Pancreatic Duct-to-mucosa *versus* Invagination or Complete External Drainage Anastomosis in Case of Small Pancreatic Duct after Pancreaticoduodenectomy: Comparative Historical Review

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After pancreaticoduodenectomy (PD), pancreatic duct-to-mucosa anastomosis (PDM) has been usually applied which may prevent risk of pancreatic fistula (PF). In cases with a small pancreatic duct, however, PDM is difficult to complete. Procedures involving the invagination (IV) or complete external tube drainage (CED) are supposed to be alternative options for anastomosis. We retrospectively compared clinical results between PDM and IV or CED in 104 patients with a tiny pancreatic duct who underwent PD. The 77 patients undergoing PDM (the control group) and 27 patients undergoing other procedures, including 19 for CED and 8 for IV, were comparatively examined. Fatty pancreas was commonly observed in CED group. Pancreaticoje-junostomy was significantly more frequently applied in CED group, and the operating time in the IV group was significantly longer than in control group ($p<0.05$). The anastomotic time in CED group tended to be shorter than those in control and IV groups (18 *versus* 29 and 37 min). The incidences of PF were not significantly different among groups (31% in control, 47% in CED and 14% in IV, respectively); however, a grade B or C level of PF was not observed in the IV group. PDM is often difficult to achieve and inadequate suturing may injure the pancreatic parenchyma in cases of very small pancreatic duct. Re-evaluation of the CED or IV procedure as an alternative option was suggested to be warranted.

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Introduction

Surgical techniques and adequate perioperative manage-ment after pancreaticoduodenectomy (PD) has been improved recently (1,2) and, however, morbidities associated with anastomotic procedures between the pancreas and the intestine (stomach or jejunum) remain problematic, such as pancre-atic fistula (PF).(3,4) Pancreatic duct-to-mucosa anastomosis (PDM) has been widely and usually applied worldwide to prevent PF by matching both orifices with a tiny suture.(5) However, in cases of a pancreas with a small pancreatic duct

of less than 3 mm, suturing is often difficult and inadequate suturing might injure the pancreatic ducts and its parenchyma. In some cases, insertion of a drainage tube or finding the duct seemed to be difficult. Thus, alternative options were necessary in such cases.

In our surgical experience for the 20 years between 1994 and 2013, the procedure of pancreatic anastomosis changed. (6) Between 1994 and 1999, we applied pancreaticogastros-tomy or -jejunostomy by the invagination (IV) procedure with a lost stent tube in the pancreatic duct. This procedure has also been widely applied worldwide because of its low

rate of PF.(5,7) However, we have changed the anastomotic procedure to pancreaticojejunostomy since 2000. In the early part of this period starting in 2000, the complete external tube drainage of pancreas juice (CED) was sometimes applied. Subsequently, in the late part of this period, the PDM procedure with a lost stent tube was applied. CED was developed by Miyagawa et al., which has the advantage of avoiding fatalities because the procedure itself is very simple; however, clinical usefulness was not fully clarified yet.(8,9) The PDM procedure was mainly applied even in very small pancreatic ducts at the recent time (10) and, however, the prevalence of PF still remains in cases with a soft pancreas by applying such a suturing technique.(11) By considering the difficulty of PDM in cases with a very small pancreatic duct, the previous procedure was supposed to be preferable.

Clarifying the relative advantages and problems associated with IV or CED in comparison with PDM procedures based on early-term our experiences is required. The present study thus retrospectively and historically examined 104 patients who underwent pancreatic anastomosis after PD and compared clinical or surgical records and postoperative early outcomes between each procedure to clarify the clinical usefulness of IV or CED.

Patients and Methods

Patients

Between 1994 and 2014, 168 patients with peri-pancreatic pancreatobiliary diseases underwent pancreaticoduodenectomy at the Department of Surgical Oncology at Nagasaki University Hospital. Of these patients, 104 showed a non-dilated (small size of less than 3 mm) pancreatic duct with a soft pancreas. The patients consisted of 67 men and 37 women with a mean (± standard deviation (SD)) age of 66.1 ± 12.5 years (range, 25-87 years). Underlying pancreatobiliary diseases among the enrolled patients included pancreatic carcinoma (n=14), intraductal papillary mucin-producing neoplasm (n=9), ampullary carcinoma (n=16), bile duct carcinoma (n=42), gall bladder carcinoma (n=5), other pancreatic tumors (n=11) and benign disease (n=7).

The present study compared clinical and operative findings and postoperative complications among PDM (n=77; a control group), IV (n=8) and CDE groups (n=19). This study involved a retrospective historical analysis and was not a randomized control study. The patient information was obtained by opt-out procedure. The ethics of the present study was approved by the Institutional Review Board at Nagasaki University Hospital (#17041721) at April 18,

2017. There were no conflict of interest (COI) in this study and this was approved by COI committee of Nagasaki University Hospital at April 17, 2017. These procedures were performed by co-author, Y. Sumida.

Operative Procedures and Perioperative Management

In pancreaticoduodenectomy, pyrolus-preserving pancreaticoduodenectomy (PD) was performed in 45 patients and subtotal stomach-preserving PD was performed in 59. In anastomosis, pancreaticogastrostomy was performed in 7 patients and pancreaticojejunostomy was performed in 97. In the PDM group, the pancreas and seromuscular layer of the jejunum were anastomosed by interrupted suture using 4-0 absorbable suture thread and the pancreatic duct was sutured to the jejunal mucosa by interrupted suture using 5-0 absorbable suture thread with a lost tube stent (Figure 1a). The CED and IV technique are also indicated in Figures 1b and c. In the procedure of CED (Figure 1b.), the 5mm-in-diameter of drainage tube was placed into the pancreatic duct and the tube was completely tied with pancreatic duct at the resected stump using the rapidly absorbable suture thread to drain all pancreatic juice via tube outside. The pancreas and seromuscular layer of the jejunum were anastomosed by interrupted suture as well as the procedure of PDM. In the procedure of IV, in case of pancreatico-jejunostomy (Figure 1C-a), pancreatic tube was not placed and the pancreatic stump was covered by double sutures with the all layer and submucosal layer of the intestinal stump. In case of pancreaticogastrostomy (Figure 1C-b), the gastric anterior wall was cut and opened and the pancreatic parenchyma and all layer of the stomach were anastomosed by interrupted suture using absorbable suture thread inside the stomach. A lost tube stent was placed and fixed with the pancreatic duct by ligation with absorbable suture thread and, finally, the gastric wall was sutured after anastomosis. The duodenum or gastric stump was anastomosed with an end-to-side procedure via the antecolic route. Anastomotic sites were sprayed with 3.0 ml of fibrin glue (Beriplast P®; Aventis Behring, USA) to prevent pancreatic fistula in 78 patients. The grade of pancreatic fistula was defined according to the *International Study Group of Pancreatic Surgery (ISGPS)* grading.(12)

Statistical Analysis

Data are expressed as mean ± SD. Data from different groups were compared using one-way analysis of variance (ANOVA) and examined by student's *t*-test or Dunnett's multiple comparison test. A two-tailed *P* value <0.05 was
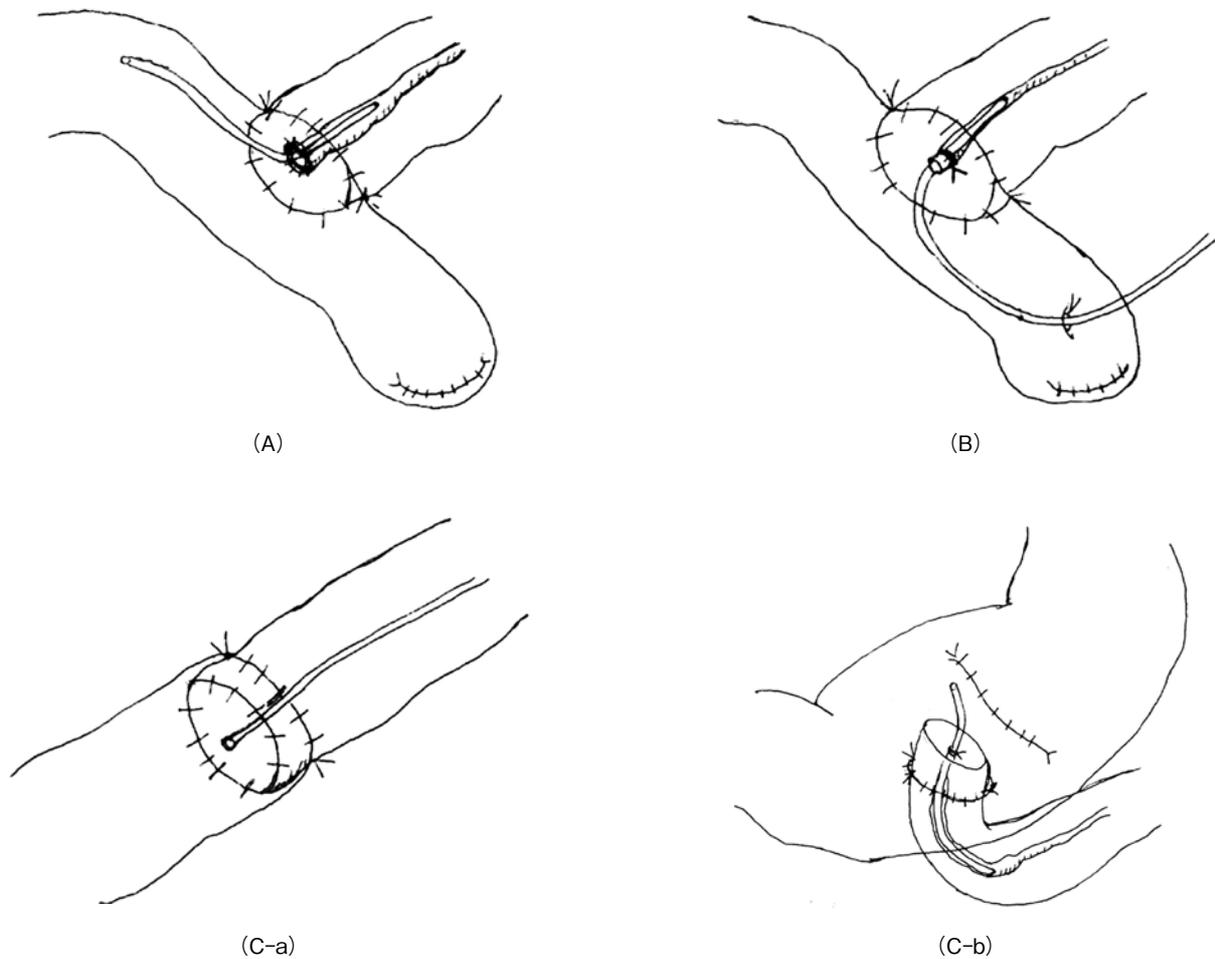
Figure 1: Anastomotic techniques: (a) pancreatic duct-to-mucosa (PDM) anastomosis with tight anastomosis between pancreatic cut stump and intestinal seromuscular layer; (b) complete external tube drainage of pancreas juice (CED) without duct-to-mucosa anastomosis; and (c) invagination procedure (IV) anastomosis in pancreaticogastrostomy or -jejunostomy.

considered significant. SPSS for Windows version 18.0 software (SPSS, an IBM Company, Chicago, IL) was used for all statistical analyses.

Results

Demographics, Clinical Parameters and Early Outcomes

Age, gender, main diseases, background pancreas, comorbidity and preoperative laboratory data did not differ significantly among the groups (Tables 1 and 2). The prevalence of fatty pancreas in the CED group was significantly higher than that in the control group (p<0.05) (Table 2). The degree of experience of the main operators did not differ significantly among the groups. Pancreaticojejunostomy was significantly more frequently applied in the CED group than in the control group (p<0.05) (Table 2).

Surgical records showed that blood loss and transfusion did not differ significantly among the groups (Table 2). Operating time in the IV group was significantly longer than in the control group (p<0.05) (Table 1). The anastomotic time in the CED group tended to be shorter than those in the control and IV groups, but the differences were not statistically significant (Table 1). The rate of pancreaticogastrostomy in the CED group was lower than that in the IV group (p<0.05). Tumor stage in malignancies did not differ significantly among the groups (Table 2).

Postoperative laboratory data and complications in the early postoperative period are indicated in Tables 1 and 2. The lowest total protein level after surgery in the IV group tended to be lower than that in the control group, but the difference was not statistically significant (Table 1). Weight loss and other laboratory data after surgery did not differ significantly among the groups (Table 1), nor did the dura-

tion of hospitalization. The incidences of PF did not differ significantly among the groups; however, grade B or C level of PF was not observed in the IV group (Table 2). The prev-

alence rates of other complications and diabetes also did not differ significantly among the groups (Table 2).

Table 1. *Patient demographics and surgical records with continuous parameters in each anastomosis group*

	PDM (control) group (n=77)	CED group (n=19)	CED group (n=19)
Age (years)	67 ± 12	63 ± 17	63 ± 17
Preoperative laboratory values			
Hemoglobin (g/dl)	12.2 ± 2.4	12.7 ± 3.3	12.0 ± 1.7
Platelet (x10^4/mm^3)	15.8 ± 12.1	9.4 ± 10.5	11.6 ± 11.3
Prothrombin activity (%)	94.4 ± 16.5	94.1 ± 26.2	87.6 ± 12.7
Creatinine (mg/dl)	1.0 ± 0.3	0.9 ± 0.2	1.7 ± 1.8
Total protein (g/dl)	6.9 ± 0.7	7.1 ± 0.6	7.0 ± 0.9
Albumin (g/dl)	3.9 ± 0.6	4.1 ± 0.6	3.9 ± 0.4
Bilirubin (mg/dl)	2.1 ± 2.7	2.5 ± 3.1	1.1 ± 0.4
Alkaline phosphatase (IU/L)	564 ± 510	534 ± 66	535 ± 523
Amylase (IU/L)	125 ± 161	118 ± 108	93 ± 49
Cholinesterase (IU/L)	181 ± 111	149 ± 162	210 ± 82
Total cholesterol (mg/dl)	185 ± 62	193 ± 55	162 ± 38
Blood sugar (mg/dl)	117 ± 44	126 ± 41	110 ± 27
Hemoglobin A1C (%)	5.9 ± 1.2	5.5 ± 1.2	5.4 ± 0.6
Exocrine pancreatic function test (%)	63 ± 16	66 ± 12	63 ± 6
Surgical records			
Intraoperative bleeding (ml)	1271 ± 802	1672 ± 1323	1544 ± 323
Red cell transfusion (ml)	376 ± 585	584 ± 943	474 ± 472
Operating time (min)	585 ± 177	727 ± 243	770 ± 157*
Anastomotic time of pancreas (min)	29 ± 9	18 ± 11 §	37 ± 7
Body weight loss after surgery during hospital stay (kg)	-3.4 ± 3.1	-4.3 ± 3.9	-2.7 ± 1.5
Postoperative laboratory values#			
Total protein (g/dl)	5.3 ± 0.8	4.8 ± 0.8	4.5 ± 0.8 †
Albumin (g/dl)	2.8 ± 0.5	2.8 ± 0.6	2.7 ± 0.5
Total bilirubin (mg/dl)	2.9 ± 2.9	2.6 ± 2.5	3.0 ± 2.2
Amylase (IU/L)	76 ± 51	78 ± 86	76 ± 27
Cholinesterase (IU/L)	360 ± 490	410 ± 443	507 ± 309
Total cholesterol (mg/dl)	96 ± 35	85 ± 24	78 ± 19
Duration of hospital stay (days)	26 ± 36	32 ± 35	26 ± 18

Continuous data are expressed as mean ± SD. *p<0.05 *vs.* control group
§ p=0.1, # Minimum or maximum data after surgery during hospital stay.
† p=0.09 *vs.* control group

Table 2. *Patient demographics and surgical records with categorical parameters in each anastomosis group*

	PDM (control) group (n=77)	CED group (n=19)	IV group (n=8)
Gender			
Male/female	52/25	10/9	5/3
Diseases			
Pancreatic cancer	11	2	1
IPMN	4	3	2
Biliary tract cancer	34	4	4
Ampullar cancer	14	1	1
Gall bladder cancer	4	1	0
Other malignancy	6	5	0
Benign diseases	4	3	0
Background of pancreas			
Normal pancreas/fatty/accompanied pancreatitis	73/0/5	11/4/4**	5/1/2
Comorbidity			
Diabetes (no/yes)	60/17	13/6	7/1
Smoking (no/yes)	51/26	15/4	5/3
Alcoholism (no/yes)	43/34	14/5	3/5
Attack of pancreatitis (no/yes)	72/5	14/5	8/0
Operators			
Staff/fellow/resident	41/34/2	12/6/1	5/3/0
Pancreatic anastomosis			
pancreaticogastrostomy/pancreaticojejunostomy	12/65	1/18*	5/3
Pancreatic duct tube stent (no/yes)	0/77	0/19	1/7
Lymph node dissection (D0/1/2 or more)	0/5/72	2/2/15	1/1/6
Tumor stage in malignant diseases (I or II/III or IV)	23/50	4/12	2/6
Postoperative complications			
Pancreatic fistula (no/A/B/C) †	53/16/6/2	10/6/2/1	7/1/0/0
Intra-abdominal infection (no/yes)	57/20	11/8	7/1
Hemorrhage (no/yes)	71/6	17/2	8/0
Prolonged ascites (no/yes)	69/8	16/3	5/3#
Reoperation (no/yes)	70/7	18/1	8/0
Postoperative diabetes (no/yes)	62/15	14/5	6/1

*p<0.05 *vs.* IV group, **p<0.05 *vs.* control group, #p=0.09 *vs.* control group
† ISGPS classification for pancreatic fistula[12]
IPMN; intraductal papillary mucin-producing neoplasm

Discussion

PD is a standard procedure performed to achieve complete removal of peri-pancreatic head malignancies with surrounding tissues. Central pancreatectomy or pancreatic transection is performed in cases with benign disease, trauma or low-grade malignancies of the pancreas. In these situ-

ations, pancreaticojejunostomy with duct-to-mucosa anastomosis has been established to prevent leakage of pancreas juice,(4-6,9,10,11) but PF still remains as a problematic complication in small pancreatic ducts with a soft pancreas. (3,4,8,9) Complication of PF in the soft pancreas is thus a significant obstacle to recovery after PD, and may lead to lethal complications or prolonged hospitalization. Although

duct-to-mucosa anastomosis is preferable, this procedure is technically difficult in such a situation. Incomplete anastomosis or injury of the anastomotic site by the suturing needle may lead to anastomotic leakage and pronounced PF.

An invagination procedure in pancreaticojejunostomy or pancreaticogastrostomy has also been reported. This procedure was applied because of a low incidence of pancreatic leakage; unfortunately, disadvantages in the long term after surgery in comparison with duct-to-mucosa anastomosis were pointed out. However, by considering the operative safety, the invagination procedure is supposed to be a useful option to secure severe PF in cases with a small pancreatic duct.

In the present study, we focused on the surgical results in patients with a soft pancreas and a small pancreatic duct, which is a risk factor of postoperative PF, by historical examination at a single institute. Although we first applied complete external tube drainage of pancreas juice, we changed the procedure because the trend of pancreatic anastomosis was towards duct-to-mucosa suturing anastomosis in Japan. While we applied the CED procedure, however, severe postoperative PF was rarely observed. Therefore, we attempted to compare the advantages and disadvantages between each procedure in the present study. In this cohort, the CED procedure might be used in cases with a fatty fragile pancreas because suturing of the duct or pancreas substance would be difficult. A previous report showed that surgical injury was a concern in fatty pancreas. Any technical effort in anastomosis might not resolve pancreas injury or tear. In cases of pancreaticogastrostomy, the invagination method with a lost tube stent was applied in our series. However, other background parameters such as disease, co-morbidity and preoperative laboratory data did not differ among the groups.

With respect to a comparison of the surgical records among the groups, the levels of operator experience were similar among the groups, although the anastomotic procedure was decided by the teaching staff (author A.N.). CED anastomosis was mainly performed for pancreaticojejunostomy. Pancreaticogastrostomy was basically performed in the 1990s in line with our department protocol.(6) The main reason for changing the anastomotic procedure from pancreaticogastrostomy to pancreaticojejunostomy was the latter's technical simplicity; furthermore, we experienced a severe complication with pancreaticogastrostomy. Specifically, at day 7 after operation in one case, the anastomotic pancreas fell down after a large hiccup and vomiting by the patient; re-anastomosis of pancreaticojejunostomy was then

necessary. In cases with a small remnant pancreas or inflammatory adhesion with splenic vein, it is difficult to perform vertical mobilization for attachment to the posterior wall of the stomach. Thus, our decision changed to pancreaticojejunostomy in the present series. However, pancreaticogastrostomy was still selected in western and some Japanese institutes.(13,14) Otherwise, the extent of dissection or tumor factors did not differ significantly among the groups. Anastomotic time was the lowest in the CED group because of the simplicity of its procedure; operating and anastomotic times were the longest in the IV group. In this technique, seromuscular suture covering the pancreatic stump was additionally necessary, which might have led to the longer time. A similar technique was reported in China and a simpler procedure of invagination was recommended.(15) If simple invagination is safe and not associated with a pancreatic fistula, operating and anastomotic times should be significantly shortened.

With respect to the patient outcomes, serum protein level was lower due to prolonged ascites in the IV group than in the other groups in our series. In this group, the background patient demographics, preoperative status and extent of dissection did not differ significantly compared with those in the other groups, so the anastomotic procedure itself should be one of the reasons for this complication. By considering the IV technique in pancreaticogastostomy or -jejunostomy, mobilization and bending of pancreatic substance were additionally necessary. Furthermore, it was speculated that intestinal covering suture might cause edema of the intestines. As the rate of other complications and nutritional status did not differ significantly among the groups, the lengths of hospital stay were eventually similar in the groups. Previous reports regarding the invagination procedure did not show the specific postoperative complications.

In conclusion of our series, prospective and randomized controlled trials in cases of a soft pancreas with a small pancreatic duct comparing PDM, CED and IV have yet to be undertaken. As the next step, prospective trials should be performed to clarify the benefits and problems associated with these procedures. By considering the retrospective surgical results, a CED or IV procedure was thought to be a useful alternative option in cases in which the PDM procedure is technically difficult.

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