The texture of the resection site of the pancreas in DP is generally not affected by chronic inflammation and is considered to be healthy and exocrine-functional, because the disease is always located peripheral to the resection line. Instead, stump thickness, parenchymal thickness, stump area, and parenchymal area were significant risk factors for POPF, and parenchymal thickness and parenchymal area, which reflected the parenchymal volume, showed the lowest and second lowest $P$ values in univariate analyses (Table 3). Abundant pancreatic parenchyma is essentially considered to have rich pancreatic exocrine function, as Frozanpor et al. [16] reported that a large volume of remnant pancreatic gland increased the risk of POPF. We chose just stump thickness in multivariate analyses as an index of remnant pancreatic volume because it is simple and easy to understand. The key to reducing the POPF rate after DP suggested by multivariate analysis was closure of the pancreatic remnant, especially in a pancreas with abundant and highly-functioning exocrine gland.

Previous studies on stapler use for pancreatic transection have reported various results, "beneficial" [6, 10], "hazardous" [18], or "disputable" [2, 3, 14]. The study by Bassi et al. [10] is the only randomized controlled trial, and reported that the stapler technique showed better results in comparison to suture closure, with a POPF rate of 14 versus 33 %. The merits of a stapler are considered to be convenience and possibility of simultaneous closure of the pancreatic parenchyma and MPD. Several types of stapler were used in the present study. TLH was used in order to adjust the staple height to accommodate tissue thickness. The staple height when closed varied from 1.5 to 2.5 mm. Another type of stapler, a triple-row cartridge with a cutter, was applied for both transection and closure, with selection of the stapler height according to the texture and thickness. The staple height when open/closed is 2.5 mm/1.0 mm in the white, 3.5 mm/1.5 mm in the blue, 3.8 mm/1.8 mm in the gold, and 4.1 mm/2.0 mm in the green cartridge of Echelon or GIA Universal, and 2.0–3.0 mm/0.75–1.5 mm in the camel, 3.0–4.0 mm/1.5–2.25 mm in the purple, and 4.0–5.0 mm/2.25–3.0 mm in the black cartridge of Endo-GIA Ultra Tri-Staple, which has a broader range of staple height. There is some literature about the indication for stapler use for pancreatic division. Kah Heng et al. [22] reported that the use of a stapler on a soft pancreas led to a high risk of POPF after DP. Eguchi et al. [19] reported that applying a stapler for a pancreatic stump thickness of more than 13 mm had a significant risk of POPF.

The results of the present study suggested that a triple-row stapler was safer than a double-row stapler, although our experience was limited. The indication, knack, and technique of a triple-row stapler should be considered in its use, because there has been increasing interest in performing laparoscopic pancreatic resection. Nakamura et al. [23] emphasized the importance of prolonged peri-firing compression which effectively prevented POPF after laparoscopic DP. Sepesi et al. [24] reported the importance of selection of the stapler's height. Okano et al. [25] noted that the "slow parenchymal flattening technique" should be useful to reduce the thickness of the pancreatic parenchyma. It is estimated from these studies that instant and violent compression by a stapler seems to cause crushing and tearing of the capsule of the pancreatic remnant and the development of POPF. Persistent exposure of pancreatic juice from small branches in the cut end of the torn capsule is suspected to contribute to MPD failure, resulting in major leakage. Although the remnant pancreas is usually highly-functional ''soft pancreas'', not only the tactile sensation but also the vulnerability of the remnant pancreas should be considered an important factor.

The compression index, which is defined as stump thickness divided by the stapler height when closed, was also a significant risk factor. This suggests that selection of stapler height according to the individual pancreatic thickness or texture would be important in preventing POPF. However, it was difficult to set the cut-off value of stump thickness or compression index for preventing POPF statistically. The compression index analyzed in this study was produced by using a mixture of double-row and triple-row staplers. Prospective collection of data from triple-row staplers not only in low risk pancreas but also in thick pancreatic stump, with appropriate staple height and unified technique, and understanding the compression index in triple-row stapler use is awaited. Limitations of this study are the retrospective design of the study, single center experience, selection of the type of stapler by trend, and possible bias of increasing experience over time.

Detailed preoperative evaluation of the remnant pancreatic parenchyma at the planned resection site by imaging modalities would mean that a suitable stapler could be used that would not tear the normal pancreatic capsule. A "high risk" pancreas with abundant parenchyma might be safely transected not only by a triple-row stapler but also by additional procedures, such as coverage, anastomosis, or transpapillary stenting [5, 7–9, 12, 13, 18]. Failure of the pancreatic stump due to pancreatic ductal back pressure in the early postoperative period was reported by Hashimoto et al. [26]. They stated that low pancreatic ductal back pressure was secured by preoperative endoscopic decompression of Wirsung's duct, and that it was worsened by intravenous opioid use.

Moreover, the detailed procedures of compressing, dividing, and closing the pancreatic remnant, by applying devices without injury to the remnant pancreatic capsule, based on the patient's individual pancreatic characteristics, are considered to be mandatory for the prevention of clinically relevant POPF after DP.

## Conclusions

Clinically relevant POPF after DP still occurs with high frequency. The most important risk factor was suggested to be the thickness of the pancreatic stump. A triple-row stapler was shown to be superior to a double-row stapler in the prevention of POPF. Appropriate application of devices according to the remnant volume of the individual pancreas and further experience of triple-row stapler use with gentle maneuvering are urgently needed.

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ORIGINAL ARTICLE

# Schematic Pancreatic Configuration: A Risk Assessment for Postoperative Pancreatic Fistula After Pancreaticoduodenectomy

**Motokazu Sugimoto · Shinichiro Takahashi · Naoto Gotohda · Yuichiro Kato · Takahiro Kinoshita · Hidehito Shibasaki · Masaru Konishi**

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**Abstract**
*Introduction* Postoperative pancreatic fistula (POPF) remains a serious complication after pancreaticoduodenectomy (PD). Preoperative risk assessment of POPF is desirable in careful preparation for operation. The aim of this study was to assess simple and accurate risk factors for clinically relevant POPF based on a schematic understanding of the pancreatic configuration using preoperative multidetector computed tomography.
*Methods* Three hundred and eighteen consecutive patients who underwent PD in the National Cancer Center Hospital East between November 2006 and March 2013 were investigated. Pre-, intra-, and postoperative clinicopathological findings as well as pancreatic configuration data were analyzed for the risk of clinically relevant POPF. POPF was defined according to the International Study Group of Pancreatic Fistula classification. POPF grade A occurred in 52 patients (16.4 %), grade B in 84 (26.4 %), and grade C in 6 (1.9 %).
*Conclusions* Independent risk factors for POPF grade B/C included main pancreatic duct diameter (MPDd) < 2 mm ($P = 0.001$), parenchymal thickness ≥ 8 mm ($P = 0.018$), not performing portal vein/superior mesenteric vein resection ($P = 0.004$), and amylase level of drainage fluid on postoperative day 3 ≥ 375 IU/L ($P < 0.001$). Pancreatic configuration data including MPDd and parenchymal thickness were good indicators of clinically relevant POPF.

**Keywords** Postoperative pancreatic fistula · Pancreaticoduodenectomy · Pancreatic configuration · Main pancreatic duct diameter · Parenchymal thickness

## Introduction

Postoperative pancreatic fistula (POPF) is still a devastating complication after pancreaticoduodenectomy (PD), because it is intractable, needs prolonged drain insertion, and can lead to further morbidity and mortality. It is generally reported that the incidence of clinically relevant POPF after PD is 7.6–36.4 %,[1–5] in accordance with the definition of the International Study Group of Pancreatic Fistula (ISGPF).[6] To reduce the incidence of POPF after PD, accurate preoperative assessment of POPF risk, as well as appropriate surgical techniques and perioperative management especially for high-risk cases, is required. Preoperative assessment of risk factors in a simple, objective way could be utilized in a widespread manner. For instance, a surgical trial with stratification of patients according to the definitive POPF risk may enhance the statistical power for a specific procedure.

Multidetector computed tomography (MDCT) to create a picture of the pancreas may express the POPF risk inherent in the pancreas. A small main pancreatic duct (MPD) is widely accepted as a significant risk factor for POPF after PD,[5,7–16] and so is a thick pancreas for POPF after distal pancreatectomy,[17,18] both of which can be demonstrated quite simply by MDCT. Schematic understanding of the pancreatic configuration by referring to preoperative MDCT findings, as established in our previous study of distal pancreatectomy,[18] may enable evaluation of preoperative risk factors for POPF after PD. The aims of this study were to assess simple and objective parameters using preoperative MDCT, compare their prognostic value for clinically relevant POPF with that of other preoperative, intraoperative, and postoperative parameters, and educe accurate risk factors available preoperatively.

M. Sugimoto · S. Takahashi (✉) · N. Gotohda · Y. Kato · T. Kinoshita · H. Shibasaki · M. Konishi
Department of Digestive Surgical Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwa-no-ha, Kashiwa, Chiba Prefecture 277-8577, Japan
e-mail: shtakaha@east.ncc.go.jp

## Materials and Methods

### Patients and Clinical Data Collection

Three hundred and eighteen consecutive patients who underwent PD with curative intent at the National Cancer Center Hospital East between November 2006 and March 2013 were retrospectively investigated. Clinicopathological data were reviewed from the medical records. All patients underwent preoperative contrast-enhanced MDCT focusing on the pancreas and surrounding region as a part of the diagnostic workup, and PD was indicated for suspected malignancy. During this period, the reconstruction method for the remnant pancreas and postoperative management were standardized. The study was approved by the institutional review board of the National Cancer Center.

### Operative Techniques

Subtotal stomach-preserving PD was performed in most of the cases, whereas conventional resection with antrectomy was performed particularly in cases with a gastric tumor. D2 lymphadenectomy was routinely performed with skeletonization of the arteries of the hepatoduodenal ligament, and removal of the retroportal pancreatic lamina on the right aspect of the mesenteric artery, paraaortic lymph node sampling, or extended resection including adjacent organs was performed based on the surgeon's decision to achieve curative resection. The pancreas was divided using a scalpel, ultrasonically activated device, or a combination of both. Segmental resection of the portal vein (PV) and/or superior mesenteric vein (SMV) was performed when a periampullary tumor was inseparable from the vein. For reconstruction, end-to-side pancreaticojejunostomy was performed using the modified technique first described by Kakita et al.[19] (Fig. 1). For the outer layer, two to four interrupted sutures penetrating the pancreatic parenchyma and picking up the seromuscular layer of the jejunum were placed using 3–0 nonabsorbable monofilament sutures with a straightened needle. Next, the pancreatic duct and full thickness jejunal wall were fixed as the inner layer with 8 to 14 interrupted stitches using 5–0 or 6–0 absorbable monofilament sutures, according to the size of the MPD. Then approximation of the jejunal wall and the pancreatic stump was accomplished with ligation of the outer layer stitches to cover fully the cut surface of the pancreas. A 6-Fr short internal drainage tube was placed through the pancreatic duct with an anchoring suture using one of the inner layer stitches, except in cases with an exceedingly dilated MPD. The number of stitches and the size of the suture material were at the surgeon's discretion for each case. No autologous grafts, artificial grafts, or sealing agents were applied in covering the anastomosis. Jackson–Pratt-type closed suction drains were placed near the pancreaticojejunal and choledochojejunal anastomoses, avoiding direct contact with vascular structures. Pancreatic consistency, especially at the pancreatic resection site, was evaluated subjectively as soft or hard by the surgeon during the operation.

### Perioperative Management

D-Amy (in International units per liter) and drainage fluid culture were evaluated on POD 1, 3, and 5 and as necessary. Drains were removed when the drainage fluid did not show high D-Amy or signs of infection after POD 3–6. In cases showing signs of infection in the drainage fluid, drain replacement via the ordinary tract created at operation was performed under fluorography on POD 7–10, to prevent drain occlusion and achieve effective drainage. Postoperative CT was not planned routinely but was carried out if clinical symptoms suggested an intraabdominal inflammatory complication. In cases with drainage failure, percutaneous drainage was facilitated by CT or ultrasonographic guidance. An oral diet was restarted on POD 3 in general, and was not prohibited unless delayed gastric emptying or anastomotic failure in the digestive passage was diagnosed radiologically. Somatostatin and its analogs were never administered perioperatively in an attempt to prevent or treat POPF. Readmission for surgical complications within 30 days after discharge was evaluated. The POPF cases focused on in this study were "clinically relevant," consistent with grades B and C of the ISGPF criteria.

### Schematic Understanding of Pancreatic Configuration

The configuration of the pancreatic stump was evaluated in detail.[18] The pancreatic stump was recognized as an eclipse, the MPD as a circle, and the parenchyma as the difference between the whole stump and MPD, as shown in Fig. 2. Parameters including stump thickness, stump width, and MPD diameter (MPDd) were measured using axial and coronal 2-mm-slice high-resolution MDCT, at the pancreatic resection site, which was determined with reference to the positional relationship with the adjacent vessels (Fig. 3). Pancreatic thickness was considered to be the length of the pancreas in an approximately ventrodorsal direction and vertical to the MPD, whereas pancreatic width was considered to be the length of the pancreas in an approximately cephalocaudal direction and vertical to the pancreatic thickness. Parameters including parenchymal thickness, parenchymal width, MPD area, stump area, and parenchymal area were defined and calculated using each formula (Fig. 2). The resection site was determined mainly by preoperative MDCT, confirmed by intraoperative ultrasound, and occasionally changed to a distal site because of the finding of microscopic malignancy in a frozen biopsy of the stump, with consideration of obtaining a secure tumor margin and the remnant pancreatic volume.

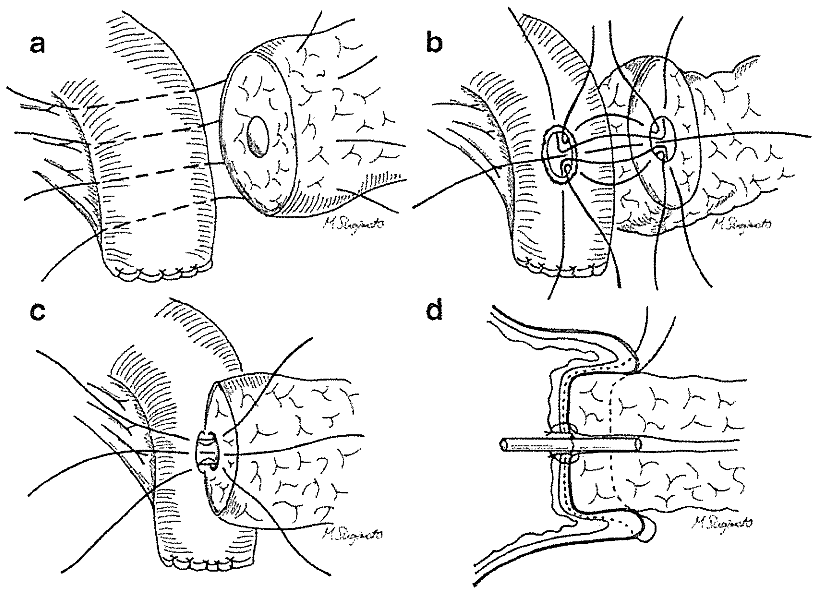


**Fig. 1** Reconstructive procedure of end-to-side pancreaticoduodenectomy. **a** Four interrupted sutures penetrating the pancreatic parenchyma and picking up the seromuscular layer of the jejunum were placed for the outer layer, using 3–0 nonabsorbable monofilament sutures with a straightened needle. **b** The posterior wall of the pancreatic duct and full thickness jejunal wall were fixed as the inner layer with five interrupted stitches using 5–0 absorbable monofilament sutures. Outer layer stiches are omitted in figure. **c** The anterior wall of the inner layer of pancreatic duct and full thickness jejunal wall were fixed with three interrupted stitches using 5–0 absorbable monofilament sutures. Outer layer stiches are omitted in figure. **d** Approximation of the jejunal wall and the pancreatic stump was accomplished with ligation of the outer layer stitches to fully cover the cut surface of the pancreas. A 6-Fr short internal drainage tube was placed through the pancreatic duct with an anchoring suture using one of the inner layer stitches

### Statistical Analysis

Preoperative patient characteristics, pancreatic configuration data, intraoperative factors, and D-Amy, representing postoperative data, were compared between patients who did and did not experience clinically relevant POPF in univariate logistic regression analysis. Covariates reported to be risk factors for POPF were included.[3–5,7–16,20–23] Categorical variables are summarized as numbers and percentages, and continuous variables are presented as median±standard deviation. Preoperative and intraoperative factors achieving statistical significance at a 0.1 level in univariate analysis were included in multivariate analysis. Receiver operating characteristic (ROC) curves were used and area under the curve (AUC) was analyzed, to determine the cut-off value with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, and to identify especially predictive variables in pancreatic configuration data. One postoperative parameter, among D-Amy on POD 1, 3, and 5, was also included in multivariate analysis, although it was not considered causative or predictive. Then multivariate logistic regression analysis was conducted to identify independent risk factors or associated parameters for POPF grade B/C during the perioperative period. Odds ratios (OR) with 95 % confidence intervals (95 % CI) were obtained. All $P$ values were based on two-sided statistical tests, setting the significance level as 0.05. All statistical analyses were performed using SPSS Statistics version 19.0 software (SPSS, Chicago, IL, USA).

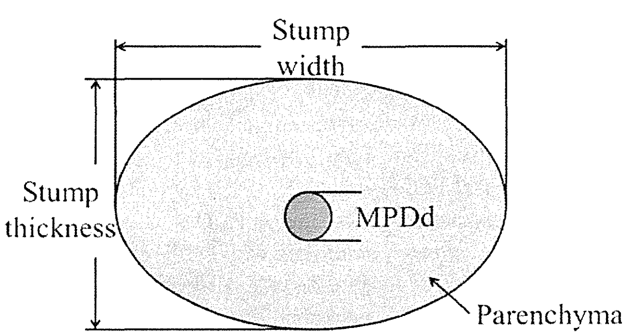


**Fig. 2** Schematic configuration of pancreatic stump. *MPDd* main pancreatic duct diameter (in millimeters). *parenchymal thickness* stump thickness−MPDd (in millimeters), *parenchymal width* stump width−MPDd (in millimeters), *MPD area* 1/4×MPDd×MPDd×π (in square millimeters), *stump area* 1/4×stump width×stump thickness×π (in square millimeters), *parenchymal area* stump area−MPD area (in square millimeters)

## Results

### Postoperative Outcome

The postoperative course with respect to POPF in 318 patients is tabulated in Table 1. POPF grade A was observed in 52 cases (16.4 %), grade B in 84 cases (26.4 %), and grade C in 6

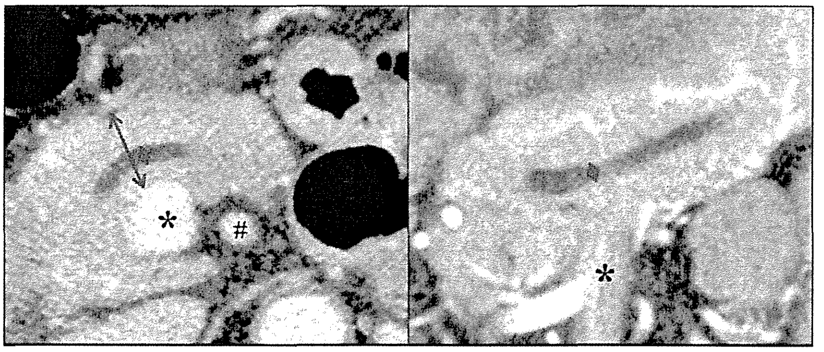


**Fig. 3** Assessment of pancreatic thickness and main pancreatic duct by preoperative MDCT. Pancreatic thickness and main pancreatic duct diameter (*MPDd*) were measured at the resection site in axial (*left*) and coronal (*right*) views of preoperative MDCT. *Large arrow* pancreatic thickness; *small arrow* MPDd. *Asterisk* denotes superior mesenteric vein. *Number sign* denotes superior mesenteric artery

cases (1.9 %). Patients with POPF grade B/C experienced prolonged drain insertion (29±21 vs. 6±5 days), higher need for percutaneous drainage (22.2 vs. 2.3 %), prolonged postoperative hospital stay (33±20 vs. 13±12 days), and higher mortality (2.2 vs. 0.0 %), compared with patients who did not develop POPF (POPF grade A/none). Reoperation was never performed with an intention to manage POPF. The detailed reasons for 30-day readmission were mild transient anorexia in three patients, cholangitis in two, and delayed gastric emptying in two, with POPF grade A/none, whereas intraabdominal bleeding (POPF grade C) in one patient with POPF grade B/C. Both of the mortality cases underwent radiologic intervention for aneurysmal rupture induced by POPF and died of subsequent liver failure.

## Evaluation of Risks for Clinically Relevant POPF

Factors reported or assumed to be associated with clinically relevant POPF after PD were compared between the patient groups with POPF grade A/none and POPF grade B/C by univariate analysis (Tables 2). Of the preoperative factors, patients with high BMI and pathological condition other than pancreatic cancer had a significantly higher incidence of POPF grade B/C ($P<0.001$ and $P<0.001$), whereas patients without diabetes showed a tendency for a higher incidence ($P=0.051$). Of the pancreatic configuration data, MPDd, stump width, parenchymal thickness, parenchymal width, and parenchymal area differed significantly between patients with POPF grade A/none and POPF grade B/C ($P<0.001$, $P=0.003$, $P<0.001$, $P<0.001$, and $P<0.001$, respectively). ROC curves for pancreatic configuration data are shown in Fig. 4. Values of AUC in these data were as follows; MPDd, 0.764; stump thickness, 0.523, stump width, 0.614; parenchymal thickness, 0.709; parenchymal width, 0.687; stump area, 0.589; and parenchymal area, 0.656. These results indicated that parameters with "fair accuracy" were MPDd and parenchymal thickness (AUC≥0.700). When a cut-off value of 2 mm was applied for MPDd, sensitivity was 42.2 %; specificity, 89.5 %; PPV, 61.3 %; NPV, 79.7 %; and accuracy 76.1 %, whereas sensitivity was 68.9 %; specificity, 71.9 %; PPV, 49.2 %; NPV, 85.4 %; and accuracy, 71.1 % when the cut-off value was 3 mm. When a cut-off value of 8 mm was applied for parenchymal thickness, sensitivity was 71.1 %; specificity, 64.5 %; PPV, 44.1 %; NPV, 85.0 %; and accuracy, 66.4 %. Of the intraoperative factors, soft pancreas and not performing PV/SMV resection were significantly associated with clinically relevant POPF ($P<0.001$ and $P=0.001$, respectively). Of the postoperative data, D-Amy on POD 1, 3, and 5 differed significantly between patients with POPF grade A/none and POPF grade B/C ($P=0.005$, $P<0.001$, and $P<0.001$, respectively). D-Amy on POD 3≥375 was considered to be most strongly associated with POPF grade B/C, because it is the criterion for POPF grade A. BMI≥25 kg/m$^2$, absence of diabetes, pathological condition other than pancreatic cancer, MPDd<2 mm, parenchymal thickness≥8 mm, soft pancreas, not performing PV/SMV resection, and POD 3 D-Amy≥375 IU/L were included in multivariate analysis of POPF grade B/C. Independent risk factors for clinically relevant POPF were MPDd<2 mm (OR, 3.589 (95 % CI, 1.665–7.737), $P=0.001$), parenchymal thickness≥8 mm

**Table 1** Postoperative outcome after PD

| | Overall ($n=318$) | POPF grade A/none ($n=228$) | POPF grade B/C (n=90) |
|---|---|---|---|
| Drain insertion (days) | 7±17 | 6±5 | 29±21 |
| Percutaneous drainage | 25 (7.9 %) | 5 (2.3 %) | 20 (22.2 %) |
| Reoperation | 3 (0.9 %) | 2 (0.9 %) | 1 (1.1 %) |
| Postoperative hospital stay (days) | 15±18 | 13±12 | 33±20 |
| 30-day readmission | 8 (2.5 %) | 7 (3.1 %) | 1 (1.1 %) |
| Mortality | 2 (0.6 %) | 0 (0.0 %) | 2 (2.2 %) |

*PD* pancreaticoduodenectomy, *POPF* postoperative pancreatic fistula

**Table 2** Characteristics of patients and univariate analysis of risk factors for clinically relevant POPF after PD

| Parameter | Overall ($n$=318) | POPF grade A/none ($n$=228) | POPF grade B/C ($n$=90) | $P$ |
|---|---|---|---|---|
| Preoperative factors | | | | |
| Age | 69±11 | 69±11 | 70±10 | 0.489 |
| Sex (male) | 207 (65.1 %) | 149 (68.3 %) | 58 (64.4 %) | 0.879 |
| BMI (kg/m$^2$) | 21.5±3.1 | 21.0±3.0 | 22.8±3.1 | <0.001* |
| ASA score (1/2/3) | 109/192/17 | 77/138/13 | 32/54/4 | 0.607 |
| Diabetes | 73 (23.0 %) | 59 (27.1 %) | 14 (15.6 %) | 0.051 |
| Coronary artery disease | 18 (5.7 %) | 12 (5.5 %) | 6 (6.7 %) | 0.626 |
| Preoperative biliary drainage | 161 (50.6 %) | 121 (55.5 %) | 40 (44.4 %) | 0.167 |
| Preoperative therapy | 12 (3.8 %) | 11 (5.0 %) | 1 (1.1 %) | 0.152 |
| Albumin (g/dL) | 3.8±0.4 | 3.8±0.4 | 3.9±0.5 | 0.958 |
| Creatinine (mg/dL) | 0.8±0.2 | 0.7±0.2 | 0.8±0.2 | 0.581 |
| Pathological diagnosis (pancreatic cancer) | 158 (49.7 %) | 131 (60.1 %) | 27 (30.0 %) | <0.001* |
| Pancreatic configuration data | | | | |
| MPDd (mm) | 3.8±3.4 | 4.7±3.6 | 2.2±1.7 | <0.001* |
| Stump thickness (mm) | 12.4±3.7 | 12.4±3.9 | 13.0±3.3 | 0.941 |
| Stump width (mm) | 24.0±6.3 | 24.0±6.4 | 27.0±5.7 | 0.003* |
| Parenchymal thickness (mm) | 7.7±3.7 | 7.0±3.5 | 9.9±3.5 | <0.001* |
| Parenchymal width (mm) | 20.5±7.9 | 19.3±8.0 | 24.4±6.3 | <0.001* |
| Stump area (mm$^2$) | 235.2±99.5 | 230.8±104.3 | 255.9±84.5 | 0.086 |
| Parenchymal area (mm$^2$) | 211.9±91.1 | 199.6±90.5 | 247.3±84.9 | <0.001* |
| Intraoperative factors | | | | |
| Soft pancreas | 172 (54.1 %) | 99 (45.4 %) | 73 (81.1 %) | <0.001* |
| Extended lymph node dissection | 14 (4.4 %) | 9 (4.1 %) | 5 (5.6 %) | 0.531 |
| Pancreatic resection at PV-SMV level | 272 (85.5 %) | 194 (89.0 %) | 78 (86.7 %) | 0.676 |
| PV/SMV resection | 61 (19.2 %) | 55 (25.2 %) | 6 (6.7 %) | 0.001* |
| Operation time (min) | 363±76 | 361±79 | 366±70 | 0.774 |
| Estimated blood loss (mL) | 812±669 | 802±651 | 844±711 | 0.230 |
| Transfusion | 52 (16.4 %) | 37 (17.0 %) | 15 (16.7 %) | 0.924 |
| Postoperative data | | | | |
| POD 1 D-Amy (IU/L) | 2,029±48,783 | 462±36,399 | 13,530±68,325 | 0.005* |
| POD 3 D-Amy (IU/L) | 134±5,666 | 51±2,183 | 1,964±9,696 | 0.001* |
| POD 5 D-Amy (IU/L) | 107±12,385 | 46±2,439 | 1,267±21,583 | 0.001* |

Differences between the two groups were evaluated using logistic regression analyses

*POPF* postoperative pancreatic fistula, *PD* pancreaticoduodenectomy, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *MPDd* main pancreatic duct diameter, *PV/SMV* portal vein and/or superior mesenteric vein, *POD* postoperative day, *D-Amy* amylase level of drainage fluid

*$P$<0.05

(2.214 (1.146–4.278), $P$=0.018), not performing PV/SMV resection (5.564 (1.721–17.994), $P$=0.004), and POD 3 D-Amy ≥ 375 IU/L (13.044 (6.114–27.826), $P$<0.001) (Table 3).

### Validation of Combination of Pancreatic Configuration Data as Risk Factor for Clinically Relevant POPF

There were 43 patients (13.5 %) with both MPDd<2 mm and parenchymal thickness≥8 mm. They were significantly associated with POPF grade B/C (9.458 (4.576–19.545), $P$<0.001), with sensitivity, 34.4 %; specificity, 94.7 %; PPV, 72.1 %; NPV, 78.5 %; and accuracy, 77.7 %.

## Discussion

The present study investigated predictive factors for clinically relevant POPF after PD, and demonstrated the significance of schematic understanding of pancreatic configuration as a preoperative risk factor. Soft pancreatic texture has been widely recognized as an important risk factor, but is problematic as it

**Table 3** Multivariate analysis of risk factors for clinically relevant POPF after PD ($n$=318)

| Parameter | OR | 95 % CI | $P$ |
|---|---|---|---|
| BMI≥25 kg/m² | 2.137 | 0.897–5.095 | 0.087 |
| Absence of diabetes | 1.367 | 0.568–3.293 | 0.486 |
| Pathological condition other than pancreatic cancer | 0.467 | 0.183–1.187 | 0.110 |
| MPDd<2 mm | 3.589 | 1.665–7.737 | 0.001* |
| Parenchymal thickness≥8 mm | 2.214 | 1.146–4.278 | 0.018* |
| Soft pancreas | 1.317 | 0.497–3.492 | 0.580 |
| Not performing PV/SMV resection | 5.564 | 1.721–17.994 | 0.004* |
| POD 3 D-Amy≥375 IU/L | 13.044 | 6.114–27.826 | <0.001* |

Independent risk factors for clinically relevant POPF were evaluated using logistic regression analysis

*POPF* postoperative pancreatic fistula, *PD* pancreaticoduodenectomy, *OR* odds ratio, *95 % CI* 95 % confidence interval, *BMI* body mass index, *MPDd* main pancreatic duct diameter, *PV/SMV* portal vein and/or superior mesenteric vein, *POD* postoperative day, *D-Amy* amylase level of drainage fluid

*$P$<0.05

is revealed intraoperatively in a subjective way, lacks quantitative analysis, and has imperfect predictive value. Recent Japanese multicenter data from 1,239 patients showed that clinically relevant POPF occurred in 142 (21.9 %) of 648 cases with soft pancreas and 36 (6.1 %) of 591 cases with hard pancreas.[3] Clinical parameters including D-Amy and blood test data in the postoperative period can be the basis

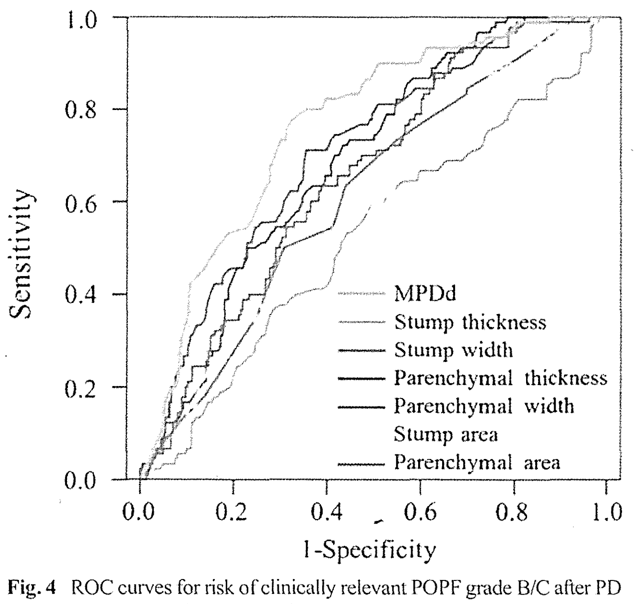


**Fig. 4** ROC curves for risk of clinically relevant POPF grade B/C after PD in schematic pancreatic configuration data. Values of AUC: MPDd, 0.764; stump thickness, 0.523, stump width, 0.614; parenchymal thickness, 0.709; parenchymal width, 0.687; stump area, 0.589; parenchymal area, 0.656. *POPF* postoperative pancreatic fistula, *PD* pancreaticoduodenectomy, *MPDd* main pancreatic duct diameter

for early drain removal[24] or an early marker of latent fistula, and possibly reflect other ominous clinical conditions. D-Amy is of course a reliable postoperative factor associated with POPF,[3,20] because D-Amy on POD 3 is itself a definitive ISGPF criterion. Conversely, accurate and reliable risk factors for POPF that can be detected preoperatively will allow pancreatic surgeons to carry out preventive measures against postoperative complications. This study indicates the utility of schematic pancreatic configuration data as a prognostic marker for POPF after PD. MPDd, stump width, parenchymal thickness, parenchymal width, and parenchymal area were significantly correlated with POPF grade B/C in univariate analysis. AUC to determine the cut-off value showed that MPDd and parenchymal thickness were especially important among the pancreatic configuration data. A cut-off value of 2 mm for MPDs was more accurate than that of 3 mm, and it seemed to be a good clinical benchmark of difficult anastomosis in our operative setting. Thick pancreatic parenchyma with well-preserved exocrine function and small MPDd, which made the anastomotic technique physically difficult, might frequently result in leakage of pancreatic juice, injury of the anastomotic tissue, and infection, and lead to clinically relevant POPF. These two parameters were independent predictive factors, as were not performing PV/SMV resection and high D-Amy on POD 3, and surpassed soft pancreatic consistency in multivariate analysis. The combination of MPD< 2 mm and parenchymal thickness≥8 mm showed high specificity (94.7 %) and NPV (78.5 %). Preoperative MDCT is expected to allow earlier and more objective and precise measurement of pancreatic configuration data than were other methods of measurement, such as intraoperative ultrasound or direct measurement of the stump or resected specimen with a ruler.

Regarding other options using imaging modalities, Tajima et al.[25,26] reported that the time-signal intensity curve profile correlated with fibrosis of the pancreas in a dynamic MRI study, and a relationship between fibrosis and MPD dilation was suggested.[26] Atrophic pancreas caused by chronic inflammation revealed increased fibrosis, decreased exocrine function, and a low risk of POPF.[27,28] Conversely, Mathur et al. reported that patients with fatty pancreas had increased risk of POPF and showed decreased pancreatic fibrosis, blood vessel density, and MPDd.[29] MPDd and parenchymal thickness assessed by preoperative MDCT might be accurate indicators of the degree of fibrosis and fatty infiltration of the pancreas. Investigating the relationships among pancreatic configuration data, detailed histopathological findings, and operative outcome should be the next concern. Parameters such as the absence of diabetes, high BMI, pathological condition other than pancreatic cancer, soft pancreatic consistency, and not performing PV/SMV resection might be associated with histopathological alteration of the pancreatic parenchyma.

The incidence of clinically relevant POPF in the current study seemed to be relatively high.[1–5] Although evaluation of POPF using the definition of the ISGPF is convenient and important in the worldwide effort to reduce complications, there may still exist dilemmas and inter-institutional differences in its interpretation and application. In some cases, it is difficult to identify the origin of intraabdominal infection as POPF or another cause. We have a policy of drain management to perform an exchange procedure under fluorography on POD 7–10 in cases in which signs of infection are observed in the drainage fluid. Patients who underwent exchange procedure were considered to be grade B, even if the true origin was unclear. Our patient population had a relatively low rate of reoperation (1.0 %), 30-day readmission (2.5 %), and mortality (0.6 %).[1,30,31] Aggressive management to obtain effective drainage was given priority to reduce septic and lethal complications in our institution.

There are some limitations to our study. First, although we tried to standardize the surgical management in this single institution study and identify objective preoperative predictors of POPF, this study should be reproduced. Second, the shape of the actual surgical stump is not exactly elliptical, and that of the MPD is not a circle. The pancreatic parenchymal area at the resection site calculated on the basis that schematic configuration did not express POPF risk as accurately as did parenchymal thickness. The schematic pancreatic configuration was a good indicator of the risk of clinically relevant POPF; however, a volumetric imaging modality may have superiority in meticulous evaluation of the pancreatic configuration and volume.[32,33] Last, in cases in which the extent of tumor was beyond expectation, remeasurement by MDCT should be performed at the modified resection site intraoperatively, although these cases were rare. In fact, in most cases (85.5 %), the pancreas was divided at the PV/SMV level, which was consistent with the assessment by preoperative MDCT. Imaging modalities that facilitate more convenient and precise rendering ability and reflect the histopathological findings and function of the remnant pancreas are anticipated in the near future.

Appropriate surgical technique and perioperative management as well as understanding accurate risk factors are mandatory to reduce POPF. Efforts to reduce the incidence of POPF have encompassed various modifications of the anastomotic technique and pharmacological measures, pancreaticogastrostomy or pancreaticojejunostomy, duct-to-mucosa, invagination, the use of stents, internal or external drainage, application of topical agents to the anastomotic site, placement of an autologous graft such as omentum or falciform ligament on the anastomotic site, and prophylactic administration of somatostatin or its analog.[16,34–38] Preoperative patient stratification using accurate risk factors may lead to careful management in high-risk patients, and well-designed surgical trials can be exploited to improve the surgical technique and perioperative management. Pancreatic configuration data based on preoperative MDCT may be useful to evaluate the risk of POPF accurately, simply, and objectively. In the future, we believe that the reconstruction technique should be tailored to the individual patient according to the definitive risk of POPF.

## Conclusions

MPDd and parenchymal thickness were identified as independent risk factors for clinically relevant POPF after PD, based on a schematic understanding of the pancreatic configuration. These parameters were assessed by preoperative MDCT in a simple and objective way, and the prognostic value was comparable to that of other preoperative, intraoperative, and even postoperative risk factors. The combination of MPDd<2 mm and parenchymal thickness≥8 mm was significantly associated with clinically relevant POPF, with high accuracy.

**Conflict of interest** None

**Sources of funding for research and/or publication** None

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Original Paper

# Infection Control for Prevention of Pancreatic Fistula after Pancreaticoduodenectomy

*Shin Kobayashi, Naoto Gotohda, Yuichiro Kato, Shinichiro Takahashi, Masaru Konishi and Taira Kinoshita*

Department of Surgical Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Corresponding author: Naoto Gotohda, 6-5-1, Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan; Tel.: +81-4-7133-1111, Fax: +81-4-7131-4724; E-mail; ngotohda@east.ncc.go.jp

**Key Words:** Pancreaticoduodenectomy; Soft pancreas; Pancreatic fistula; Infection control.

**ABSTRACT**

**Background/Aims:** Effectiveness of infection control for prevention of pancreatic fistula (PF) after pancreaticoduodenectomy (PD) is not clear. We analyzed the impact of infection on the development of PF and examined the effect of enhanced infection control to prevent PF. **Methodology:** Amylase level (D-amylase) and bacterial culture (D-culture) of drainage fluid were evaluated on POD 1, 3, 5 and 7, in 90 consecutive patients with soft pancreas who underwent PD. The study period was divided into two periods. The relationship between D-amylase and D-culture was examined, and the clinicopathological factors predicting PF were analyzed in the first period. Then, anti-infection measures were introduced in the second period, and the effect of enhanced infection control was examined. **Results:** Twenty-nine out of 58 patients (50.0%) developed PF in the first period. D-amylase were higher in patients with D-culture infection than in those without it ($p<0.05$). D-amylase above 10,000IU/L on POD1 and D-culture infection on POD3 were independent predictive factors for PF by multivariate analysis ($p<0.01$). After introduction of enhanced infection control in the second period, four out of 32 patients (12.5%) developed PF. The rates of PF and D-culture infection were significantly reduced ($p<0.05$). **Conclusions:** Infection of drainage fluid is related to an increased level of amylase, resulting in PF. Enhanced infection control can effectively prevent PF after PD in soft pancreas.

## INTRODUCTION

Although the mortality after pancreaticoduodenectomy (PD) has decreased to 1-2% with the recent advancement of surgical techniques, perioperative management, and centralization of case volumes, the morbidity still remains as high as 30-60% (1-4). Among those morbidities, pancreatic fistula (PF) is the most feared complication, which can potentially lead to devastating consequences (5-9). Soft pancreas is one of the most important risk factors for PF, and its rate was reported to be as high as 21-32% in soft pancreas (8,10-14). It is well recognized that septic sequelae of PF, such as abscess and pseudoaneurysm, lead to longer hospitalization and even death (5-9). Recently, it was reported that intraperitoneal infection is related to the occurrence of PF. Pratt *et al.* suggested that intraperitoneal infection was a key factor in late-onset PF (7). However, it has not been clear when intraperitoneal infection occurs and how it affects the development of PF. Role of infection control for prevention of PF remained unclear.

We analyzed the impact of infection on the development of PF and examined the effect of enhanced infection control to prevent PF. The aims of this study were: i) to clarify when infection of drainage fluid occurs and how it affects the development of PF; ii) to examine predictive factors for PF; and iii) to verify the effect of enhanced infection control for prevention of PF.

## METHODOLOGY

From July 2008 to December 2010, 142 consecutive patients underwent PD at the Department of Surgery, National Cancer Center Hospital East (NCCHE), Kashiwa, Japan. Among those 142 patients, 90 patients with soft pancreas were enrolled in this study. The texture of the pancreas, either soft or hard, was judged from the intraoperative findings by the operating surgeons. The study period was divided into two periods. The first period was from July 2008 to December 2009, and the second period was from January 2010 to December 2010. Amylase level in drainage fluid (D-amylase) and bacterial culture of drainage fluid (D-culture) were evaluated on postoperative day (POD) 1, POD3, POD5 and POD7. The relationship between D-amylase and D-culture was examined, and the predictive factors for PF were analyzed in the first period. Then, anti-PF measures that were determined according to the predictive factors in the first period were introduced in the second period, and the rates of PF were compared between the two periods. The study protocol was approved by the institutional review board of the National Cancer Center Hospital.

### Surgical technique

For PD, subtotal stomach-preserving pancreaticoduodenectomy (SSpPD) was the procedure of choice at NCCHE. Reconstruction was performed by a modification of the method described by Child (15), with pancreatojejunal anastomosis performed by duct-to-mucosa, end-to-side pancreaticojejunostomy. Pancreatic duct-to-jejunal mucosal anastomosis was performed with 8 to 16 interrupted sutures using monofilament slowly absorbable material (5-0 PDS-II, Johnson&Johnson Co., USA, or 5-0 Maxon, Covidien Co., USA). The pancreatic stump and jejunal seromuscular layer were closely approximated with 3 to 6 interrupted sutures using monofilament non-absorbable material (3-0 Nespylene, Alfresa Pharma Co., Japan) as described

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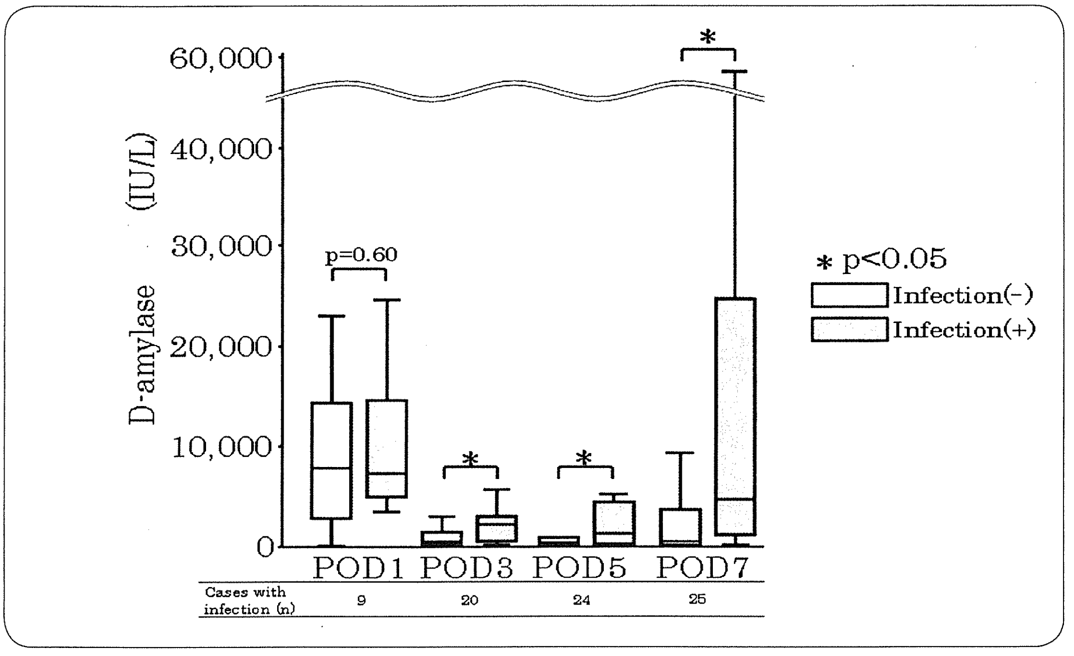


**FIGURE 1.** Amylase level in drainage fluid with and without infection. D-amylase in patients with D-culture infection was significantly higher than that without infection from POD3 to POD7 ($p$<0.05).

**TABLE 1.** ISGPF grade of pancreatic fistula.

| Variables | Fistula (-) | Grade A | Grade B | Grade C |
|---|---|---|---|---|
| Drain amylase | ≦3 x serum value | >3 x serum value | >3 x serum value | >3 x serum value |
| Clinical condition | Well | Well | Often well | Ill appearance/bad |
| Specific treatment* | No | No | Yes/No | Yes |
| US/CT | Negative | Negative | Negative/positive | Positive |
| Drainage≧3wks | No | No | Usually yes | Yes |
| Signs of infection | No | No | Yes | Yes |
| Readmission | No | No | Yes/No | Yes/No |
| Sepsis | No | No | No | Yes |
| Reoperation | No | No | No | Yes |
| Death | No | No | No | Yes |

ISGPF: International Study Group of Pancreatic Fistula; US: Ultrasound; CT: Computed Tomography; *Specific treatment includes parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.
(Adapted with permission from Bassi C, et al. (5))

by Kakita *et al.* (16) a 6-Fr polyethylene tube was placed in the main pancreatic duct as a lost stent. Abdominal lavage was performed with 3,000mL warm saline after digestive tract reconstruction.

### Surgical drains

Two round closed suction drains, either 19-Fr or 24-Fr depending on the operator's preference, were placed near the pancreatic and biliary anastomoses. Drains were usually removed on POD7 in the first period if the drainage fluid was clear and D-amylase was less than three times the upper limit of normal serum amylase level.

### Evaluation of pancreatic fistula

Output of closed suction drains was recorded every day, and any measurable amount, usually above 2-3mL per day, was evaluated for D-amylase and D-culture on POD1 to POD7. The presence and the grade of PF were evaluated according to the classification by the International Study Group of Pancreatic Fistula (ISGPF) (5). Details of the ISGPF classification are described in **Table 1.** The upper limit of serum amylase level at NCCHE

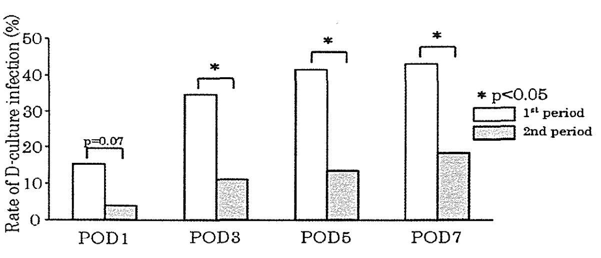


**FIGURE 2.** Rate of drainage fluid infection in two periods. The rate of D-culture infection was significantly reduced in the second period from POD3 to POD7 ($p<0.05$).

**TABLE 2.** Patient characteristics.

| Variables | | 1st period (n=58) | | 2nd period (n=32) | | *p* |
|---|---|---|---|---|---|---|
| **Age** | years* | 70 | (24-87) | 66 | (32-83) | 0.08 |
| **Gender** | male/female | 34 / 24 | | 20 / 12 | | 0.54 |
| **Preoperative biliary drainage** | yes/no | 27 / 31 | | 16 / 16 | | 0.46 |
| **Preoperative bile infection** | yes/no | 17/ 41 | | 9 / 23 | | 0.55 |
| **Indications for operation** | n | | | | | 0.36 |
| Pancreatic origin | | 24 | (41.4%) | 13 | (40.6%) | |
| *Ductal adenocarcinoma* | | 10 | (17.3%) | 6 | (18.8%) | |
| *IPMN* | | 9 | (15.6%) | 5 | (15.6%) | |
| *Neuroendocrine tumor* | | 2 | (3.4%) | | | |
| *SPT* | | 2 | (3.4%) | 2 | ( 6.3%) | |
| *Pancreatitis* | | 1 | (1.7%) | | | |
| Bile duct origin | | 21 | (36.2%) | 12 | (37.5%) | |
| *Bile duct adenocarcinoma* | | 19 | (32.8%) | 12 | (37.5%) | |
| *Benign stricture* | | 2 | (3.4%) | | | |
| Gallbladder adenocarcinoma | | 3 | (5.2%) | 1 | ( 3.1%) | |
| Ampullary adenocarcinoma | | 6 | (10.4%) | 3 | ( 9.4%) | |
| Duodenal adenocarcinoma | | 2 | (3.4%) | 2 | ( 6.3%) | |
| Gastric adenocarcinoma | | 2 | (3.4%) | 1 | ( 3.1%) | |
| **Type of procedure** | n | | | | | 0.31 |
| SSpPD | | 47 | (81.0%) | 28 | (87.5%) | |
| PD | | 7 | (12.1%) | 4 | (12.5%) | |
| HPD (SSpPD+hepatectomy) | | 4 | (6.9%) | | | |
| **Operative time** | minutes* | 350 | (202-562) | 344 | (250-717) | 0.90 |
| **EBL** | mL* | 857 | (246-3281) | 788 | (161-4884) | 0.33 |
| **Blood transfusion** | yes/no | 14 / 44 | | 5 / 27 | | 0.25 |
| **Pancreatic duct size** | n | | | | | 0.41 |
| <3mm | | 39 | (67.2%) | 20 | (65.6%) | |
| ≧3mm | | 19 | (32.8%) | 12 | (37.5%) | |

*Numerical variables are presented as median (range); IPMN: Intraductal Papillary Mucinous Neoplasm; SPT: Solid Pseudo-Papillary Tumor; SSpPD: Subtotal Stomach-Preserving Pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; HPD: Hepato-Pancreaticoduodenectomy; EBL: Estimated Blood Loss.

**TABLE 3. Pathogens cultured from drainage fluid in 1st period.**

| Pathogen | Patients (n) |
|---|---|
| *Enterococcus faecalis* | 8 |
| *Klebsierra pneumoniae* | 8 |
| *Pseudomonas aeruginosa* | 4 |
| *Enterobacter cloacae* | 3 |
| *Enterococcus faecium* | 3 |
| *Escherichia coli* | 3 |
| *Enterobacter aerogenes* | 2 |
| *Staphylococcus aureus* | 1 |
| 11 other organisms | 11 |

PF: Pancreatic Fistula; EBL: Estimated Blood Loss; PV: Portal Vein.

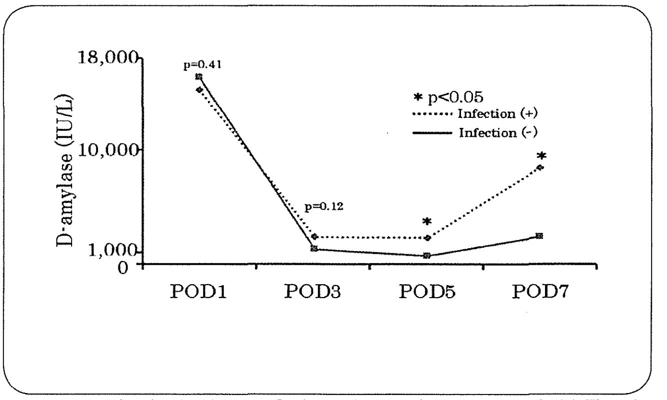


**FIGURE 3.** Amylase level in drainage fluid according to infection status on POD3. The subsequent change in amylase level in patients with D-amylase above 10,000IU/L on POD1 is shown. Amylase level in patients with infection was significantly higher from POD5 to POD7 ($p$<0.05).

was 125IU/L. In this study, any case in which drains were not removed by POD10 because of amylase-rich drainage fluid was considered as grade B irrespective of the drainage volume and length of drain insertion. Grades B/C PF were considered clinically important and were investigated in this study. Neither prophylactic nor therapeutic octreotide was administered for the management of PF.

**Bacterial culture of drainage fluid (D-culture)**

D-culture was performed on POD1, POD3, POD5 and POD7. On each day, a fresh specimen was aspirated from the drainage tube with sterile technique and incubated on sheep's agar plates for 48 hours. Any bacteria that formed $10^5$ colony forming units /mL were analyzed in the present study.

**Other perioperative management**

Preoperative biliary drainage was performed either by percutaneous transhepatic cholangio-drainage (PTCD), percutaneous transhepatic gallbladder drainage (PTGBD), or endoscopic naso-biliary drainage (ENBD), when the serum level of total bilirubin exceeded around 5mg/dL or depending on the operator's preference. Preoperative bile culture was performed, if possible. Prophylactic antibiotics, usually one gram of cefazolin (CEZ), were given to all patients before incision and every three hours only during operation in the first period. They were changed to an appropriate alternative in accordance with the bacteria, if any, found in the preoperative biliary drainage fluid. Other perioperative infection control was performed according to the guidelines issued by the Centers for Disease Control in the United States (17). Oral intake was started with clear liquid on POD1 and soft solid food on POD3. Patients were discharged home after oral intake was fully tolerated and all drains were removed.

**Statistical analysis**

All data were recorded in a database for analysis (Microsoft Excel and SPSS 11.0 J for Windows). Differences between numerical variables were analyzed by Mann-Whitney U-test and those between categorical variables were analyzed by $\chi^2$ statistics. Multivariate analysis was performed with logistic regression test. A $p$ value of less than 0.05 was considered significant.

**RESULTS**

Ninety consecutive patients with soft pancreas, 58 patients in the first period and 32 patients in the second, were enrolled in the present study. Patient characteristics in each period are described in **Table 2**. None of the patient characteristics was statistically different between the two periods.

In the first period, grade B/C PF was found in 29 patients (50.0%); grade B in 26 patients (44.8%) and C in three patients (5.2%). Median value of D-amylase in the first period was 7843IU/L on POD1, 764IU/L on POD3, 306IU/L on POD5, and 1204IU/L on POD7. The number of patients with D-culture infection was nine on POD1, 20 on POD3, 24 on POD5, and 25 on POD7. Pathogens found in D-culture are shown in **Table 3**. Comparison of D-amylase in patients with and without D-culture infection is shown in **Figure 1**. D-amylase was significantly higher in patients with D-culture infection than in those without infection on POD3 to POD7 ($p$<0.05), although the difference was not significant on POD1 ($p$=0.60). Median value of D-amylase decreased from POD1 to POD5 and increased on POD7 irrespective of D-culture infection, but the increase from POD5 to POD7 in patients with D-culture infection was about 30-fold higher than that in those without infection. The only risk factor for increased D-amylase on POD7 from POD5 was D-culture infection on POD7 (odds ratio (OR): 7.2, 95% confidence interval (CI): 1.4-37.4).

To examine predictive factors for PF, clinicopathological factors within five postoperative days were analyzed in the first period (**Table 4**). The cut-off value of D-amylase was established by drawing the receiver operating characteristic curve. D-culture infection on POD3 and D-amylase above 10,000 IU/L on POD1 were independent predictive factors by multivariate analysis (OR: 74.6% and 35.9, 95% CI: 6.4-873 and 3.9-327, respectively). Other factors, such as non-dilated main pancreatic duct, were not significant predictors of PF. Among 36 patients with one or two predictive factors present, 28 patients developed PF, while only one patient developed PF among those without any of the two factors (sensitivity: 96.6%, specificity: 72.4%, positive predictive value: 77.8%, negative predictive value: 95.5%) The only case that developed grade B PF in the absence of the two factors was managed conservatively.

According to the aforementioned results in the first period, we introduced anti-infection measures in the second period (**Table 5**). The number of patients with D-culture infection was one on POD1 (3.1%), four on POD3 (12.5%), five on POD5 (15.6%), and six on POD7 (18.8%), which were significantly fewer than those in the first period on POD3 to POD7 ($p$<0.05) (**Figure 2**).

**TABLE 4.** Analysis of clinicopathological factors predicting pancreatic fistula in 1st period.

| Variable | PF (n=29) | | No PF (n=29) | | *p* value | | Odds ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | univariate | multivariate | |
| Age ≧75 yr | 8 | (93.8%) | 9 | (79.6%) | 0.50 | | |
| Male | 19 | (65.6%) | 15 | (57.1%) | 0.21 | | |
| Preoperative biliary drainage | 12 | (43.8%) | 15 | (59.2%) | 0.30 | | |
| Preoperative bile infection | 10 | (34.5%) | 7 | (24.1%) | 0.28 | | |
| Pancreatic origin | 9 | (37.5%) | 15 | (71.4%) | 0.09 | | |
| Pancreatic ductal adenocarcinoma | 3 | (15.6%) | 7 | (53.1%) | 0.15 | | |
| Operative time ≧360min | 16 | (53.1%) | 10 | (51.0%) | 0.09 | | |
| EBL ≧1200mL | 10 | (6.3%) | 4 | (14.3%) | 0.06 | | |
| Blood transfusion (+) | 7 | (25.0%) | 7 | (32.7%) | 0.62 | | |
| Pancreatic duct ≧3mm | 6 | (28.1%) | 13 | (65.3%) | 0.04 | 0.33 | |
| PV resection | 2 | (6.3%) | 3 | (28.6%) | 0.50 | | |
| Other organ resection | 3 | (9.4%) | 1 | (2.0%) | 0.31 | | |
| D-amylase POD1 ≧10,000IU/L | 21 | (65.6%) | 6 | (12.2%) | < 0.001 | 0.001 | 35.9 (3.9-327) |
| D-amylase POD3 ≧1000IU/L | 20 | (68.8%) | 7 | (14.3%) | 0.001 | 0.59 | |
| D-amylase POD5 ≧1000IU/L | 14 | (53.1%) | 4 | (8.2%) | 0.003 | 0.35 | |
| D-culture infection POD1 (+) | 8 | (25.0%) | 1 | (2.0%) | 0.01 | 0.71 | |
| D-culture infection POD3 (+) | 18 | (59.4%) | 2 | (6.1%) | < 0.001 | 0.001 | 74.6 (6.4-873) |
| D-culture infection POD5 (+) | 20 | (71.9%) | 4 | (16.3%) | < 0.001 | 0.32 | |

PF: Pancreatic Fistula; EBL: Estimated Blood Loss; PV: Portal Vein.

**TABLE 5.** Anti-infection measures that introduced in the 2nd period.

1) Prophylactic antibiotics were changed from CEZ to PIPC.

2) PIPC was administered during and after operation until POD3.

3) Volume of intraperitoneal lavage before fascial closure was increased from 3000mL to at least 5000mL.

4) Surgical drains were removed on POD5/6 if D-amylase on POD1 was below 10,000IU/L and a negative result of D-culture on POD3 was confirmed after 48 hours of incubation.

CEZ: Cefazolin; PIPC: Pentocillin; POD: Postoperative Day; D-Amylase: Amylase Level in Drainage Fluid; IU/L: International Units Per Liter; D-Culture: Bacterial Culture of Drainage Fluid.

Length of surgical drain placement was significantly shortened in the second period from the first period (median; 6 *vs.* 13 days, $p<0.01$). Subsequently, grade B PF was identified in four patients (12.5%) while no patient developed grade C PF in the second period. The rate of PF significantly dropped from 50.0% in the first period to 12.5% in the second period ($p<0.01$) (**Table 6**). During the same period, overall PF rates including both soft and hard pancreas significantly dropped from 39.5% (32/81) to 8.3% (5/60) ($p<0.01$). Postoperative hospitalization was significantly shorter in the second period than in the first period (13 days *vs.* 24 days, $p<0.01$). Other postoperative complications are described in **Table 7**. Only one patient required re-admission, for general malaise. There was one death (1.1%) throughout the entire period, due to liver failure after transarterial embolization for pseudo-aneurysm rupture of the common hepatic artery.

## DISCUSSION

It is widely accepted that infection is related to PF. However, bacterial cultures of drainage fluid have been evaluated only at drain removal or after the development of PF (18-20). It has not been clear when infection occurs

**TABLE 6.** Rate of pancreatic fistula in two periods.

| | 1st period (n=58) | 2nd period (n=32) | p |
|---|---|---|---|
| **Pancreatic fistula** | 29 (50.0%) | 4 (12.5%) | <0.01 |
| Grade B | 26 | 4 | |
| Grade C | 3 | 0 | |

**TABLE 7.** Other postoperative complications.

| | 1st period (n=58) | 2nd period (n=32) | p |
|---|---|---|---|
| Abdominal fluid collection / abscess | 15 (25.9%) | 4 (12.5%) | 0.26 |
| With antibiotics only | 12 | 4 | |
| With IVR drainage | 3 | 0 | |
| Wound infection / fat lysis | 13 (22.4%) | 2 ( 6.3%) | 0.04 |
| Biliary anastomosis failure | 2 (3.4%) | 0 | 0.58 |
| Pseudo-aneurysm rupture | 3 (5.2%) | 0 | 0.44 |
| Pseudo-membranous colitis | 3 (5.2%) | 0 | 0.44 |
| Liver abscess | 2 (3.4%) | 0 | 0.58 |
| Delayed gastric emptying | 2 (3.4%) | 0 | 0.58 |

IVR: Interventional Radiology.

and how infection affects the development of PF. In this analysis, D-amylase in patients with D-culture infection was significantly higher than that without infection from POD3 to POD7 ($p<0.05$), and the increase in D-amylase from POD5 to POD7 in patients with D-culture infection was about 30-fold higher than that without infection. Pratt *et al.* reported that the presence of infection was a key factor in development of late-onset PF (7), and in our study, D-culture infection on POD7 was the only risk factor for an increase in D-amylase on POD7 from POD5 (OR: 4.4, 95% CI: 1.2-15.6). Our data clearly demonstrated that infection of drainage fluid was related to an increased level of amylase.

In this analysis, D-culture infection on POD3 was the strongest predictive factor for PF in the first period (OR: 74.6, 95% CI: 6.4-873). *Enterococcus faecalis/faecium, Klebsierra pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae/aerogenes* and *Escherichia coli* were the seven most frequent bacteria, accounting for 53.4% of pathogens and 79.3% of cases of D-culture infection in the first period. These enteric organisms were consistent with the results of previous studies (18,20), and were mostly resistant to CEZ. Biliary organisms found after PD were also similar to the above results (21). Preoperative bile infection was significantly related to D-culture infection on POD3 and POD5 in the first period ($p<0.05$). Therefore, we considered that intraoperative bacterial contamination was the main source of D-culture infection, and introduced anti-infection measures in the second period (**Table 5**). The rate of D-culture infection significantly dropped in the second period from POD3 to POD7 ($p<0.05$) (**Figure 2**), and the rate of PF was significantly lower in the second period than in the first period (12.5% *vs.* 50.0%, $p<0.01$) (**Table 5**). A change in D-amylase according to the status of D-culture infection on POD3 was found in patients with D-amylase above 10,000IU/L on POD1 (**Figure 3**). D-amylase in patients with infection significantly increased, with the development of PF, while D-amylase in patients without infection sharply dropped after POD3. It was thus clearly demonstrated that infection of drainage fluid is a key factor in the development of PF, and enhanced infection control effectively prevented PF in the second period. Based on these results, we speculate that there are two physiopathological mechanisms of development of PF in soft pancreas. One is a transient leak, probably from a branched pancreatic duct in the stump, which is manifested as D-amylase above 10,000IU/L on POD1. The other is failure of closure of branched pancreatic ducts due to infection, which presents as D-culture infection on POD3 and a subsequent high D-amylase. Bacterial contamination of surgical field was found to be a risk factor of anastomotic leakage in colorectal surgery (22,23). The same seemed to be true of pancreatojejunal anastomosis. Enhanced infection control effectively minimized the impact of bacteria in the early postoperative period and later prevented the development of PF.

As for the length of surgical drain placement, it was significantly shorter in the second period than in the first period ($p<0.01$). Kawai *et al.* reported that early removal of surgical drains on POD4 prevented infectious complications after PD (18). Our criterion to remove surgical drains on POD5/6 seemed to effectively minimized the occurrence of infectious complication and the development of PF. At the same time, we did not observe any intra-abdominal abscess that required IVR drainage in the second period. Early drain removal on POD4 in all patients required subsequent IVR drainage of intra-abdominal abscess in 7.4% of patients after PD (2). Our enhanced infection control and selective drain removal policy effectively minimized infectious complications as well as prevented subsequent intra-abdominal abscess drainage. We consider that the status of D-culture infection is the critical factor in the management of PF and advocate selective early drain removal policy.

This analysis has several limitations. It was a single institutional study and the study population was not large. Although the surgical indications, procedures and perioperative management were similar among high-volume centers, the details differed among centers and even among patients. Our results need to be verified in a multi-institutional setting. However, these limitations do not preclude the importance of the present study since our findings were demonstrated with statistical significance. A future perspective is to conduct a prospective multi-institutional study to verify the impact of infection on the development of PF and the effect of infection control for prevention of PF after PD in soft pancreas.

In conclusion, the present study has several important findings: i) Infection of drainage fluid is related to an increased level of amylase; ii) D-amylase above 10,000IU/L on POD1 and D-culture infection on POD3 were independent predictive factors for PF. A transient leak probably from a branched pancreatic duct in the stump and failure of closure of branched pancreatic ducts due to infection are two possible physiopathological mechanisms for the development of PF; iii) surgical drains can be selectively removed early in the absence of these two factors; and iv) enhanced infection control can effectively prevent PF after PD.

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Original Paper

# Surgical Management for the Reduction of Postoperative Hospital Stay following Distal Pancreatectomy

*Kiyoshi Yoshikawa, Masaru Konishi, Shinichiro Takahashi, Naoto Gotohda, Yuichiro Kato and Taira Kinoshita*
Department of Hepato-Biliary and Pancreatic Surgery, National Cancer Center East Hospital, Chiba, Japan
Corresponding author: Masaru Konishi, MD, PhD, Hepato-Biliary and Pancreatic Surgery Division, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa-shi, Chiba, 277-8577, Japan
Tel: +81471331111, Fax: +81471314724, E-mail: mkonishi@east.ncc.go.jp

**KEY WORDS:**
Distal pancreatectomy, Closed active drain, Pancreatic fistula

## ABSTRACT

**Background/Aims:** Pancreatic fistula remains a major cause of postoperative morbidity in patients undergoing pancreatectomy and is generally difficult to cure. None of the several surgical techniques and devices available for managing pancreatic remnant have been clinically evaluated.
**Methodology:** We retrospectively reviewed medical records of 120 consecutive patients who underwent distal pancreatectomy at our institution between October 1992 and September 2009. Furthermore, we divided these cases into 3 periods based on 2 points at which we changed our surgical strategy. One was September 2004, when we introduced a stapling technique for managing remnant pancreas. The other was November 2006, when we started using a closed active drain. We evaluated the incidence of pancreatic fistula, risk factors for its development, and our strategy in the perioperative period.
**Results:** The overall and clinical pancreatic fistula rates gradually decreased but were not significant. The persistent drainage period gradually reduced from 19 days to 8 days ($p$=0.071) over a time period. Postoperative hospital stay was significantly reduced from 24 days to 14 days ($p$=0.026).
**Conclusions:** Utilization of a stapling technique and closed active drain significantly reduces postoperative hospital stay.

## INTRODUCTION

Pancreatic resection, including pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), is being increasingly used in the management of benign and malignant neoplasms, chronic pancreatitis, and trauma because it provides a reliable treatment option with favorable outcomes (1). Over the last 2 decades, advances in operative techniques and perioperative management have led to a substantial decrease in mortality associated with DP. However, the morbidity associated with DP remains substantial (2). Similar to other institutions, we have modified our management of pancreatic remnant and postoperative drainage. Here, we sought to evaluate the incidence of, and attempted to identify the risk factors for, the development of pancreatic fistula (PF) in a consecutive series of patients undergoing DP at a single institution. Other complications, such as delayed gastric emptying (DGE) and intra-abdominal abscess, were also assessed.

## METHODOLOGY

We retrospectively reviewed 120 consecutive patients who underwent DP for pancreatic disease at our institution between October 1992 and September 2009. Patients undergoing combined pancreatic resection with gastrectomy were excluded from the analysis. Demographic data, intraoperative factors, and the clinical course were documented for each patient.

Complications were classified according to the criteria of Dindo *et al.* (3) and grade II or greater complications were regarded as clinical complications. The definition and grading system for PF followed the International Study Group of Pancreatic Fistula (ISGPF) criteria (4). DGE was defined in accordance with the International Study Group of Pancreatic Surgery classification (5).

### Surgical procedure

From 1992 to 1999, we used conventional techniques for pancreatic resection that included the use of a knife for cutting the pancreatic parenchyma; the remnant pancreatic parenchyma was closed using a fish-mouth closure. From 1999, we started using an ultrasonically activated device (USAD; Harmonic ACE™; Ethicon Endo-Surgery Inc., Cincinnati, OH, USA) to transect the pancreatic parenchyma. Ligation of the main pancreatic duct was performed when possible. Penrose drains were also placed near the pancreatic remnant and left subphrenic space. Since 2004, we have routinely used a Linear Stapler (LS) (PROXIMATE TLH Linear Stapler 60mm, Johnson & Johnson Medical, Ethicon, Tokyo, Japan). Ligation of the main pancreatic duct was not generally performed and was decided by the surgeon. From November 2006, we initiated routine placement of a closed active drain (Channel drain; Bard, Bard Medical Division, Georgia, USA) near the pancreatic remnant and left subphrenic space.

For invasive ductal carcinoma, extended lymphadenectomy, including regional (N1) and peripancreatic (N2) lymph node dissection based on the Japanese Classification of Pancreatic Cancer (6), was performed with DP. Combined resection of the portal vein and retroperitoneal structures, including the left adrenal gland, Gerota's fascia, and para-aortic lymph nodes (N3), was also performed if curative resection was possible.

### Checking the amylase level of drain fluid, drain cultures

The amylase level of drain fluid was checked in all cases except for 8 between the 3rd and 7th postoperative day, as recommended by ISGPF. We also prospectively checked drain cultures from the 1st, 3rd, 5th and 7th postoperative days in 29 consecutive cases from April 2008 (provided the drain was persistent). After the 7th postoperative day, cultures were only checked when required by the doctor on call.

### Three-period division and exclusion criteria

We divided the 120 consecutive patients into 3 periods based on the points at which we changed our surgical strategy. The first group included 45 patients who underwent operations from September 1992 to September 2004. In these patients, the pancreatic parenchyma was transected using conventional procedures or USAD techniques. The second group included 25 patients who underwent DP from September 2004 to November 2006 in whom LS was routinely used. The third group included 50 patients who underwent DP from 2006 to 2009 in whom a closed active drain was inserted.

In the 1992-2004 series, although conventional and USAD techniques were usually performed, the stapling technique was used in 5 cases to transect the pancreatic parenchyma. Since 2004, the pancreatic remnant has been managed by conventional fish-mouth closure or USAD techniques if the line of resection is close to the resected tumor or gastroduodenal artery or when safe insertion of LS is difficult. This was the case in 17 patients. A closed active drain was inserted in 3 patients from the 2004–2006 series. These patients were excluded from this study as the standard procedure was not followed.

### Statistical analysis

Statistical analysis was performed using SPSS 11.5J statistical software (Chicago, IL, USA). Comparison between the 3 groups was performed using the chi-square and Kruskal–Wallis tests. Univariate analysis was performed with a Mann–Whitney U-test. Statistical significance was defined as $p<0.05$.

## RESULTS

**Table 1** shows the results of univariate and multivariate analyses of our 120 consecutive patients. Multivariate analysis revealed only operation time as a risk factor for clinical PF ($p=0.048$). In terms of other complications, 15 patients developed DGE, 2 developed chylous ascites and 1 sustained gastric perforation due to necrosis of the stomach. **Table 2** shows the entire study group

TABLE 1 Risk Factors for Clinical PF after DP

| | Did not develop PF (n=73) | Clinical PF (n=47) | *p*-value (univariate) | *p*-value (multivariate) |
|---|---|---|---|---|
| Age (years) | 62 (26-84) | 59 (25-83) | 0.994 | |
| Gender (male) | 39 | 24 | 0.800 | |
| BMI[1] | 21.2 (13.5-28.4) | 21.0 (13.9-31.2) | 0.910 | |
| Indication for surgery | | | 0.220 | |
| IDCs[2] | 31 | 30 | | |
| Staple closure | 44 | 19 | 0.034 | 0.227 |
| Ligation of MPD[3] | 33 | 22 | 0.863 | |
| Duration of the operation (min) | 170 (72-583) | 235 (131-630) | <0.001 | 0.048 |
| Blood loss (mL) | 370 (12-5657) | 660 (132-9800) | 0.003 | 0.786 |
| Blood transfusion | 1 | 4 | 0.056 | |
| IORT[4] | 3 | 10 | 0.003 | 0.081 |
| Closed active drain | 37 | 16 | 0.073 | |

[1]Body mass index
[2]Invasive ductal carcinomas
[3]Main pancreatic duct
[4]Intraoperative radiotherapy

divided into 3 time periods based on surgical management. Age, gender, body mass index, indications for surgery and concomitant diabetes mellitus were similar among all 3 groups. **Table 3** shows surgical characteristics and short-term outcomes for these 3 periods. The surgical procedure and other major organ resection rates were similar. Operation time and amount of blood loss were significantly shorter and lesser, respectively, in the 2006-2009 group. No mortalities were reported. The clinical PF rate and period of persistent drainage showed a downward trend. Postoperative hospital stay was significantly shorter in the 2006-2009 group compared with the 1992-2004 group.

## DISCUSSION

Despite significant improvements in the short-term outcome after pancreatic operations, PF fol-

TABLE 2 Study Period Divided into 3 Periods on the Basis of Surgical Management and Patients' Background

| | 1992-2004 (n=40) | 2004-2006 (n=16) | 2006-2009 (n=41) | *p*-value |
|---|---|---|---|---|
| Management of pancreatic remnant | | | | |
| Conventional or USAD[1] | 40 | 0 | 0 | |
| Staple closure alone | 0 | 16 | 39 | |
| Staple and suture closure | 0 | 0 | 2 | |
| Drain | | | | |
| Open method | 40 | 16 | 0 | |
| Closed method | 0 | 0 | 41 | 3 |
| Age (years) | 57.0 (35-78) | 62.5 (26-84) | 64.0 (25-83) | 0.388 |
| Gender (male) | 19 (47.5%) | 8 (50.0%) | 23 (56.1%) | 0.734 |
| BMI | 21.6 (16.2-28.4) | 22.1 (16.8-27.5) | 21.0 (13.5-31.2) | 0.998 |
| Indications for surgery | | | | 0.229 |
| IDCs | 21 (52.5%) | 5 (33.3%) | 23 (56.1%) | |
| Diabetes mellitus | 11 (27.5%) | 2 (12.5%) | 8 (19.5%) | 0.426 |

[1]Ultrasonically activated device

TABLE 3 Surgical Characteristics and Short–Term Outcomes

| | 1992-2004 (n=40) | 2004-2006 (n=16) | 2006-2009 (n=41) | *p*-value |
|---|---|---|---|---|
| Surgical procedure | | | | 0.390 |
| DP with S[1] | 34 | 13 | 37 | |
| SPDP[2] | 3 | 3 | 2 | |
| DP-CAR[3] | 3 | 0 | 2 | |
| Other major organ resection | | | | 0.442 |
| Left adrenal gland | 8 | 1 | 8 | |
| Liver resection | 1 | 0 | 2 | |
| Portal vein | 5 | 0 | 1 | |
| Bowel resection | 2 | 1 | 2 | |
| Other | 7 | 4 | 7 | |
| Duration of surgery (min) | 238.5 (100-630) | 169 (100-322) | 196 (72-583) | 0.010 |
| Blood loss (mL) | 583 (90-9800) | 439 (40-3533) | 319 (12-5657) | 0.034 |
| Blood transfusion | 2 | 1 | 2 | 0.976 |
| IORT | 7 | 0 | 0 | 0.005 |
| Total PF[4] | 31 (77.5%) | 9 (56.3%) | 26 (63.4%) | |
| Clinical PF | 19 (47.5%) | 5 (31.3%) | 12 (29.3%) | |
| Persistent drainage (days) | 19 (4-102) | 12 (3-190) | 8 (3-61) | |
| | | * | | |
| Postoperative hospital stay (days) | 24 (7-128) | 19.5 (8-94) | 14 (8-84) | |
| | | ** | | |

[1]Distal pancreatectomy with splenectomy; [2]Spleen preserving distal pancreatectomy; [3]Distal pancreatectomy with celiac axis resection; [4]Pancreatic fistula. *: 0.071, **: 0.026