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Relationship Between Grade of Fibrosis in Pancreatic Stump and Postoperative Pancreatic Exocrine Activity After Pancreaticoduodenectomy: With Special Reference to Insufficiency of Pancreaticointestinal Anastomosis

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Abstract

Background: Pancreaticoduodenectomy (PD) has become a standard operation for malignant and benign periampullary diseases. Although the operative mortality of PD has decreased to less than 4% in hospitals with many cases of PD, the leakage of pancreaticointestinal anastomosis (PIA) still carries a substantial risk of lethal outcome. The aim of this study was to evaluate the local factors that affect the incidence of PIA leakage by evaluation of exocrine function and fibrosis in the pancreatic remnant following PD.

Method: Twenty-eight patients (17 pancreatic disease, 8 bile duct cancers and 3 ampullary cancers) underwent PD with complete extracorporeal pancreatic juice drainage. The cut-end of the pancreatic remnant was histologically studied for its grade of fibrosis in comparison with the exocrine activity of the pancreatic remnant (EAPR) calculated by the value of the product of volume of drained pancreatic juice and its amylase activity. The influences of those factors and other clinicopathologic data on PIA outcome were evaluated.

Results: The histological grade of fibrosis in the pancreatic stump was inversely correlated with EAPR ($r_s = 0.5848$, $p = 0.0011$). Three patients had major leakages and 6 had minor leakages of PIA; all the patients with leakages had biliary or ampullary diseases, but not pancreatic diseases. The incidence of leakage of PIA was significantly higher in the patients with high values of EAPR ($p < 0.05$). None with EAPR less than 10^7 had PIA leakage. The incidence of PIA leakage in low-grade fibrosis of the pancreatic stump was significantly higher than that in high-grade fibrosis ($p < 0.05$). Other clinicopathologic data did not influence the incidence of leakage of PIA.

Conclusions: The degree of fibrosis in the pancreatic stump is significantly related to the EAPR and affects the development of PIA insufficiency as a local factor.

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Key words: pancreaticoduodenectomy, periampullary disease, complication, exocrine activity, fibrosis

Introduction

Pancreaticoduodenectomy (PD) has become popular as a standard operation in patients with malignant and benign diseases of the pancreas and other periampullary organs. The operative mortality for this operation has now decreased to less than 4% in hospitals with many cases of PD¹⁻³. The leading causes of mortality following PD are postoperative bleeding and abdominal abscess, which are induced from insufficiency of pancreaticointestinal anastomosis (PIA)¹⁻⁷. Recent papers have reported that the important factors for insufficiency of PIA are malnutrition, creatinine clearance, total bilirubin⁸ and also hospital volume^{3,6}. Birkmeyer et al.⁹ have published an article on the relationship of hospital volume to perioperative mortality and survival rate after PD. They stressed the importance of experience in performing this special operation to prevent complications.

The causes of insufficiency of PIA include the experience that is related to perioperative technical skill, poor general conditions of patients and the local conditions of the organs on operated. Experiences suggest that the condition of the pancreas is an especially important factor in performing anastomosis. A hard and firm pancreas as a result of the fibrosis frequently observed in pancreatic cancer and chronic pancreatitis is easy to suture without anastomotic leakage. On the other hand, a soft and fragile pancreas, as mainly found in bile duct or ampullary cancer, is thought to be technically difficult to perform anastomosis on with occasional anastomotic leakages. In addition to the technical difficulties, a soft pancreas has more activity of exocrine function that causes a breakdown of anastomosis by digestion. Once anastomotic leakage of PIA occurs in a patient with a soft pancreas, it induces gross bleeding in the abdominal cavity due to injuries to the large vessels around the anastomosis.

Assessment of the risk of PIA insufficiency is very important before performing PD⁷⁻⁹. The factors significantly increasing the risk of pancreatic anastomotic leakage by univariate logistic regression analysis include ampullary or duodenal disease, and soft pancreatic texture after PD⁸. Freiss et al.⁷

concluded that the degree of pancreatic fibrosis, the difficulties of performing a proper PIA, and subsequently the potential risk of postoperative complications can easily be predicted preoperatively. However, the results in the literature remain controversial, and few reports provide details of operative techniques and the local conditions of the pancreatic remnant that are closely related to PIA insufficiency.

In this study, we tried to identify the local factor of pancreatic remnant that influences the completion of PIA through the degrees of fibrosis in pancreatic remnant from the histological and biochemical points of view, and objectively attempted to assess the exocrine activity and degree of fibrosis in the pancreatic remnant that might be closely related to anastomotic leakage of PIA.

Patients and Methods

Patients and operations

Nineteen male and 9 female patients (17 with pancreatic diseases, 8 with bile duct cancers and 3 with ampullary cancers) that had PD or pylorus-preserving PD (PpPD) with complete extracorporeal pancreatic juice drainage via a pancreatic tube were examined.

Senior surgeons in our hospital under the same supervisor performed the operations. The PIA in this study was made by end to side anastomosis by one layer without performing a mucosa-to-mucosa anastomosis. The PIA was made with an interrupted 4-0 Vicryl[®] (polyglactin 910) thread. A pancreatic tube (Sumitomo Bakelite, Tokyo, Japan) was inserted into the main pancreatic duct of the pancreatic remnant from the cut-end and tied to the wall of the main pancreatic duct for complete exteriorized drainage of pancreatic juice. The transected end of the residual pancreas was not oversewn and only put some sutures for hemostasis. The pancreatic tube was drained via the transhepatic root. The type of reconstruction we used followed a modified version of Child's method¹⁰. Two peripancreatic drainage tubes were placed adjacent to PIA and choledochojejunostomy. To evaluate the general preoperative condition, hemoglobin, red blood cell counts, albumin, total protein, blood urea nitrogen,

creatinine, total bilirubin, liver function (AST, ALT, LDH), and blood glucose level, all of which are reported to be factors influencing the outcome of PIA^{8,11}, were measured.

Definitions of leakage of PIA

The leakage of PIA was divided into two categories; minor and major. A minor anastomotic leak was defined as recovery of drained fluid that contained more than 1,000 IU/l of amylase from the peripancreatic drains for 3 successive days after postoperative day 5, but without clinical symptoms. A major leakage denoted radiologically demonstrable leakages shown by the extravasation of contrast media or the conditions of minor leakage above mentioned with clinically obvious breakdown symptoms like high fever, and fluid collection.

Assessment of fibrosis in pancreatic stump

The tissues of the pancreatic stump obtained at surgery were fixed in Formalin, dehydrated, and embedded in paraffin. In addition, we routinely examined the pancreatic stump histologically for surgical margin of tumor during operation by frozen section. The pancreatic tissues that indicated a mirror image of the pancreatic stump anastomosed with jejunum were postoperatively processed with hematoxylin and eosin (HE) and Masson trichrome staining for accurate estimation of the degree of fibrosis. The category of fibrosis was divided into two types; intralobular fibrosis and perilobular fibrosis. Each type was assessed by the criteria of Klöpper and Maillet¹² into degrees from 0 (none) to 3 (severe) by a pathologist who had no information on the clinical course of any patient. The sum of degrees of each fibrous type represented the degree of fibrosis in the pancreatic stump of each patient. The grade of fibrosis in the pancreatic stump was divided into two categories: weak, i. e. fibrosis of grade 0 to 3 and heavy, i. e. grade 4 to 6 according to Klöpper's criteria.

Exocrine activity of pancreatic remnant (EAPR)

To investigate the exocrine pancreatic activities in the pancreatic stump that was anastomosed with the jejunum, we originated exocrine activities of the

pancreatic remnant (EAPR), that was expressed by the value of the product of the volume of drained pancreatic juice (ml) through the pancreatic tube and its amylase activity (IU/l) on postoperative days 7, 10 and 14. The largest value of EAPR was taken as the EAPR of each patient. Amylase was measured by the enzymatic method (normal range in serum: 30~110 IU/l) and in high activity case with dilution.

Statistics

Statistical comparisons of laboratory data were made with the Mann-Whitney U test. The correlation between the grade of fibrosis of the pancreatic stump and EAPR was evaluated statistically by Spearman's rank correlation coefficient. The relationship among fibrosis level of the pancreatic remnant, EAPR and incidence of insufficiency of PIA, was examined by Fisher's exact probability test. A *p* value below 0.05 was considered significant.

Results

Grades of fibrosis in pancreatic stump in periampullary diseases

The profiles of each case, grade of fibrosis, EAPR and the outcome of PIA in each case were shown in **Table 1**. In cases with weak fibrosis, the parenchyma of the pancreatic stump was colored purple in Masson trichrome staining (**Figs. 1a and 1b**) in comparison with the case with heavy fibrosis colored in blue that showed fibrosis (**Figs. 1c and 1d**). In pancreatic diseases, 13 out of 17 had heavy fibrosis, while only 1 out of 8 bile duct cancers and 1 out of 3 ampullary cancers had heavy fibrosis (**Table 2**).

EAPR in periampullary diseases

EAPR in each case was shown in **Table 1**. EAPR in all cases with the cancers of bile duct and the ampullary tumor was more than 1×10^7 , while 11 out of 17 (64.7%) pancreatic diseases were less than 1×10^7 (**Table 3**).

Relationship between grade of fibrosis in pancreatic stump and EAPR

The relationship between the grade of fibrosis in the pancreatic stump and EAPR was shown in **Fig 2**.

Table 1 Summary of the cases

Cases	Age	Sex	Disease	Ope	Fibrosis	EAPR ($\times 10^7$)	Leakage
1	82	M	Panc Head Ca	PD	1	4.46	—
2	65	M	Panc Head Ca	PD	4	0.00002	—
3	84	M	Panc Head Ca	PD	4	1.4	—
4	69	F	Panc Head Ca	PD	4	0.0002	—
5	45	M	Panc Head Ca	PD	4	0.27	—
6	53	M	Panc Head Ca	PD	5	1.7	—
7	50	M	Panc Head Ca	PD	5	0.0091	—
8	68	M	Panc Head Ca	PD	6	0.019	—
9	66	F	Panc Head Ca	PpPD	6	0.0066	—
10	35	F	Panc Head Ca	PD	6	0.0073	—
11	67	F	Panc Head Ca	PD	6	0.0082	—
12	68	M	Muc Cstadenoma	PpPD	1	3.7	—
13	49	F	Muc Cstadenoma	PpPD	2	4.02	—
14	58	F	Muc Cstadenoma	PpPD	4	0.0108	—
15	53	M	Chr Pancreatitis	PpPD	1	1.5	—
16	61	M	Chr Pancreatitis	PpPD	5	0.35	—
17	55	M	Chr Pancreatitis	PpPD	6	0.053	—
18	60	F	Bile Duct Ca	PpPD	1	1	major
19	71	F	Bile Duct Ca	PD	1	1.08	minor
20	67	M	Bile Duct Ca	PD	1	1.23	minor
21	56	M	Bile Duct Ca	PD	1	1.74	minor
22	62	M	Bile Duct Ca	PD	2	1.5	minor
23	33	M	Bile Duct Ca	PD	2	1.4	major
24	74	M	Bile Duct Ca	PD	4	1.01	major
25	50	M	Bile Duct Ca	PpPD	1	9.4	minor
26	58	F	Ampullary Ca	PD	1	1.3	minor
27	58	M	Ampullary Ca	PpPD	3	2.9	—
28	57	M	Ampullary Ca	PpPD	5	1.56	—

Panc: Pancreas, Ca: Cancer, Muc: Mucinous, Chr: Chronic

PD: Pancreaticoduodenectomy, PpPD: Pylorus preserving pancreaticoduodenectomy

The degree of fibrosis in the pancreatic stump was significantly related to the exocrine activity of the pancreatic remnant. The relation was proved to be significant by correlation coefficient by rank ($r_s = 0.5848$, $n = 28$, $p = 0.0011$).

Incidence of PIA leakage

Three cases had major PIA leakages and 6 had minor leakages (Table 1). These cases with PIA leakage were found in the cases with bile duct cancer except for one case with the ampullary carcinoma (Table 4). It was noted that no PIA leakage was found among the pancreatic diseases. The patients with minor PIA leakage healed with drainage and intravenous hyper alimentation and 2 patients with major leakage (cases 18 and 23) required reoperation to manage the breakdown of PIA. There were no significant differences in

measured preoperative albumin, AST, ALT, LDH, creatinine, and bilirubin between leakage patients and non-leakage patients (Table 5).

Relationship among grade of fibrosis in stump, EAPR and PIA leakage

The correlation between the grade of fibrosis in the stump and PIA leakage was shown in Table 6. The incidence of insufficiency of PIA was significantly higher in the cases with low grade fibrosis (grade 0-3) in the pancreatic stump and high EAPR (more than 10^7) (Table 7). In the cases with PIA leakage, all cases had EAPR more than 10^7 (Fig 2).

Discussion

Although PD is still thought to be risky for the periampullary diseases, such as the tumor of the

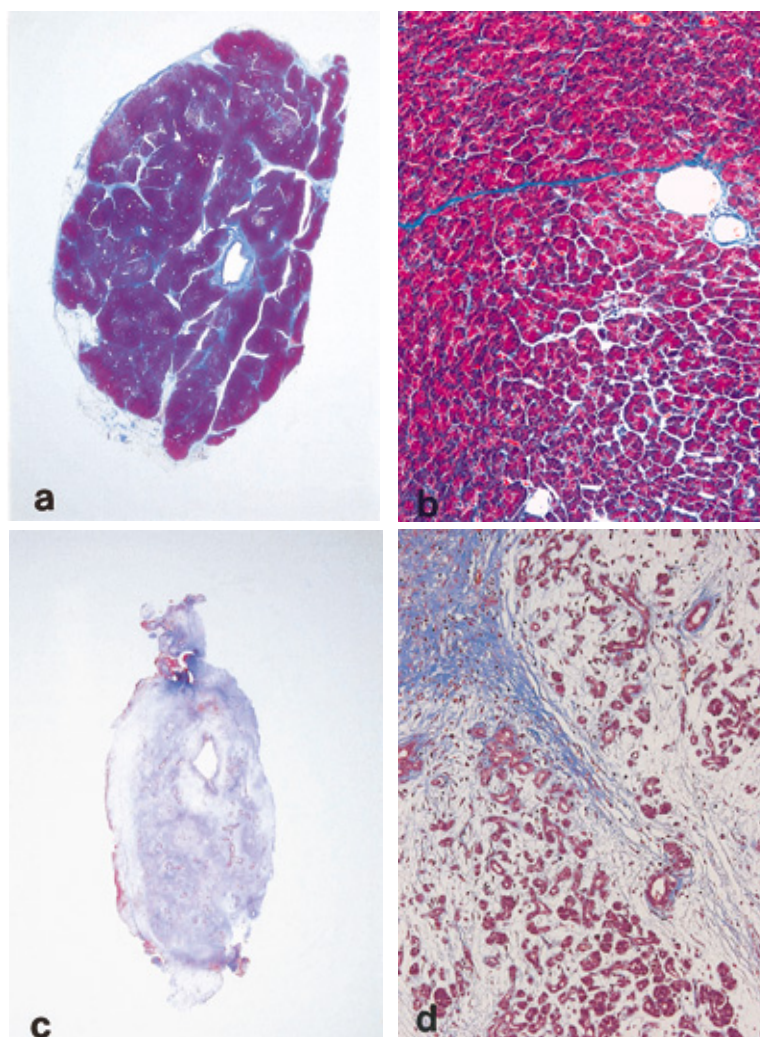


Fig. 1 Photomicrographs of pancreatic stump stained with Masson trichrome method and heavy fibrosis (Grade 6) shown by fiber tissues stained in blue (c: $\times 4$, d: $\times 80$). Weak fibrosis (Grade 1) with preserved exocrine cells stained in purple. (a: $\times 4$, b: $\times 80$)

Table 2 Grade of fibrosis of pancreatic stump in examined diseases

	Grae of fibrosis	
	1 ~ 3	4 ~ 6
Pancreatic disease	4	13
Bile duct cancer	7	1
Ampullary cancer	2	1

Table 3 EAPR in examined diseases. No cases with EAPR less than 10^7 in bile duct cancer and ampullary cancer

	EAPR	
	$< 10^7$	$10^7 \leq$
Pancreatic disease	11	6
Bile duct cancer	0	8
Ampullary cancer	0	3

Table 4 PIA leakage in examined cases

	Cases	Leakage	
		Major	Minor
Pancreatic disease	17	0	0
Bile duct cancer	8	3	5
Ampullary cancer	3	0	1

Major: Clinical evidence of leakage

Minor: Amylase activity in drainage; over 1,000IU/l for 3 days after postoperative day 5

head of the pancreas, ampullary tumor and carcinoma of the lower bile duct, PD is essential to cure it. Recently, the incidence of major complication after PD, such as an insufficiency of PIA, has been decreased by the progress of operative experiences and procedures. Yeo et al.¹ reported that the

Table 5 Preoperative clinical parameters in case with PIA leakage(+) and (-)

Parameters	PIA leakage (-)	PIA leakage (+)	
Hb (mg/dl)	12.1 ± 1.2	13.0 ± 1.8	NS
RBC (10 ⁴ /mm ³)	380 ± 50	427 ± 62	NS
Albumin (g/dl)	3.5 ± 0.5	3.4 ± 0.6	NS
TP (g/dl)	6.2 ± 1.0	7.2 ± 0.7	NS
BUN (mg/dl)	11.6 ± 4.1	10.1 ± 4.0	NS
Creatinine (mg/dl)	0.7 ± 0.2	0.8 ± 0.2	NS
AST (U/dl)	39 ± 28	33 ± 12	NS
ALT (U/dl)	47 ± 30	37 ± 26	NS
LDH (U/dl)	299 ± 64	318 ± 68	NS
Total bilirubin (mg/dl)	2 ± 2.3	1.5 ± 1.4	NS
Blood glucose (mg/dl)	124 ± 33	112 ± 39	NS

NS: not significant

Table 6 PIA leakage and Grade of fibrosis in pancreatic stump

Grade of Fibrosis	PIA Leakage	
	+	-
1 ~ 3	8	3
4 ~ 6	1*	16

PIA: Pancreaticointestinal anastomosis

*p = 0.0095, Fisher's exact method

Table 7 PIA leakage and EAPR

EAPR	PIA Leakage	
	+	-
<10 ⁷	0	11
10 ⁷ ≤	9*	8

PIA: Pancreaticointestinal anastomosis

EAPR: Exocrine activities of pancreatic remnant

*p = 0.0025, Fisher's exact method

operative mortality for this operation was now decreasing to less than 4% in hospitals with many experiences of PD. However, once the leakage of PIA is induced, the patients are suffering from various complications, such as peritonitis, abscess formation and bleeding from adjacent major vessels. That implies that PIA still carries a substantial risk of lethal outcome. At present, no perfect way for prevention of leakage has been developed so far.

The factors that affect the incidence of PIA leakage consist of many components. Previous reports^{8,13} showed that PD induces many complications as routine operative procedure and

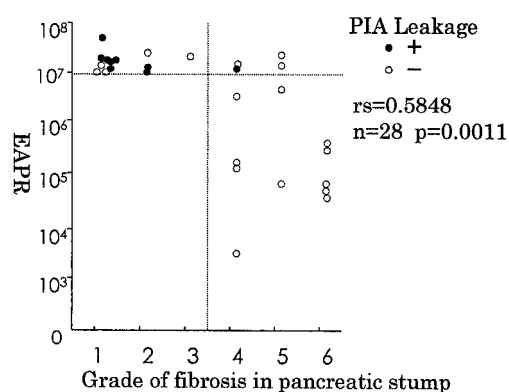


Fig. 2 Relationship between grade of fibrosis in pancreatic stump and EAPR. Negative correlation between grade of fibrosis and EAPR was revealed. There were no PIA leakage (●) in cases with EAPR less than 10⁷.

that several factors like age, duration of jaundice, total bilirubin and creatinine clearance et al. have some significance in PIA leakage. The effect of those general factors on PIA leakage is still controversial, and in our study physical conditions shown by the data of AST, ALT and so on, did not influence the incidence of PIA insufficiency (Table 5). That is consistent with other data shown by Hanegouwen et al¹¹. However, those general factors were believed to some extent to be factors affecting the PIA insufficiency, many surgeons believed that the local factor, especially, condition of the pancreas was another counterpart and regarded it as a more important element. Yeo et al.¹⁴ regarded the texture at the transected neck, mean length of remnant

mobilization and mean diameter of the pancreatic duct, as pancreas factors besides general parameters. However, the estimation of texture at the transected neck was simply divided into 3 categories, hard, intermediate and soft without definitive criteria and local factors were not fully investigated.

In this study, we paid attention to the precise estimation of pancreatic stump as a local factor from biochemical and histological points of view. In Japan, complete extracorporeal drainage of pancreatic juice by the special pancreatic drainage tube after PD is one of the standard methods to protect the PIA and is adopted by our institution. We thought that the quality and quantity of the pancreatic juice drained from the pancreatic remnant via pancreatic drainage tube might be one of the markers of EAPR. In addition, the pathological examination on the surgical stump of pancreatic remnant was used not only for checking the surgical margin but also for evaluation of fibrosis of the pancreatic remnant. We evaluated the histological grade of fibrosis in the pancreas stump in detail by Klöppel's criteria¹². From our results, the degree of the fibrosis in the pancreatic stump was correlated with value of EAPR and the insufficiency of PIA was developed only in patients with high EAPR. The evidence shows that the breakdown of PIA is not induced in patients with low EAPR.

In the present series, 9 of 28 patients developed a pancreatic leakage after PD defined as elevated amylase in drained fluid (minor leakage) and radiologically evident leakage with clinical symptoms (major leakage). It was noted that PD for pancreatic diseases did not develop PIA leakage. This partly coincided the previous report that revealed the higher incidence of PIA leakage in ampullary cancer than pancreatic counterpart¹¹. Lowy et al.¹⁵ reported that a histological diagnosis of other than pancreatic adenocarcinoma was associated with an increased incidence of pancreatic anastomotic leakage in periampullary tumors. The cases with pancreatic disease had hard pancreatic tissue due to fibrosis induced by cancer involvement or inflammation. It was technically easy to perform the PIA in hard and fibrotic pancreas. When the pancreas is soft and fragile, even an atraumatic needle causes a small leakage of pancreatic juice.

As shown in **Table 2**, the grade of fibrosis in the pancreatic stump is heavy in pancreatic disease and weak in bile duct and ampullary cancers. EAPR calculated from amylase activity and the volume of pancreatic juice was low (less than 10⁷) in pancreatic diseases, while all the cases with bile duct and ampullary cancer had high EAPR (**Table 3**).

Recent reports agree that the postoperative outcome is related to the experience of the hospital that performs PD. The decrease of complication rates should be expected if PD is performed in restricted centers with much experience^{3,6,9}. First of all, the surgical technique influences the postoperative condition of anastomosis. Howard¹⁶ reported that PIA leakage may be preventable by the technique which he applied. He changed his PIA method from end-to-end anastomosis to end-to-side one with subsequently better results. In his study, he paid attention to the diameter of the main pancreatic duct and on the condition of the pancreatic stump. Sikora and Posner¹⁷ extensively reviewed the literature and related the incidence of pancreaticoenteric anastomotic fistulas to the type of anastomotic technique used by the various authors. They concluded that the technique is very important for completing the operation. In addition to technique to perform PD, we insist on the importance of the condition of the pancreatic remnant, because no complications on PIA were induced in fibrous and firm pancreas with low exocrine activities.

Thus, the way to reduce the complication related to the pancreatic remnant is to understand and to deal properly with the risk of each case by estimating the probability of PIA leakage. For this purpose, it is very useful to evaluate the risk for PIA by measuring the grade of fibrosis in the pancreatic stump. As routine work, the surgical margin of the pancreatic stump was examined histologically for the presence of malignant cells. The intraoperative examination on the surgical stump of the pancreatic remnant by frozen section, even in hematoxylin-eosin staining, made it possible to assess the exocrine condition of the pancreatic remnant. The level of fibrosis in the pancreatic stump correlated well with the chemical evaluation of exocrine activity of the pancreatic remnant.

The information of level of the fibrosis in residual pancreas can also be given on the surgeon's demand.

Even if surgeons treated perfectly the pancreatic stump, perfect prevention is not in our hand, because we cannot get the dried and non-secreted stump in the soft pancreas. For those cases with a soft and fragile stump, we may use the chemotherapeutic agents for prevention of leakage of PIA. One of the candidates mentioned in the literature is perioperative somatostatin analogues treatment aiming at decreased exocrine secretion. However, the effect of somatostatin analogues is controversial^{15,18}.

In the future, a more potent agent than somatostatin analogues for reduction of the exocrine activity will be developed. When we apply an agent in the future, scientific estimation of the risk by using EAPR and grades of fibrosis of pancreatic stump will be useful. Although PD is a complicated and troublesome operation, local control, especially in the pancreatic remnant, will introduce good postoperative results. Our data shown here clearly revealed that the patient with high-grade fibrosis did not develop the PIA leakage. The importance of the evaluation of the risk of leakage of PIA by assessing the grades of fibrosis of pancreatic stump will be appreciated.

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