Int Surg 2011;**96:**220–227

Complications After Pancreaticoduodenectomy for Pancreatic Cancer: A Retrospective Study

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Postoperative complications, such as pancreatic fistulae, after pancreaticoduodenectomy for pancreatic cancers are associated with surgical outcomes of patients with pancreatic cancers. A total of 160 patients with pancreatic cancers undergoing pancreaticoduodenectomy were retrospectively analyzed. Patients were grouped into a fistulae group (n = 34) and a nonfistulae group (n = 126). The fistulae group had a significantly higher morbidity rate than the nonfistulae group ($P < 0.0001$), but hospital mortality was not different in both groups ($P = 0.481$). There was a higher incidence of intra-abdominal hemorrhage in patients with pancreatic fistulae than in those without fistulae. Two patients in fistulae group underwent reoperation. Patients with pancreatic fistulae had significantly longer hospital stay than those without fistulae. Pancreatic duct diameter, smoking, years of tobaccos consumption, preoperative jaundice, and surgical hours were associated with risk of fistulae on univariate analysis. In a multivariate analysis, diameter of pancreatic duct, surgical hours, and preoperative jaundice were independent risk factors of pancreatic fistulae. Incidence of pancreatic fistulae after pancreaticoduodenectomy is significantly influenced by the size of pancreatic duct diameter, surgical time, and preoperative jaundice. Early postoperative hemorrhage could be cautiously prevented. The survival is not significantly impacted by pancreatic fistulae.

Key words: Pancreatic fistula – Pancreaticoduodenectomy – Pancreatic cancer

Treatment of pancreatic cancer with pancreaticoduodenectomy (PD) is a challenge to many surgeons. The most common complications after PD are the pancreatic fistulae, delayed gastric emptying, and intraabdominal abscess formation. The incidence of pancreatic fistulae is around 5% to 40% of patients after PD, depending on the definition used,[1–3] and is highly associated with operative mortality.[3]

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Many factors influence the outcomes of patients after PD. The way to manage the residual pancreatic stump after pancreatic resection impacts the smooth postoperative recovery. Technical modifications, including pancreatic duct occlusion, placement of internal stent, and pancreaticogastrostomy, do not seem to improve the outcomes in prospective, randomized trials.[4,5] Therefore, it is paramount to search effective surgical techniques to reduce the complications, especially pancreatic fistulae, after PD.[5] We evaluated our clinical data retrospectively to identify the risk factors that influence the morbidity and mortality after PD, especially for pancreatic fistulae.

Patients and Methods

From January 1994 to December 2007, 160 patients underwent elective PD for pancreatic cancer and were pathologically diagnosed as pancreatic adenocarcinoma. The patient medical files were reviewed retrospectively; the interested parameters, including patient demographics, history, surgical types, anastomotic types, and risk factors of pancreatic cancers, pancreatic fistula, and the length of hospital stay, were analyzed. The inclusion condition was that patients treated surgically had a clear pathologic diagnosis of pancreatic cancer, whereas the exclusion condition was that patient had biliary cancer or unclear diagnosis. The definition of pancreatic fistula used was that defined by the International Study Group on Pancreatic Fistula Definition. Pancreatic fistula was further classified into A, B, and C types.[4,7] The numbers of patients in A, B, and C types of fistulae were 9, 23, and 2, respectively. All these 34 patients with pancreatic fistulae were classified as the fistulae group; the remaining 126 patients in nonfistulae group had no pancreatic fistulae. Both groups were compared on age, sex, history of jaundice, use of tobacco and alcohol, weight loss, histologic diagnosis, sizes of the tumors and pancreatic duct, types of pancreatic anastomosis, surgical time, and related complications.

Surgical techniques

All 160 operations underwent standard PD, and the types of anastomosis were decided by surgeons who were in charge of patients on the basis of the specific surgical situation. When the diameter of the pancreatic duct was more than 2 mm and the texture of remnant of pancreatic stump was hardened, an end-to-side, duct-to-mucosa, 3-layer pancreaticojejunal (PJ) anastomosis was performed by using interrupted 6/0 prolene sutures. A polyvinyl catheter with multiple side-holes was put into the pancreatic duct in patients with PJ anastomosis; it was exited via a small enterotomy in the free end of the jejunal loop and went out through a small incision in the abdominal wall. The serosa close to the enterotomy site was stitched to the peritoneum of abdominal wall. Whereas the pancreatic parenchyma was soft and the pancreatic duct was less than 2 mm in diameter, an end-to-end invagination of pancreaticoenterotomy would be performed.

Following PJ anastomosis, an end-to-side, single layer, interrupted hepaticojejunostomy was performed on the same jejunal loop. A gastrojejunostomy was sutured with double layers, continuously hand-sewn in the mucosa layer and interrupted in the serosa layer. A nasogastric tube was placed into the afferent jejunal limb of the anastomosis. In all patients with PD, external drainages were positioned behind pancreatic anastomosis and around the biliary anastomosis and were externalized through a separate stab incision in the anterior abdominal wall. In the jejunal part distal to the pancreatojejunostomy, a depression tube was placed and externalized to reduce the pressure in the jejunum.

Perioperative management

All patients with obstructive jaundice received vitamin K1 preoperatively, and no preoperative percutaneous cholangial drainage was performed. Prophylactic antibiotics and a histamine-2–receptor blocker were administered after operation. Somatostatin or octreotide was only prescribed to patients with pancreatic fistulae or pancreatitis. All patients were managed with intensive care for 1 to 3 days on the basis of the patient's condition. Daily output from all external drainage tubes, especially pancreatic duct catheter, was recorded. The nasogastric tube was secured functionally until appearance of bowel sound that usually occurred on day 3 to 5 after surgery. Patients were fasted at least for 5 days; the realimentation gradually proceeded if no complications occurred.

The peripancreatic drains were generally removed on day 5 if patients recovered uneventfully. Otherwise, they were kept in situ, and a sonography or contrast computed tomography scan might be ordered to examine intra-abdominal conditions. The amylase levels in serum and drain fluid were measured on suspicion of pancreatic fistulae. The

pancreatic duct external drain was connected to a drainage bag with soft easy flow, and no closed suction drain was used. It was remained in situ for about 5 to 6 weeks postoperatively and then was locked prior to removal in outpatient clinic if no evidence of pancreatic fistula occurred. Otherwise, pancreatic fluid was allowed to drain freely until the daily output was less than 5 mL.

Statistical analysis

Continuous data were expressed as means ± SDs. Multivariate analysis of clinical risk factors for pancreatic fistula was performed with pancreatic fistula as independent factor. A χ^2 test (or Fisher's exact test, when appropriate) and the independent *t* tests were used to compare categoric and continuous variables, respectively. Log-rank and Cox regression multivariate analyses were performed. A significant difference was considered when $P < 0.05$. Statistical software (SPSS 13.0 for windows, SPSS, Chicago, Illinois) was used for the statistical analysis.

Results

Of 160 patients undergoing elective PD, 133 underwent PD (83.13%), and 27 underwent pylorus-preserving PD (PPPD; 16.88%). Among 34 patients with pancreatic fistula, the proportions in type A, B, and C were 26.47% (*i.e.*, 9 of 34), 67.65% (*i.e.*, 23 of 34), and 5.88% (*i.e.*, 2 of 34), respectively. Overall, the pancreatic fistula rate was 21.25% (*i.e.*, 34 of 160), and severe pancreatic fistulae (*i.e.*, types B and C) were 15.6% (*i.e.*, 25 of 34). Patients with type A fistulae experienced transient elevation of levels of amylase and recovered uneventfully. Patients with type B pancreatic fistulae had clinical visible leakage, fever, leukocytosis, and long hospital stay, and they required percutaneous drainage of an infected intra-abdominal collection (n = 3). The other patients were treated conservatively with total parenteral nutrition, antibiotics, and somatostatin. Two patients with type C pancreatic fistulae underwent reoperation and finally recovered successfully.

Considering the risk factors for pancreatic cancer, 31.25% (*i.e.*, 50 of 160 patients) had smoked, for a median of 25 years (IQR, 15–30 years), a median of 25 cigarettes each day (IQR, 18.75–30 cigarettes daily) and had a median history of alcohol intake of 100 mL each day (IQR, 50–250 mL daily) for a median of 10 years (IQR, 5–25 years). Twenty-two patients had concomitant diabetes. Table 1 summarizes a comparison of baseline demographics of patients in both groups. No significant differences were found between both groups in age, sex, days of jaundice, consumption of tobacco or alcohol, the presence of comorbid illness, weight loss, and size of tumor mass. Among the results of univariate analysis of factors that might be potentially associated with pancreatic fistulae, 5 factors, including pancreatic duct diameter ($P = 0.000$), smoking ($P = 0.000$), years of tobacco consumption ($P = 0.027$), preoperative jaundice ($P = 0.006$), and surgical hours ($P = 0.005$), were associated with risk of pancreatic fistula on univariate analysis (Table 1). A multivariate analysis entering into these 5 factors showed that diameter of pancreatic duct was the independent risk factor to pancreatic fistula ($P = 0.000$), followed by surgical hours ($P = 0.014$) and preoperative jaundice ($P = 0.02$; Table 2).

Table 3 shows the postoperative outcomes. There was a higher incidence of intra-abdominal hemorrhage in patients with pancreatic fistulae than in those without fistulae (17.6% versus 4%; $P = 0.005$). Of 6 patients with intra-abdominal hemorrhage, 5 patients had gastrointestinal hemorrhage in the fistulae group on day 2, 6, 8, 11, and 23 after surgery, respectively; the hemorrhage came from arterial bleeding posterior wall of stomach (n = 1), stress gastric ulcer (n = 2), gastrointestinal anastomosis and extravasations from surgical edge of stomach (n = 2), and the hemorrhage in 1 patient was secondary to pancreatic fistula and intra-abdominal severe infection. In the nonfistulae group, 5 patients experienced gastrointestinal hemorrhage on the first postoperative day, as bleeding from gastric ulcer (n = 1) and gastrojejunostomy (n = 4) that was sutured by a mechanical stapler. Acute renal failure was developed following massive hemorrhage in 1 patient. Among a total of 11 gastrointestinal hemorrhage occurrences in this series, 5 occurred after mechanical stapler–performed gastrointestinal anastomosis (Table 3). All patients with gastrointestinal hemorrhage were managed with gastroscopy or surgery. Two patients underwent reoperation to control bleeding; the remaining 9 patients were treated conservatively with endoscope.

The morbidity referred all the complications in respective group. The morbidity rates in the fistulae and nonfistulae groups were 55.9% and 11.9%, respectively ($P = 0.000$; Table 3). Three occurrences in each group required reoperation, but the reoperation rate was not significantly different (8.8%

Table 1 Univariate analysis of baseline demographics and risk factors of patients with and without pancreatic fistulae

	Fistulae group (n = 34)	Nonfistulae group (n = 126)	X^2/Z	*P*
Nominal parameter				
Sex			2.251	0.134
Male	24 (70.6)	71 (56.3)		
Female	10 (29.4)	55 (43.7)		
Smoking			14.93	0.000
Yes	16 (47.1)	20 (15.9)		
No	18 (52.9)	106 (84.1)		
Alcohol use			2.068	0.150
Yes	11 (32.4)	26 (20.6)		
No	23 (67.6)	100 (79.4)		
Weight loss			1.13	0.288
Yes	9 (26.5)	3 (18.30)		
No	25 (73.5)	103 (81.7)		
Jaundice			7.481	0.006
Yes	23 (67.6)	52 (41.3)		
No	11 (32.4)	74 (58.7)		
Surgical type			1.333	0.248
PD	31 (91.2)	102 (81)		
PPPD	3 (8.8)	24 (19)		
Anastomotic mode			0.028	0.868
Duct-to-mucosa	29 (85.3)	106 (84.1)		
Invagination	5 (14.70)	20 (15.9)		
Pancreatic stent			0.494	0.781
External	19 (55.9)	62 (49.2)		
Internal	11 (32.40)	48 (38.1)		
Nil	4 (11.8)	16 (12.7)		
Quantitative data				
Age, years, mean ± SD	60.50 ± 10.413	54.98 ± 12.88	5.524	0.023
Days of jaundice, median (IQR)	20 (0–42)	0 (0–36)	−1.842	0.065
Smoking, years, median (IQR)	0 (0–25)	0 (0–10)	4.919	0.027
Alcohol use, years, median (IQR)	0 (0–5.75)	0 (0–5)	0.338	0.561
Diameter of tumor, XXX, mean ± SD	2.59 ± 1.019	2.48 ± 1.01	0.001	0.972
Surgical time, hours, No. (IQR)	8 (6–9)	7 (6–8)	7.715	0.000
Pancreatic duct size, mm, median (IQR)	2 (2–3)	3 (3–4)	33.7	0.000

IQR denotes interquatile range. Data are represented as numbers and percentages; continuous data are shown as mean ± SD, and remaining values are medians with IQR in parentheses.

versus 2.4%; $P = 0.213$). In the fistulae group, the reasons for reoperation included small arterial hemorrhage on posterior wall of stomach on postoperative day 11 (n = 1), complete rupture of pancreatojejunal anastomosis on day 28 after surgery (n = 1), and thrombosis in superior mesenteric artery on day 11 (n = 1). Conversely, indications for reoperation in the nonfitstulae group were gastrojejunostomy outlet limb strangulation and intestinal adhesive obstruction on day 60 after PD (n = 1),

Table 2 Multivariance stepwise logistic analysis of 5 risk factors for pancreatic fistula

Variable	B	SE	Wald	*df*	*P*	Exp(b)
Smoke	0.109	1.163	0.0091	1	0.925	1.116
Years of smoking	0.055	0.042	1.736	1	0.188	1.056
Jaundice	1.717	0.737	5.431	1	0.020	5.571
Operative time, hours	−0.405	0.164	6.071	1	0.014	0.667
Diameter of pancreatic duct, mm	2.204	0.448	24.198	1	0.000	9.062
Constant	−4.224	2.528	2.791	1	0.095	0.015

Table 3 Complications and outcomes after PD

Variable	Fistulae group (n = 34)	Nonfistulae group (n = 126)	χ^2	*P*
Intra-abdominal hemorrhage	6 (17.6)	5 (4)	7.825	0.005
Delayed gastric emptying	4 (11.8)	20 (15.9)	0.105	0.745
Intra-abdominal fungal infection	2 (5.9)	0 (0)	3.497	0.044
Pneumonia	2 (5.9)	1 (0.8)	1.51	0.219
Peritonitis after stent removal	0 (0)	3 (2.4)	0.038	1.0
Gastrojejunostomy obstruction	1 (2.9)	2 (1.6)	0.000	1.0
Wound dehiscence	1 (2.9)	0 (0)	0.497	0.481
Dehiscence of pancreatoenterostinosis	1 (2.9)	0 (0)	0.497	0.481
Acute pancreatitis	1 (2.9)	0 (0)	0.497	0.481
Adhesive intestinal obstruction	0 (0)	1 (0.8)	0.000	1.0
Pharyngeal fungal infection	1 (2.9)	0 (0)	0.497	0.481
Acute renal failure after GI bleeding	0 (0)	1 (0.8)	0.000	1.0
Reoperation	3 (8.8)	3 (2.4)	1.553	0.213
Morbidity	19 (55.9)	33 (26.2)	10.76	0.001
Hospital mortality	1 (2.9)	0 (0)	0.497	0.481

GI, gastrointestinal. Data are number and percentage.

wound dehiscence on postoperative day 2 (n = 1), and hemorrhage from gastrojejunal anastomosis and local ulcer around anastomosis (n = 1). Three patients in the nonfistulae group had regional peritonitis after removal of the pancreatic duct stent; treatments were managed conservatively, and no pancreatic fistulae developed. Incidence of delayed gastric emptying was similar in fistulae group versus nonfistulae group (11.8% versus15.9%; P = 0.745). The other complications in the fistulae group included pneumonia (n = 2), intra-abdominal infection (n = 2), and acute pancreatitis (n = 1).

Hospital mortality was higher in fistulae group than nonfistulae group; however, the difference was not significant [2.94% (1 of 34 patients) versus 0.00%; P = 0.054; Table 3]. In the fistulae group, 1 patient died of peritonitis and hemorrhage secondary to severe pancreatic fistulae. After reoperation on concomitant superior mesenteric artery, 1 patient with pancreatic fistulae refused treatment and was discharged from hospital. Patients with type A pancreatic fistulae had no clinical manifestations (n = 9). Of 24 patients with type B pancreatic fistulae, 2 had severe abdominal fungus infection resulting from pancreatic leakage and long-term use of antibiotics; 1 had pancreatitis and was treated conservatively. The length of hospital stay in patients with pancreatic fistulae was longer than those without pancreatic fistulae (mean ± SD, 26.9 ± 9.2 versus 17.9 ± 5.8; P = 0.000).

Patients were followed up for 4 years. The successful follow up rates were 87.88% (*i.e.*, 29 of 33 patients) in the fistulae group and 73.02% (*i.e.*, 92 of 126 patients) in nonfistulae group. The survival analysis demonstrated that pancreatic fistulae did not impact survival significantly (Fig. 1). Even though survival time in the fistulae group was shorter than in the nonfistulae group, the difference was not significant (mean ± SD, 10.70 ± 1.46 versus 15 ± 1.58; mean ± SD, 15.46 ± 2.18 versus 17.10 ± 1.27; χ^2= 0.312; P = 0.576). Cox regression analysis indicated that pancreatic fistula had no significant impact for the survival (Wald = 0.302; P = 0.582).

Discussion

Radical PD can be achieved in approximately 20% to 25% patients. The postoperative complications, especially pancreatic fistulae, are unavoidable, at around 5% to 45%, and survival of patients with stages I or II disease and with radical resection at 1, 3, and 5 years is around 60%, 25%, and 15%, respectively.[5,8] Therefore, the primary prevention and early diagnosis of pancreatic cancer are important for improving the outcomes of patients. Data in our series indicated that 31.25% patients had consumed a median of 25 cigarettes daily (IQR, 18.75–30 cigarettes daily) for over 20 years and had been addicted to alcohol at median volume of 100 mL daily (IQR, 50–250 mL daily) for a median of 10 years (IQR, 5–25 years). Some patients had abdominal discomfort for as long as 6 months to 1 year and were misdiagnosed as gastritis or pancreatitis; 22 patients had a history of diabetes for 2 to 10 years. If these patients with risk factors of pancreatic cancer, such as advanced age, jaundice, diabetes, or chronic pancreatitis, were scrutinized

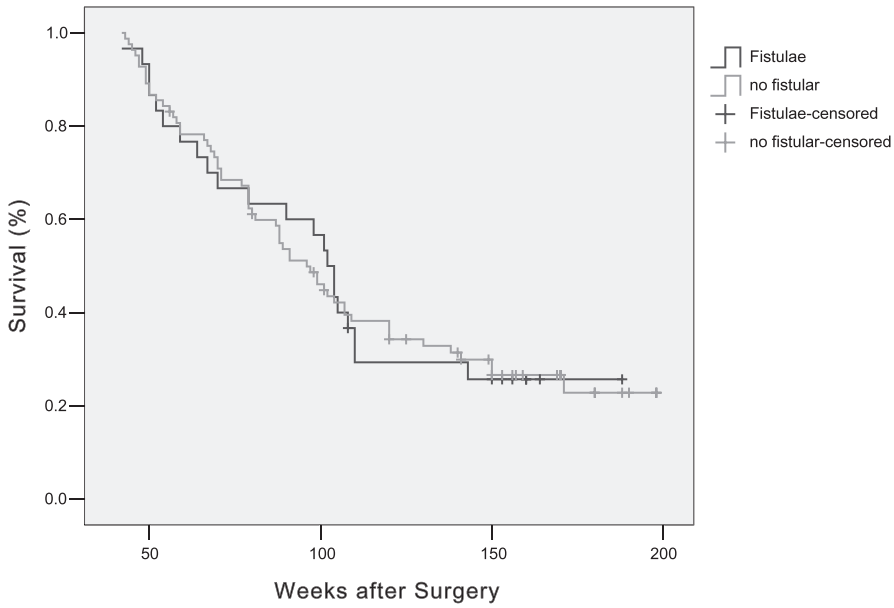

Fig. 1 The survival of patients with pancreatic cancers was not significantly impacted by pancreatic fistulae.

for pancreatic cancer earlier, the outcomes of treatment could have been better.

Main complications following PD for pancreatic cancers are pancreatic fistulae, gastrointestinal hemorrhage, and secondary sepsis.[1–4,9] The risk factors related to pancreatic fistula include technical skills of the surgeon,[10] elderly age (*i.e.*, older than 70 years), preoperative jaundice, operational blood lose, use of stent, pancreatic texture, and diameter of pancreatic duct.[4,9] The variance analysis in our study manifested that tobacco consumption, time of use tobacco, preoperative jaundice, surgical hours, and diameter of pancreatic duct had significantly impacted on the incidence of pancreatic fistulae. A further analysis with Cox regression showed that the diameter of pancreatic duct was the most significant risk factor for pancreatic fistulae, followed by operative time and preoperative jaundice. It is worthy to note that stents were used not only in end-to-side anastomosis, where the pancreatic duct was large, but also in the invagination anastomosis, where the duct size was small; the option of a type of anastomosis did not represent a confounding factor to the duct size as a significant factor to the incidence of fistulae. Longer surgical time could increase the chance of poor blood perfusion to organs, especially to the regions of anastomosis, and risk of inadequate healing. Severe preoperative jaundice may compromise the renal function; however, because of the risk of biliary leakage and infection, preoperative biliary drainage was not performed.

Treatment of residual pancreatic cuff properly is crucial, because leakage and the consequent pancreatic fistulae are the principal complication of PD. Many procedures have been reported as alternatives to the conventional PJ anastomosis to minimize leakage from this anastomosis. Our data concluded that differences in anastomosis between end-to-mucosa and invagination were not significant. This confirms the previous reports by others.[11–14] Duct occlusion without anastomosis failed to decrease postoperative complications but significantly increased the risk of endocrine pancreatic insufficiency and the pancreatic fistula rate.[15] PJ anastomosis is currently the most widely employed to reconstruct for the pancreatic stump after PD.[5] The difficulty in identifying undilated pancreatic duct may be the main reason for many surgeons to choose invagination procedure rather than PJ anastomosis. We found that pancreatic duct can be exposed easily following stepwise blunt excision and scratch of pancreatic parenchyma with a surgical knife, because the pancreatic duct may be quickly retracted into pancreatic tissue and may be hardly identified after quick and sharp division with surgical lancet, and it is helpful to manipulate PJ anastomosis under amplifier glasses.

The controversy for the role of pancreatic stent still remins.[4,5] Our data showed that no significant difference existed among patients with placement of external, internal, or nil pancreatic duct stents in terms of incidence of pancreatic fistulae. Our clinical

experience revealed that delicate surgical anastomosis is crucial in reducing the incidence of pancreatic fistulae. Our findings are in agreement with another cohort study.[16] A randomized investigation on internal stent versus no stent for duct-to-mucosa PJ anastomosis demonstrated that identical pancreatic fistula rate existed on patients with internal stent versus without and concluded that internal pancreatic duct stenting does not decrease the frequency or the severity of postoperative pancreatic fistulas.[4] Nevertheless, external stent is reported as a safe and effective procedure and is recommended to use in patients with small pancreatic duct.[2,5]

Compared with a short internal stent, no doubt, an external stent has numerous benefits in reducing the pancreatic fistula rate; it could completely diverse pancreatic juice away from the PJ anastomosis and prevent activation of pancreatic enzymes by bile, and it has less of a chance of being slipped away from the anastomosis during the first few postoperative days, when salvage of the anastomosis is extremely critical. However, the external stent is easily blocked,[4] twisted, or pulled out inadvertently. Moreover, regional chemical peritonitis might occur after removal of stent.[2] Three patients in our series developed peritonitis after removal of pancreatic stent and were required to admit to hospital for conservative treatment; fortunately, no fistulas developed. To avoid this complication, the serosa of the jejunal loop around the exit site of the tube should be sutured to the peritoneum of anterior abdominal wall, the stent should be not removed until 6 weeks after PD, when the adhesions are well formed.[1] Our measures in avoiding this event included clipping the pancreatic stent for at least 1 day prior to removal of stent, gently removing the stent followed by pressing the exit area of stent for at least 10 minutes while the patient was lying on bed, and avoiding vigorous activity or movement within the following 2 days.

The benefits of PPPD include no complications of conventional gastrectomy and preservation of the gastric function and fast recovery of gastric function. In addition, the overall complications rate, morbidity and mortality, and hospital stay in patients with PPPD are reportedly similar to PD.[5,17] Indeed, in our cohort, the incidence of delayed gastric emptying was not significantly different between patients who received PPPD and those who received conventional PD [*i.e.*, 4 of 27 patients (14.8%) versus 20 of 133 patients (15%); $P = 1.00$] and between the fistulae group and nonfistulae group ($P = 0.745$). Because the pancreatic leakage is associated with delayed gastric emptying, clinical outcomes would be worse progressively when incidence of delayed gastric emptying increased.[18]

Hemorrhage in the early postoperative period in most occurrences is usually associated with technical failure.[19] In this series, bleeding incidence in the fistulae group was significantly higher than in the nonfistulae group (17.6% versus 4%; $P = 0.005$). Among a total of 11 postoperative hemorrhage occurrences, 5 occurred after mechanical stapler–performed gastrointestinal anastomosis and were treated conservatively without reoperation. The cause in these 5 events was most likely related to the improper use of stapler. Familiarity with the stapler and guarantee of the function of the stapler are critical to avoid technical problems; alternatively, manual suture of gastrointestinal anastomosis would have less risk of bleeding even though it consumes longer time.

In conclusion, this retrospective study manifested that the significant risk factors of pancreatic fistula after PD are pancreatic duct diameter, surgical time, and preoperative jaundice; the use of duct-to-mucosa PJ anastomosis or invagination technique has no significant impact on the postoperative outcomes. It is wise to be cautious with the use of a stapler for gastrointestinal anastomosis to prevent hemorrhage in the early postoperative stage.

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