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Randomized Controlled Trial of Pancreaticojejunostomy Versus Stapler Closure of the Pancreatic Stump During Distal Pancreatectomy to Reduce Pancreatic Fistula

Manabu Kawai, MD, PhD,* Seiko Hirono, MD, PhD,* Ken-ichi Okada, MD, PhD,* Masayuki Sho, MD, PhD,†
Yoshiyuki Nakajima, MD, PhD,* Hidetoshi Eguchi, MD, PhD,‡ Hiroaki Nagano, MD, PhD,‡
Hisashi Ikoma, MD, PhD,§ Ryou Morimura, MD, PhD,§ Yutaka Takeda, MD, PhD,|| Shin Nakahira, MD, PhD,||
Kazuhiro Suzumura, MD, PhD,¶ Jiro Fujimoto, MD, PhD,¶ and Hiroki Yamaue, MD, PhD*

Objectives: The aim of this study was to evaluate in a multicenter randomized controlled trial (RCT) whether pancreaticojejunostomy (PJ) of pancreatic stump decreases the incidence of pancreatic fistula after distal pancreatectomy (DP) compared with stapler closure.

Background: Several studies reported that PJ of pancreatic stump reduces the incidence of pancreatic fistula after DP. However, no RCT has confirmed the efficacy of PJ of pancreatic stump.

Methods: One hundred thirty-six patients scheduled for DP were enrolled in this study between June 2011 and March 2014 at 6 high-volume surgical centers in Japan. Enrolled patients were randomized to either stapler closure or PJ. The primary endpoint was the incidence of pancreatic fistula based on the International Study Group on Pancreatic Fistula criteria. This RCT was registered with ClinicalTrials.gov (NCT01384617).

Results: Sixty-one patients randomized to stapler and 62 patients randomized to PJ were analyzed by intention-to-treat. Pancreatic fistula occurred in 23 patients (37.7%) in the stapler closure group and 24 (38.7%) in the PJ group ($P = 0.332$) in intention-to-treat analysis. The incidence of clinically relevant pancreatic fistula (grade B or C) was 16.4% for stapler closure and 9.7% for PJ ($P = 0.201$). Mortality was zero in both groups. In a subgroup analysis for thickness of pancreas greater than 12 mm, the incidence of clinically relevant pancreatic fistula occurred in 22.2% of the patients in the stapler closure group and in 6.2% of the PJ group ($P = 0.080$).

Conclusions: PJ of the pancreatic stump during DP does not reduce pancreatic fistula compared with stapler closure.

Keywords: distal pancreatectomy, pancreatic fistula, pancreaticojejunostomy, stapler closure

The incidence of pancreatic fistula after distal pancreatectomy (DP) remains high at 16% to 35% of cases, and it is associated with a higher incidence of life-threatening complications such as intraabdominal abscess, intraabdominal hemorrhage, or sepsis.[1–4] A strategy to decrease pancreatic fistula after DP is urgently required. Stapler closure has recently become a standard technique for pancreatic stump closure; however, the multicenter randomized DISPACT trial found that stapler closure did not significantly reduce the incidence of pancreatic fistula after DP in comparison to hand-sewn closure.[5] In addition, we previously reported that stapler closure for transection of a thick pancreas (>12 mm) significantly increased the incidence of pancreatic fistula after DP.[6,7] The most appropriate closure technique for the pancreatic stump during DP remains controversial.

Several studies have demonstrated that pancreatic fistula in a pancreaticojejunostomy (PJ) of the pancreatic stump does not occur in patients who have undergone DP.[8–10] Furthermore, our previous study reported that PJ of the pancreatic stump in DP with en bloc celiac axis resection prevents an extremely high amylase level (>4000 IU/L) in the drainage fluid.[11] Several studies have evaluated the association between high drain amylase level and pancreatic fistula.[12,13] However, no randomized controlled trials (RCTs) have confirmed the efficacy of PJ of the pancreatic stump during DP. Therefore, a randomized controlled multicenter trial was designed to evaluate whether PJ of the pancreatic stump decreases the incidence of pancreatic fistula after DP compared with stapler closure.

METHODS

Patients

Between June 2011 and March 2014, the RCT was conducted at 6 high-volume surgical centers in Japan. This RCT was approved by the Ethical Committee on Clinical Investigation of each institution and registered in accordance with ClinicalTrials.gov (NCT01384617). This study was conducted in accordance with the Declaration of Helsinki, and written informed consent was preoperatively obtained from all participating patients.

Eligible participants were adults 20 years or older who were undergoing DP with or without spleen preservation for disease of the pancreatic body or tail without distant metastasis. Both open and laparoscopic procedures were permitted in the protocol. All patients had to have an Eastern Cooperative Oncology Group performance status of at least 1 and adequate organ function the fulfilled the following criteria: white blood cell 3500/mm³ or more or less than 12,000/mm³, neutrophilic leukocyte 2000/mm³ or more, platelet 100,000/mm³ or more, hemoglobin 9.0 g/dL or more, total bilirubin less than 2.0 mg/dL, aspartate aminotransferase and alanine aminotransferase less than 150 IU/L, and creatinine less than 1.5 mg/dL. Patients with severe comorbidity, such as myocardial infarction, respiratory disorder required oxygen inhalation, liver cirrhosis, hemodialysis, or active duplicative malignant disease affecting adverse events, were excluded from this study.

Randomization

After providing written informed consent, patients undergoing DP were randomly assigned to the stapler closure or PJ group. Randomization was stratified by neoadjuvant therapy such as radio-chemotherapy or chemotherapy and institution. A central randomization system for every participating institution was applied, and randomization was done preoperatively.

Transection Line of the Pancreas

Transection line of the pancreas was preoperatively planned by assessing the location of the tumor based on a preoperative examination with multidetector-row computed tomography. The final decision for the transection line was made intraoperatively by the surgeon based on the location of the tumor and with the objective of obtaining of a safety margin. The intraoperative ultrasound was usually used to mark transection lines with a safety margin. When the transection line especially for the malignant tumor was located nearer the head of the pancreas, the pancreatic transection was performed at the right side of the portal vein. Transection line was classified as follows: "neck (at the right side of the portal vein)," "body (from the left side of the portal vein to the left of the celiac axis)," and "tail (distal to the left of the celiac axis)". Moreover, intraoperative frozen section examination of the transection margins was performed routinely. Additional resection of the transection margins was performed, if the results of the intraoperative examination were positive for cancer.

Operative Procedure

Figure 1 shows a schematic drawing of the 2 procedures, stapler closure and PJ.

In the stapler closure group, the pancreatic parenchyma was transected using Echelon 60 with a gold cartridge (Ethicon Endo-Surgery, Cincinnati, OH). Echelon 60 with a gold cartridge provides precise and uniform wide compression throughout the entire 60-mm length, with compressible thickness to 1.8 mm, and can attach 2 triple-staggered rows of titanium staples. In all cases of stapler group, the stapler was operated by manual as follows: the closure jaw was clamped carefully and slowly, taking 10 min at a fixed speed. The stapler was not released immediately after firing, and the jaws of the stapler were held shut for 1 min.

In the PJ group,[11] the pancreatic parenchyma was resected using an ultrasonic dissector and only a main pancreatic duct was resected, using a scalpel for duct-to-mucosa anastomosis. After resection of the pancreatic parenchyma, PJ end-to-side anastomosis by a Roux-en-Y limb for the pancreatic stump was performed via a retrocolic route with an appropriate length of the first jejunal loop (at least 30 cm). The anastomosis was performed in a nonstented duct-to-mucosa fashion using a single layer of interrupted 5–0 PDS-II® (polydioxanone, Johnson and Johnson Co., Tokyo, Japan). In a seromuscular-parenchymal anastomosis, nonabsorbable interrupted stitches (4–0 Novafil polybutester, Tyco Healthcare Japan Co., Tokyo, Japan) were placed in end-to-side fashion so that the jejunal wall was tightly adherent to the pancreatic stump. A tube stent was not inserted for the duct-to-mucosa anastomosis to avoid having it migrate into the duodenal side.

Postoperative management was identical in both groups. The management of the drains and checking the amylase levels of the drain fluid were standardized in this trial as follows: One 10-mm silicon drain (BLAKE drain, Ethicon Endo-Surgery, NJ) was placed near the stump of the remnant pancreas or anastomosis. The drain was inserted at least until postoperative day (POD) 3. The drain was removed on POD 3 or 4 if the drainage fluid was clear and pancreatic fistula and bacterial contamination were absent. The amylase level in drainage fluid was routinely measured on POD 1, 3, and 4 in all patients with distal pancreatectomy. Prophylactic octreotide to prevent pancreatic fistula was not administrated in this study. All patients received prophylactic antibiotics either intraoperatively only or for 1 or 2 days postoperatively.

Study Endpoints

The primary endpoint was the incidence of pancreatic fistula after DP in the 2 randomized groups. Pancreatic fistula was defined based on the guideline from the International Study Group on Pancreatic Fistula (ISGPF), that is, an amylase level in drainage fluid collected on POD 3 that is more than 3 times the serum amylase level.[15] Pancreatic fistula was classified as grade A, B, or C
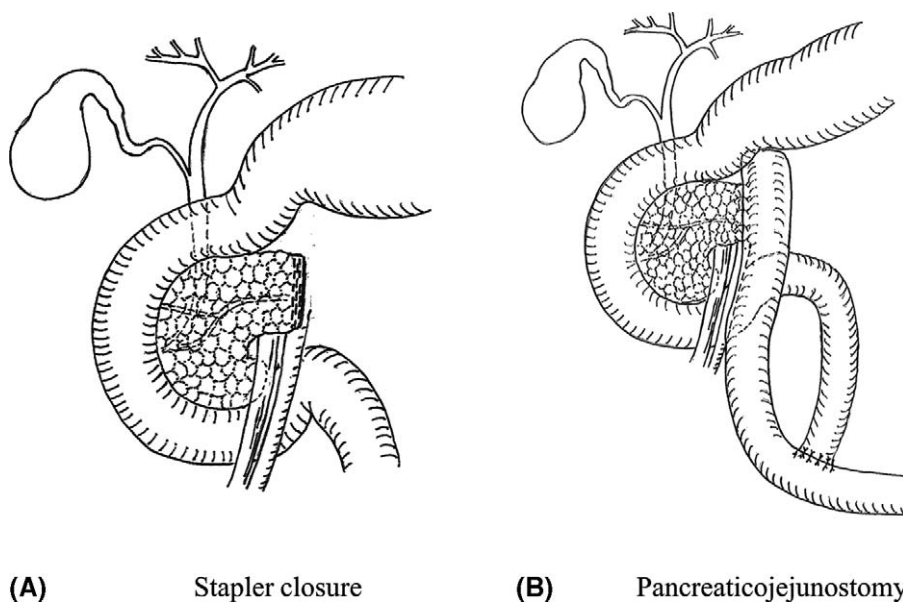
FIGURE 1. In the stapler closure group (a), the pancreatic parenchyma was transected using Echelon 60 with a gold cartridge (Ethicon Endo-Surgery, Cincinnati, OH). Echelon 60 with a gold cartridge provides precise and uniform wide compression throughout the entire 60-mm length, with compressible thickness to 1.8 mm, and can attach 2 triple-staggered rows of titanium staples. In the PJ group (b), PJ end-to-side anastomosis by a Roux-en-Y limb for the pancreatic stump was performed via a retrocolic route with an appropriate length of the first jejunal loop (at least 30 cm). The anastomosis was performed in a nonstented duct-to-mucosa fashion.

(A) Stapler closure   **(B)** Pancreaticojejunostomy

according to ISGPF clinical criteria.[15] Secondary endpoints were the incidence of clinically relevant pancreatic fistula (ISGPF grade B and C), overall postoperative morbidity, mortality, postoperative hospital stay, and incidence of pancreatic fistula stratified based on the thickness of the pancreatic parenchyma. Postoperative complications such as intra-abdominal abscess, intra-abdominal hemorrhage, and wound infection in this study were grouped according to the Clavien classification.[16] Morbidity in this study was redefined as more than grade II on the Clavien classification. Severe complications were defined in this study as a condition that was grade III or more based on the Clavien classification. Delayed gastric emptying (DGE) was defined according to a consensus definition and clinical grading of postoperative DGE proposed by the International Study Group of Pancreatic Surgery (ISGPS).[17] DGE was then classified grade A, B, or C by the ISGPS clinical criteria based on the clinical course and postoperative management. The postoperative hospital stay was defined as follows: a return to preoperative activities of daily living, no deep-site infections, normal laboratory data, no drains, and the possibility for oral nutrition above basal metabolism. Mortality was defined as death within 90 days after surgery.

Data Collection

Data were collected prospectively for all patients and included patient demographics, pathologic examination, perioperative clinical information, and complications.

Measuring the thickness of the pancreas was follows: the transection line of pancreas was prospectively recorded by the distance from the left edge of the portal vein. The thickness of the transection line of pancreas was estimated and measured by preoperative CT image based on the distance from left portal vein edge measured intraoperatively.

Statistical Analysis

The number of patients required for statistical validity (2-sided test) was based on pancreatic fistula rate. At the design of this protocol, 3 previous studies using ISGPF definition of pancreatic fistula[3,4,18] and 2 systematic reviews with meta-analysis[19,20] were referred to estimate the incidence of pancreatic fistula for stapler closure. Pancreatic fistula rate after distal pancreatectomy ranges from 20% to 31% in previous literatures. By the result, 25% as pancreatic fistula rate in the stapler closure group was estimated. As pancreatic fistula rate in pancreaticojejunostomy of the pancreatic stump ranges from 0% to 8.6% in other previous literatures,[8,9,18] 5% was expected as pancreatic fistula rate in the PJ group. Thus, pancreatic fistula rate was estimated to reduce from 25% to 5% by pancreaticojejunostomy of the pancreatic stump. We calculated that this study required 124 patients (62 in each group) to show a difference between the 2 groups at a power of 80% with a significance level of 0.05. Calculating an estimated intraoperative withdrawal rate or postrandomization exclusion of about 10%, it was necessary to enroll a total of 136 patients (68 in each group) to meet the primary endpoint of this study. Furthermore, for intention-to-treat analysis, all randomized patients were analyzed according to the assigned treatment group, except those who did not undergo DP due to peritoneal dissemination or metastasis or because they were switched to another procedure such as pancreaticoduodenectomy or total pancreatectomy. The protocol analysis incorporated only the patients who underwent the assigned procedure.

Data are expressed as means ± SD or median with range. Patient characteristics and perioperative and postoperative factors between 2 groups were compared by using χ^2 statistics, Fisher exact test, and Mann-Whitney U test. Statistical significance was defined as $P < 0.05$. The statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL).

RESULTS

During the study period of June 2011 through March 2014, 184 patients were scheduled to undergo DP for benign or malignant disease. A consort flow diagram of this RCT is shown in Figure 2. Of these 184 patients, 48 patients were excluded from the study before randomization for the following reasons: other organ resection such as colon or stomach was required (n = 9), active duplicative malignant disease affecting adverse event was present (n = 8), severe cirrhosis was present (n = 3), neutrophilic leukocyte count was not 2000/mm^3 (n = 3) or more, the patient was receiving hemodialysis (n = 2), the patient had a previous gastrectomy (n = 1) or previous jejunostomy (n = 1), and the patient refused to participate (n = 21). The remaining 136 patients were randomly assigned to stapler closure (n = 66) or PJ (n = 70). Five patients in the stapler closure group were subsequently excluded due to 4 peritoneal dissemination (n = 4) or change of procedure (1 total pancreatectomy). In the PJ group, 8 patients were subsequently excluded due to peritoneal dissemination or liver metastasis (n = 6) or change of procedure (1 pancreaticoduodenectomy and 1 central panceratectomy). Four patients who were assigned to the PJ group were switched to stapler closure or hand-sewn suture. Three patients were switched to stapler closure due to an invisible main pancreatic duct at the resection site of the pancreas, and 1 patient was switched to stapler closure due to positive cytology. No patients who were assigned to the stapler closure group were shifted to PJ due to failure of stapler closure of pancreatic stump.

Patient Characteristics

Table 1 shows the results of histologic analysis of the resected specimens, patient characteristics, preoperative status, and perioperative status. No significant difference was observed with regard to pancreatic cancer (stapler closure, n = 39; PJ, n = 44) and other disease (stapler closure, n = 22; PJ, n = 18) between the 2 groups. No significant differences existed between the 2 groups concerning other patient characteristics. Operative time was significantly longer in the PJ group; 324 min (154–568) compared with the stapler closure group; 219 min (122–626) in median (range) ($P < 0.001$), although intraoperative bleeding and the rate of transfusion were similar in both groups. Laparoscopic DP was performed in 13.1% of the stapler closure group and 17.7% of the PJ group ($P = 0.478$). The rate of spleen preservation was similar between the stapler closure group (5.2%) and the PJ group (4.8%) ($P = 0.652$).

Postoperative Complications Between Stapler Closure and PJ by Intention-to-treat Analysis

In intention-to-treat analysis, the overall incidence of pancreatic fistula occurred in 38.2% (47 of 123 patients) with no significant difference between the 2 group: 37.7% (23 of 61) in stapler closure versus 38.7% (24 of 62) in PJ ($P = 0.332$) (Table 2). Pancreatic fistula was classified into 3 categories according to ISGPF criteria.[15] The proposed clinical grading of pancreatic fistulas in 23 patients in the stapler closure group was grade A (n = 13, 21.3%), grade B (n = 8, 13.1%), and grade C (n = 2, 3.3%). In contrast, the pancreatic fistulas of 24 patients in the PJ group were classified as grade A (n = 18, 29.0%), grade B (n = 6, 9.7%), and grade C (n = 0, 0%). A clinically significant pancreatic fistula (ISGPF classification grade B/C) occurred in 10 patients (16.4%) with stapler closure and 6 patients (9.7%) with PJ ($P = 0.201$).

The overall morbidity rate in this study was 27.6% (34 of 123 patients), with no difference between the 2 group: 27.9% (17 of 61) in the stapler closure group versus 27.4% (17 of 62) in the PJ group ($P = 0.956$). No significant differences existed between the 2 groups regarding the separate incidence of DGE, intra-abdominal abscess, and intra-abdominal hemorrhage. Although 2 patients in the stapler closure group had intra-abdominal hemorrhage complicated by pancreatic fistula, complete hemostasis could be achieved by interventional radiographic techniques. Intra-abdominal hemorrhage did
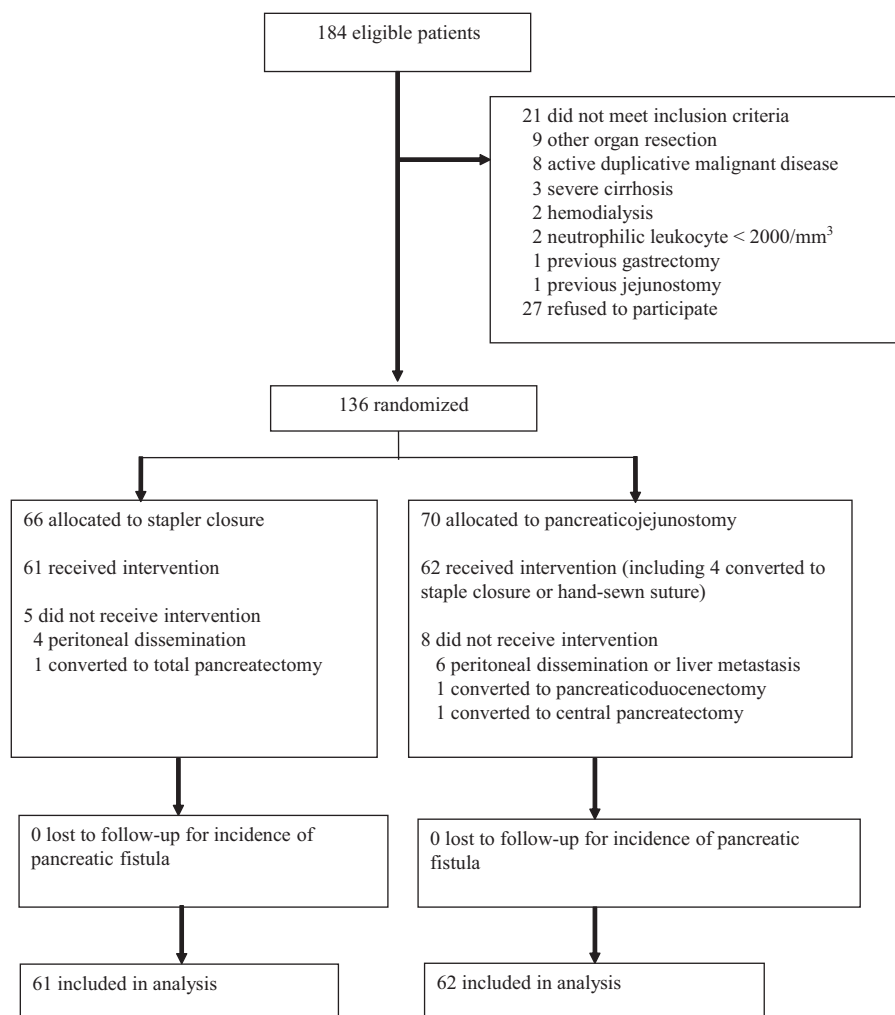
FIGURE 2. Consort diagram for the trial.

not occur in any patients in the PJ group. Only 1 patient in the PJ group had reoperation due to perforation of the stomach wall, which would be intraoperatively injured by thermal of the device on POD 2. The mortality rate in this study was zero in both groups.

In this study, 19 (15.4%) of 123 patients with distal pancreatectomy underwent laparoscopic distal pancreatectomy. No robotic distal pancreatectomy was performed. Concerning to primary endpoint of the overall incidence of pancreatic fistula, there was no significant difference between the 2 group: 47.3% (9 of 19) in laparoscopic distal pancreatectomy versus 36.5% (38 of 104) in open distal pancreatectomy ($P = 0.372$). A clinically significant pancreatic fistula (ISGPF classification grade B/C) occurred in 2 patients (10.5%) with laparoscopic distal pancreatectomy and 14 patients (13.5%) with open distal pancreatectomy ($P = 0.535$). Laparoscopic distal pancreatectomy offered the similar outcomes with open distal pancreatectomy.

Comparison Between Stapler Closure and PJ in Analysis by Protocol

Table 3 shows a comparison between stapler closure and PJ in an analysis by protocol. In this analysis, the overall incidence of pancreatic fistula was 39.5% (47 of 119 patients) with no significant difference between the 2 groups: 37.7% (23 of 61) in the stapler closure group versus 41.4% (24 of 58) in the PJ group ($P = 0.356$) (Table 3). Pancreatic fistula was classified into 3 categories according to ISGPF criteria.[15] The proposed clinical grading of pancreatic fistulas for 23 patients in the stapler closure was grade A (n = 13, 21.3%), grade B (n = 8, 13.1%), and grade C (n = 2, 3.3%). Twenty-four patients in the PJ group had pancreatic fistula classified as grade A (n = 18, 31.1%), grade B (n = 6, 10.3%), or grade C (n = 0, 0%). A clinically significant pancreatic fistula (ISGPF classification Grade B/C) occurred in 10 patients (16.4%) with stapler closure and 6 patients (10.3%) with PJ ($P = 0.334$).

The amylase level of the drainage fluid on POD 1: 1657 (92–37,410) versus 938 (122–10,660) IU/L, POD 3: 245 (12–96,687) IU/L versus 296 (18–3,454) IU/L, and POD 4: 125 (7–48,483) IU/L versus 107 (19–3,527) IU/L were similar between the stapler closure and PJ groups ($P = 0.244$, 0.722, and 0.606, respectively). Concerning the postoperative course, the day until first flatus, start of solid diet, time to drain removal, and the incidence of percutaneous drainage were similar between the stapler closure group and the PJ group.

TABLE 1. Characteristics of Enrolled Patients

	Stapling Closure (n = 61)	PJ (n = 62)	P
Age	69 ± 10	66 ± 11	0.093
Sex (male/female)	42/19	37/25	0.289
Body mass index (kg/m^2)	22.3 ± 3.0	22.5 ± 3.1	0.684
Diabetes (yes/no)	20/41	14/48	0.206
Preoperative adjuvant therapy (yes/no)	11/50	13/49	0.681
Serum hemoglobin level (g/dL)*	12.9 ± 1.7	12.5 ± 1.7	0.288
Serum creatinine (mg/dL)†	0.89 ± 0.4	0.90 ± 0.3	0.810
Serum albumin level (mg/dL)‡	4.0 ± 0.4	4.1 ± 0.5	0.358
Serum amylase level (IU/L)§	104 ± 108	76 ± 35	0.056
Serum C-reactive protein (mg/dL)‖	0.55 ± 1.32	0.34 ± 1.52	0.445
Pancreatic cancer/other disease	39/22	44/18	0.405
Pancreatic cancer	39	39	
Intraductal papillary neoplasms	9	7	
Neurondocrine tumor	5	4	
Mucinous cyst neoplasms	0	3	
Serous cyst neoplasms	1	1	
Mass-forming pancreatitis	2	1	
Other disease	5	2	
Operative time, median (range) (min)	229 (122–626)	326 (154–576)	<0.001
Intraoperative bleeding, median (range) (ml)	200 (10–3300)	279 (10–1935)	0.083
Red blood cell transfusion (yes/no)	2/59	4/58	0.348
Procedure (open/laparoscopic surgery)	53/8	51/11	0.478
Preservation of spleen (yes/no)	3/58	3/59	0.652
Dissection of SMA plexus (yes/no)	28/33	27/35	0.759
Portal vein resection (yes/no)	4/57	3/59	0.681
Celiac axis resection (yes/no)	4/57	6/56	0.527
Pancreatic texture (soft/hard)	54/7	56/6	0.746
Thickness of the pancreas (mm)¶	12.8 ± 4.8	13.6 ± 5.0	0.317

*Normal range of hemoglobin level: 12–17.5 g/dL.
†Normal range of creatinine: 0.53–1.02 mg/dL.
‡Normal range of albumin level: 3.9–4.9 g/dL.
§Normal range of amylase level: 15–150 IU/L.
‖Normal range of C-reactive protein: 0–0.3 mg/dL.
¶Thickness at the resection site of pancreas, which was measured by preoperative CT images.

Association Between Clinically Relevant Pancreatic Fistula Based on the Thickness of the Pancreas

Next, the association between the thickness of pancreas and clinically relevant pancreatic fistula was analyzed. In the stapler closure group, the thickness of the pancreas was similar in patients with or without clinically relevant pancreatic fistula (13.7 ± 3.9 mm vs 12.6 ± 5.0 mm, P = 0.516). In the PJ group, the thickness of the pancreas was also similar in patients with or without clinically relevant pancreatic fistula (13.8 ± 4.7 mm vs 11.4 ± 3.1 mm, P = 0.222). With a stratification based on 12-mm thickness at the resection site of the pancreas in the stapler closure group according to our previous reports,[6,7] the incidence of clinically relevant pancreatic fistula associated with being below this cutoff point was not significantly different between the stapler closure group and the PJ group (P = 0.485). However, among patients with a pancreas thickness >12 mm, the incidence of clinically relevant pancreatic fistula occurred in 22.2% of the stapler closure group and 6.2% of the PJ group. PJ trended to decrease the incidence of clinical relevant pancreatic fistula after DP, although there was no significant difference (P = 0.080) (Table 4).

DISCUSSION

This prospective randomized multicenter study concluded that PJ of the pancreatic stump did not significantly reduce pancreatic fistula after DP compared with stapler closure. Three previous nonrandomized studies reported that PJ of the pancreatic stump was not associated with pancreatic fistula in any patients undergoing

DP.[8–10] The results of our study conflict with available results from previous studies in which PJ of the pancreatic stump was performed. There were 2 different points between our study and previous studies, namely, the technical approach in anastomosis of PJ and the use of octreotide. With regard to the technical approach, PJ in this study was performed in duct-to-mucosa fashion, using a single layer suture of resorbable interrupted stitches, while PJ in the previous studies[8–10] was performed in a capsule-to-seromuscular fashion, using single-layer sutures after the main pancreatic duct was ligated. One RCT has reported that invagination PJ significantly reduced the incidence of pancreatic fistula after pancreaticoduodenectomy compared with duct-to-mucosa PJ,[21] while 2 other RCTs have reported that duct-to-mucosa PJ and invagination PJ are comparable for the incidence of pancreatic fistula after pancreaticoduodenectomy.[22,23] The appropriate procedure for PJ remains controversial. A second point of difference between our study and others was that prophylactic administration of octreotide was not performed in our study, although prophylactic octreotide was administrated on POD 5 to POD7 in previous studies.[8–10] Somatostatin and its analogues have well-recognized inhibitory effects on pancreatic exocrine secretion. Two recent RCTs and 1 meta-analysis found that prophylactic somatostatin and its analogues significantly reduced the incidence of pancreatic fistula after pancreaticoduodenectomy.[24–26] On the other hand, 4 other recent RCTs found that somatostatin analogues did not reduce pancreatic fistula after pancreaticoduodenectomy.[27–30] No clear evidence exists in a favor of prophylactic administration of somatostatin and its analogues to reduce the incidence of pancreatic fistula. Therefore, we believe that duct-to-mucosa PJ and no

TABLE 2. Postoperative Complications Based on Intention-to-treat Analysis

	Stapling Closure (n = 61)	PJ (n = 62)	P
Primary endpoint			
Pancreatic fistula*	23 (37.7%)	24 (38.7%)	0.332
Grade A	13 (21.3%)	18 (29.0%)	
Grade B	8 (13.1%)	6 (9.7%)	
Grade C	2 (3.3%)	0 (0%)	
Clinically pancreatic fistula†(grade B/C)	10 (16.4%)	6 (9.7%)	0.201
Secondary endpoint			
Clavien-Dindo classification	30 (49.2%)	35 (56.5%)	0.669
I	13	18	
II	9	10	
IIIa	7	6	
IIIb	0	1	
IVa	1	0	
IVb	0	0	
V	0	0	
Severe complication (IIIa or more)	8 (13.1%)	7 (11.3%)	0.757
Intra-abdominal abscess	7 (11.4%)	11 (17.7%)	0.326
Intra-abdominal hemorrhage	2 (3.3%)	0 (0%)	0.261
Delayed gastric emptying (DGE)‡	5 (8.2%)	4 (6.5%)	0.127
Grade A	5	1	
Grade B	0	2	
Grade C	0	1	
Ileus	3 (3.3%)	1 (1.6%)	0.303
Wound infection	1 (1.6%)	1 (1.6%)	0.748
Reoperation	0 (0%)	1 (1.6%)§	0.504
Mortality	0 (0%)	0 (0%)	0.999
Percutaneous drainage‖	6 (9.8%)	6 (9.7%)	0.976
Postoperative hospital stay, median (range) (days)	16 (7–98)	16 (8–130)	0.591

*Pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation.
†Clinical pancreatic fistula is defined as pancreatic fistula grade B/C based on ISGPF.
‡DGE is defined according to ISGPS in its DGE recommendation.
§Reoperation due to perforation of the stomach wall, which would be intraoperatively injured by thermal of the device on postoperative day 2.
‖Percutaneous drainage undertaken for postoperative management of intra-abdominal abscess related to pancreatic fistula.

administration of octreotide did not adversely affect the results of this study compared with the previous studies. However, most recent RCT published in 2014 concerning to somatostatin analogues demonstrated that prophylactic administration of pasireotide, a somatostatin analogue with a longer half-life, significantly reduced the incidence of clinically relevant pancreatic fistula.[31] Pasireotide may change the treatment of pancreatic fistula in the near future.

The most important reason that this study used duct-to-mucosa PJ was to decompress the main pancreatic duct and reduce pancreatic juice leakage from the branch pancreatic duct. One reasons for pancreatic fistula after DP is the increased resistance to the outflow of pancreatic juice toward the duodenum due to spasm of the sphincter of Oddi.[32] Hashimoto and Traverso[33] proposed that increased pancreatic ductal back pressure after DP was a risk factor for pancreatic stump leakage.

TABLE 3. Pancreatic Fistula and Postoperative Course based on Per-protocol Analysis

	Stapling Closure (n = 61)	PJ (n = 58)	P
Pancreatic fistula*	23 (37.7%)	24 (41.4%)	0.356
Grade A	13 (21.3%)	18 (31.1%)	
Grade B	8 (13.1%)	6 (10.3%)	
Grade C	2 (3.3%)	0 (0%)	
Clinically pancreatic fistula† (grade B/C)	10 (16.4%)	6 (10.3%)	0.334
Amylase level of drainage fluid on POD 1, median (range) (IU/L)	1657 (92–37,410)	938 (122–10,660)	0.244
Amylase level of drainage fluid on POD 3, median (range) (IU/L)	245 (12–96,687)	296 (18–3,454)	0.722
Amylase level of drainage fluid on POD 4, median (range) (IU/L)	125 (7–48,483)	107 (19–3,527)	0.606
The day until first flatus, median (range) (days)	3 (1–19)	3 (1–5)	0.686
Start of solid diet, median (range) (days)	5 (2–22)	4 (2–20)	0.816
Time to drain removal, median (range) (days)	4 (3–83)	4 (3–36)	0.268
Percutaneous drainage‡	6 (9.8%)	6 (10.3%)	0.927
Reoperation	0 (0%)	0 (0%)	0.999
Postoperative hospital stay, median (range) (days)	16 (7–98)	16 (8–130)	0.727

*Pancreatic fistula is defined according to the International Study Group of Pancreatic Surgeons (ISGPF) in its pancreatic fistula recommendation.
†Clinical pancreatic fistula is defined as pancreatic fistula grade B/C based on ISGPF.
‡Percutaneous drainage undertaken for postoperative management of intra-abdominal abscess related to pancreatic fistula.

TABLE 4. Comparison of Clinical Relevant Pancreatic Fistula Between Staple Closure and PJ Based on the Thickness* of the Pancreas

	Clinically Relevant Pancreatic Fistula†	P
Thickness of pancreas* ≦12 mm (n = 60)		
Stapler closure (n = 34)	4 (11.8%)	0.485
PJ (n = 26)	4 (15.4%)	
Thickness of pancreas* > 12 mm (n = 59)		
Stapler closure (n = 27)	6 (22.2%)	0.080
PJ (n = 32)	2 (6.2%)	

*Thickness at the resection site of pancreas.
†Clinical pancreatic fistula is defined as pancreatic fistula grade B/C based on ISGPF.

However, 1 RCT has reported that prophylactic transpapillary pancreatic stent for decompression of the pancreatic duct did not reduce pancreatic fistula after DP.[34] In that RCT, pancreatitis due to insertion of pancreatic stent was not distinguished from postoperative infectious complications, so that the data including postoperative outcomes might lead to the negative results. In this RCT, we decided to perform the clinical trial intended the decompression of pancreatic duct without using the stent. Therefore, we hypothesized that decompression of pancreatic ductal back pressure by duct-to-mucosa PJ might prevent leakage of pancreatic juice from pancreatic stump.

Aside from decompression of the main pancreatic duct, PJ was hypothesized to be superior to stapler closure for pancreatic stump because it was available regardless of the thickness of the pancreas resection site. A seromuscular-parenchymal anastomosis in PJ has a role in reducing pancreatic fistula because of the close proximity to the pancreatic stump despite the thickness of the pancreas resection site. Stapler closure of the pancreatic stump is technically easy and has become popular with many surgeons. However, stapler closure of pancreatic stump may not be useable for a thick pancreas.[6,7] In this study, the rate of clinically relevant pancreatic fistula in the PJ group tended to be lower than that in the stapler closure group for patients with a thicker pancreas (ie, >12 mm; P = 0.08), but there was no statistically significance. This finding can be explained by a thick pancreatic parenchyma being easily torn by the compression of a stapler closure; the pancreas is a fragile organ. Therefore, using stapler closure for a thick pancreatic parenchyma may allow persistent extravasation of pancreatic juice by staple malformation. Hamilton et al[35] demonstrated that resection with a stapler using mesh reinforcement greatly reduced pancreatic fistula. Also, Oláh et al[18] showed the impact of covering the stapled pancreatic stump with seromuscular patch in significantly reducing pancreas-related complications. However, patients with thick or fibrotic pancreatic parenchyma were excluded from these RCTs. Therefore, PJ of pancreatic stump might offer a reduced risk of pancreatic fistula compared with stapler closure in a thick pancreas.

Overall pancreatic fistula in the stapler group occurred in 37.7%. The incidence of overall pancreatic fistula in the stapler group was estimated to be 25%. The result in the stapler group was higher than estimated rate. However, the incidence of overall pancreatic fistula in DISPACT trial was 32%, which was approximately equal to this result. In addition, It remains still controversial which stapler cartridge is appropriate for stapler closure of the pancreatic stump. One study reported that stump closure using a white cartridge (compressible thickness to 1.0 mm) significantly decreased the incidence of clinically relevant pancreatic fistulas in comparison to that performed with a green cartridge (compressible thickness to 2.0 mm) (5% vs 31%),[36] which might indicate that stump closure using a white cartridge may be useful to achieve a tighter seal of pancreatic stump in a thin pancreas. In contrast, a white cartridge may be traumatic to hard or thick pancreatic parenchyma. Thus, there has been no data to confirm which size of cartridge should be used for stump closure of distal pancreatectomy. A prospective randomized trial would be required to confirm which size of cartridge has a superior stump closure.

PJ of the pancreatic stump may result in more dangerous complications than staple closure due to intestinal juice. Moreover, additional procedures involving the intestine may cause extra complications related to intestinal resection. However, the incidence of intra-abdominal abscess requiring percutaneous drainage was 8.1% (5 of 62) in the PJ group compared with 4.9% (3 of 61) in the stapler closure group. PJ resulted in no significant increase of intra-abdominal abscess compared with stapler closure (P = 0.331). In addition, the incidence of ileus and postoperative course, including the day until first flatus and start of solid diet, were comparable between stapler closure and PJ.

In conclusion, this study could not evaluate the superiority of PJ of pancreatic stump during DP to reduce pancreatic fistula compared with staple closure. However, PJ for pancreatic stump might offer a potential reduction of pancreatic fistula in cases with a thick pancreas. RCT by stratification of a thick pancreas is required to confirm the impact of PJ of pancreatic stump to reduce pancreatic fistula.

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