant pancreatic function in the long-term course following a pancreaticoduodenectom y, various techniques of managing the pancreatic remnant and various modi fications of the pancreati c-enteric anastomosis have thus been attempted. For assessing the quality of such surgical maneuvers, the pancreatic TI C analysis should therefore provide us with useful information because this im aging technique can predict the remn ant pancreatic function before the ordinary pancreatic function tests detect the p ancreatic insufficiency. When a patient dem onstrates a fibrotic TIC after under going a pancreaticoduodenectomy, a pancreatic TIC analysis may provide im portant additional information which can help su rgeons to consider reconstructing the pancreatic-enteric anastomosis prior to the pan creatic remnant deteriorating into an irreversible condition.

In obstructive chronic pancreatitis, a continuous occlusion of the m ajor pancreatic ductal system leads to panc reatic duct dilatation, parenchymal atrophy and, finally, the disappearance of the acinar cells, wh ereas releasing the obstruction results i n reversal of early structural and functional changes of the pancreas.[21,22] However, it is generally believe d that the m orphological changes of the pancreas in alcoholic chronic pa ncreatitis, characterized by an irregular and varying degrees of fibrosis with de struction of exocri ne parenchyma, is

irreversible and may lead to a progressive or permanent loss of pancreatic function.[7-9] Meanwhile, there is an open question of whether chronic pancreatitis is always progressive or may regress after removal of the primary lesion or causes. In this study, postoperative reversal of pancreatic TIC from type-II to type-I was recognized in 5 patients, and a conversion from type-III to type-II in one. The pancreatic histology in these patients was obstructive chronic pancreatitis with a mean fibrosis ratio of 12.1% (range 8.5-15.7) in the former and alcoholic chronic pancreatitis with a fibrosis ratio of 18.9% in the latter. In addition, these patients showed a notable recovery from the exocrine pancreatic functional deficiency after surgery. These findings suggested that pancreatic fibrosis in some patients with either obstructive or alcoholic chronic pancreatitis could be reversed following a pancreaticoduodenectomy. This is consistent with the results of experimental and clinical studies.[23,24]

In conclusion, pancreatic TICs generated by dynamic contrast-enhanced MRI correlates well with the histological degree of pancreatic fibrosis, and thus shows the ability to detect an early fibrotic change that precedes functional deterioration of the pancreatic remnant after a pancreaticoduodenectomy. This imaging technique also suggested that, following a pancreaticoduodenectomy, some patients show an improvement in pancreatic fibrosis, however, they may experience remnant pancreatic fibrosis when pancreatic anastomotic leakage occurs after surgery.

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Figure Legends

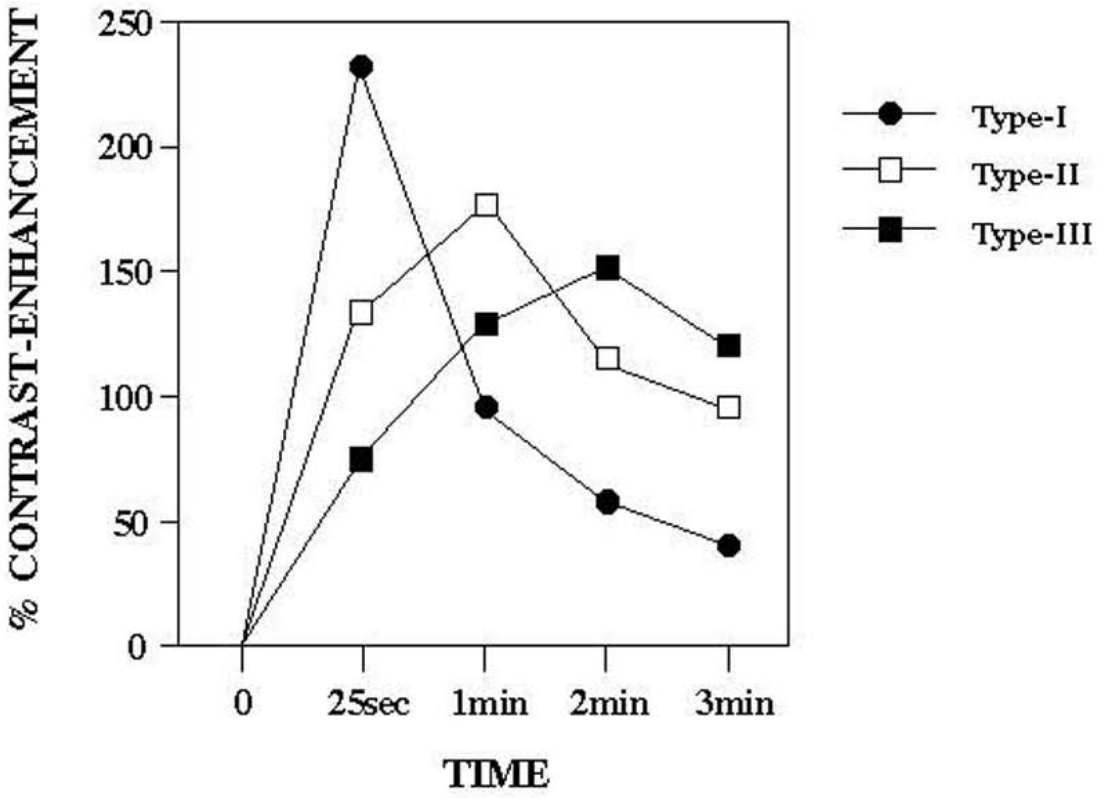

Figure 1. Patterns of the time-signal intensity curve (TIC) from dynamic contrast-enhanced magnetic resonance imaging of the pancreas

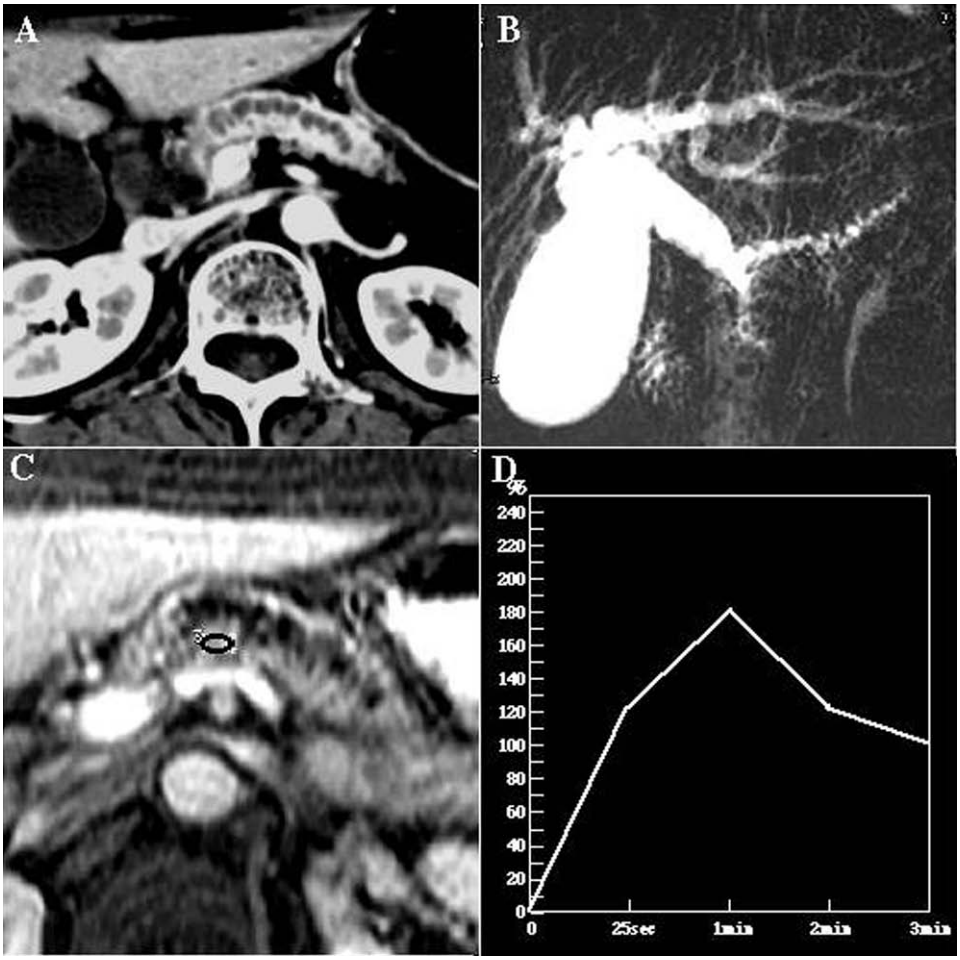

Figure 2. Representative case with a postoperative reversal of the pancreatic TIC from type-II to type-I. In this patient, a pancreatic ductal carcinoma developed in the head of the pancreas and caused an obstructive chronic pancreatitis distal to the tumor. The fibrosis ratio of the pancreas was 15.7%. (A) Preoperative abdominal contrast-enhanced CT study demonstrates a marked dilatation of the main pancreatic duct and an atrophy of the pancreatic parenchyma. (B) MRCP shows dilatation of the pancreatic duct and biliary tree. (C) Dynamic contrast-enhanced MRI image of the pancreas. The ROI is placed at the presumed line of transection for the pancreas. (D) Pancreatic TIC obtained from the ROI as in Figure 2C demonstrates type-II.

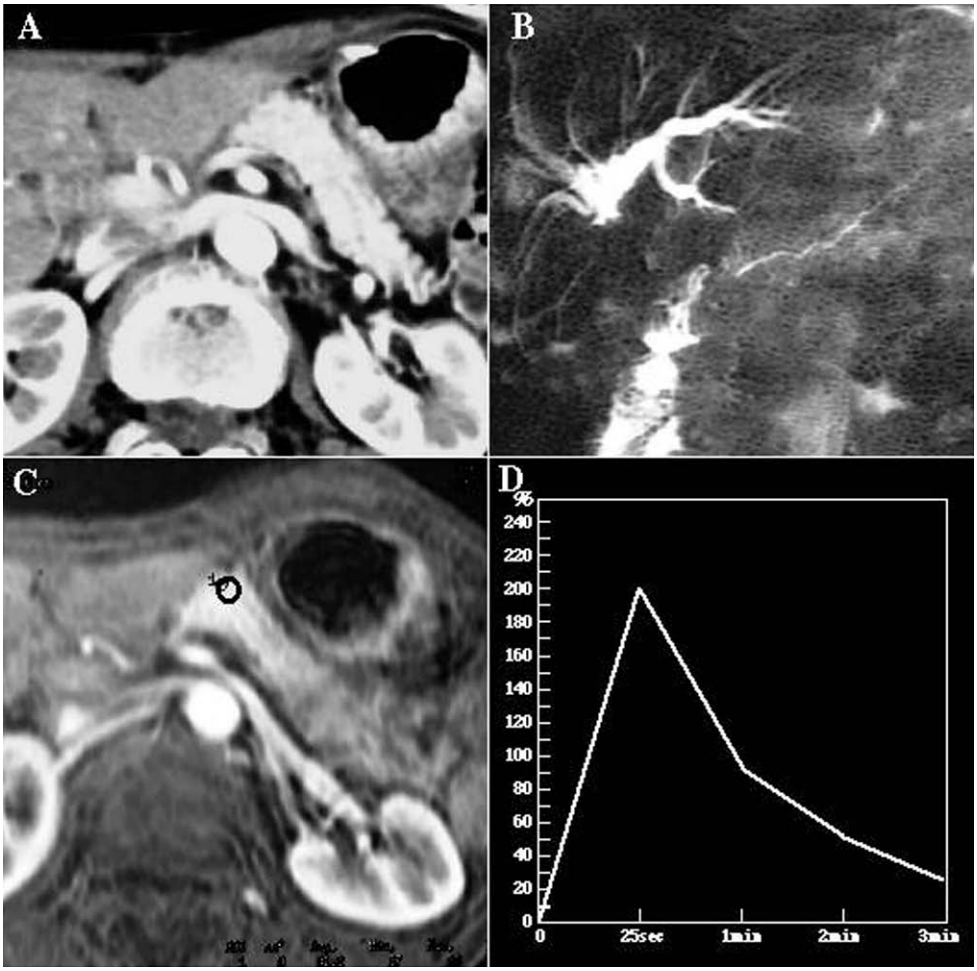

Figure 3. Postoperative imaging studies of the pancreas 3 years after a pancreaticoduodenectomy in the same patient as in Figure 2. In this patient, the pre- and postoperative values of the BT-PABA test were 38.9% and 69.0%, respectively. (A) A contrast-enhanced CT scan demonstrates a notable increase in the pancreatic parenchymal thickness and a decrease in the pancreatic duct size, compared to the preoperative findings. (B) MRCP depicts an excellent, non-dilated pancreatic duct of the remnant pancreas. (C) Dynamiccontrast-enhanced MRI image of the pancreas. The ROI is placed at the body of the remnant pancreas. (D) Pancreatic TIC obtained from the ROI as in Figure 3C demonstrates type-I.

Table 1. Univariate analysis of perioperative clinical parameters in relation to the preoperative pancreatic TIC

Variables	Type-I TIC (n = 51)	Type-II TIC (n = 20)	Type-III TIC (n = 5)	*P* value
Age (years) (mean ± SD)	64.0±9.9	66.8±7.4	69.2±6.3	0.185
Gender (M/F)	34/17	9/11	5/0	0.124
Pathology				<0.001
Bile duct carcinoma	20	1	0	
Ampullary carcinoma	15	2	0	
Gallbladder carcinoma	4	0	0	
Gastric carcinoma	2	0	0	
IPMN	6	4	0	
Pancreatic ductal adenocarcinoma	4	9	3	
Alcoholic chronic pancreatitis	0	4	2	
Preoperative laboratory values				
Albumin (g/dl)	3.9±0.4	3.6±0.6	3.8±0.5	0.187
Total bilirubin (mg/dl)	1.7±1.6	1.6±1.4	1.8±1.7	0.275
Creatinine clearance (ml/min)	66±19	65±17	64±13	0.323
BT-PABA test (%)	66.2±8.3	49.6±15.6	41.8±14.6	<0.001
Oral glucose tolerance test				0.008
Normal	31	5	0	
Impaired, Diabetic	20	15	5	
Hemoglobin A1c (%)	5.5±1.1	6.6±1.6	6.7±1.4	<0.001
Pancreatic duct size (mm)	3.2±0.9	5.7±1.2	6.1±1.6	<0.001
Pancreatic thickness (mm)	16.5±2.9	13.8±2.8	11.6±4.7	<0.001
Texture of the pancreas				<0.001
Soft	40	0	0	
Intermediate	11	5	0	
Hard	0	15	5	
Type of pancreatic resection				0.858
PPPD	36	15	4	
PD	15	5	1	
Anastomotic technique				0.085
Duct-to-mucosa	32	15	5	
Pancreatojejunoserosal	19	5	0	
Operative time (hours)	8.9±1.6	8.6±0.9	8.9±1.6	0.445
Blood loss (ml)	931±221	889±201	953±278	0.586
Blood transfusion	268±83	205±113	274±123	0.124
Pancreatic anastomotic leakage				0.033
Yes	13	1	0	
No	38	19	5	
Histology of the pancreas*				<0.001
normal	48	0	0	
obstructive chronic pancreatitis	3	16	3	
alcoholic chronic pancreatitis	0	4	2	
Fibrosis ratio of the pancreas	4.1±1.4	13.3±4.1	21.2±3.2	<0.001

TIC: time-signal intensity curve
IPMN: Intraductal papillary-mucinous neoplasm of the pancreas
BT-PABA: *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid
PPPD: pylorus-preserving pancreaticoduodenectomy
PD: pancreaticoduodenectomy
*: histology of the pancreas was examined at the cut end of the pancreas.

Table 2. Relation between the postoperative pancreatic TIC profiles and the morphologic and functional changes of the pancreatic remnants after pancreaticoduodenectomy

Pancreatic TIC profile		No. of	Pancreatic fibrosis ratio	TIC conversion after PD	Postoperative follow-up	Pancreatic duct size (mm)		Pancreatic thickness (mm)		BT-PABA test (%)		Hemoglobin A1c (%)	
Before PD	After PD	patients	at PD (%)	(months)	(months)	Before PD	After PD	Before PD	After PD	Before PD	After PD	Before PD	After PD
I	I	35	4.1±1.3	-	38.7±26.8	3.3±1.0	3.1±0.7	16.3±3.2	15.1±3.9	67.2±7.4	70.5±9.3	5.5±1.0	5.6±0.7
I	II(III)	16	4.2±1.5	32.3±26.1	45.0±27.9	3.2±0.7	5.0±1.8 [a)]	16.9±2.3	10.4±3.9 [a)]	65.8±9.7	53.1±9.8 [b)]	5.6±1.5	5.8±1.0
II	II	15	13.6±3.6	-	42.0±24.9	5.7±1.3	3.9±0.8 [a)]	14.2±2.4	12.9±3.3	50.7±16.7	55.8±8.9	6.5±1.6	7.1±2.2
II	I	5	12.1±4.4	14.4±5.4	32.3±22.2	5.8±1.3	3.2±0.6 [c)]	12.3±4.2	14.0±4.5	45.5±10.1	64.3±5.7 [d)]	6.6±0.9	6.2±0.7
III	III	4	21.6±7.5	-	30.0±28.5	5.7±2.1	4.1±1.8	11.5±4.6	12.2±4.5	40.3±12.1	44.0±7.2	6.7±1.1	6.5±1.9
III	II	1	18.9	12	36	6.5	3.6	12	14.5	48	54	6.5	6.3

TIC: time-signal intensity curve

PD: pancreaticoduodenectomy

BT-PABA: *N*-benzoyl-L-tyrosyl-*p*-aminobenzoic acid

[a)]: $p<0.001$ compared with the preoperative value.

[b)]: $p=0.028$ compared with the preoperative value.

[c)]: $p=0.015$ compared with the preoperative value.

[d)]: $p=0.019$ compared with the preoperative value.