• *CLINICAL RESEARCH* •

Risk factors of pancreatic leakage after pancreaticoduodenectomy

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Abstract

AIM: To analyze the risk factors for pancreatic leakage after pancreaticoduodenectomy (PD) and to evaluate whether duct-to-mucosa pancreaticojejunostomy could reduce the risk of pancreatic leakage.

METHODS: Sixty-two patients who underwent PD at our hospital between January 2000 and November 2003 were reviewed retrospectively. The primary diseases of the patients included pancreas cancer, ampullary cancer, bile duct cancer, islet cell cancer, duodenal cancer, chronic pancreatitis, pancreatic cystadenoma, and gastric cancer. Standard PD was performed for 25 cases, PD with extended lymphadenectomy for 27 cases, pylorus-preserving PD for 10 cases. A duct-to-mucosa pancreaticojejunostomy was performed for patients with a hard pancreas and a dilated pancreatic duct, and a traditional end-to-end invagination pancreaticojejunostomy for patients with a soft pancreas and a non-dilated duct. Patients were divided into two groups according to the incidence of postoperative pancreaticojejunal anastomotic leakage: 10 cases with leakage and 52 cases without leakage. Seven preoperative and six intraoperative risk factors with the potential to affect the incidence of pancreatic leakage were analyzed with SPSS10.0 software. Logistic regression was then used to determine the effect of multiple factors on pancreatic leakage.

RESULTS: Of the 62 patients, 10 (16.13%) were identified as having pancreatic leakage after operation. Other major postoperative complications included delayed gastric emptying (eight patients), abdominal bleeding (four patients), abdominal abscess (three patients) and wound infection (two patients). The overall surgical morbidity was 43.5% (27/62). The hospital mortality in this series was 4.84% (3/62), and the mortality associated with pancreatic fistula was 10% (1/10). Sixteen cases underwent duct-to-mucosa pancreaticojejunostomy and 1 case (1/16, 6.25%) devel-oped postoperative pancreatic leakage, 46 cases underwent invagination pancreaticojejunostomy and 9 cases (9/46, 19.6%) developed postoperative pancreatic leakage. General risk factors including patient age, gender, history of jaundice,

preoperative nutrition, pathological diagnosis and the length of postoperative stay were similar in the two groups. There was no statistical difference in the incidence of pancreatic leakage between the patients who received the prophylactic use of octreotide after surgery and the patients who did not undergo somatostatin therapy. Moreover, multivariate logistic regression analysis showed that none of the above factors seemed to be associated with pancreatic fistula. Two intraoperative risk factors, pancreatic duct size and texture of the remnant pancreas, were found to be significantly associated with pancreatic leakage. The incidence of pancreatic leakage was 4.88% in patients with a pancreatic duct size greater than or equal to 3 mm and was 38.1% in those with ducts smaller than 3 mm (P = 0.002). The pancreatic leakage rate was 2.94% in patients with a hard pancreas and was 32.1% in those with a soft pancreas (P = 0.004). Operative time, blood loss and type of resection were similar in the two patient groups. The incidence of pancreatic leakage was 6.25% (1/16) in patients with duct-to-mucosa anastomosis, and was 19.6% (9/46) in those with traditional invagination anastomosis. Although the difference of pancreatic leakage between the two groups was obvious, no statistical signific-ance was found. This may be due to the small number of patients with duct-to-mucosa anastomosis. By further analyzing with multivariate logistic regression, both pancreatic duct size and texture of the remnant pancreas were demonstrated to be independent risk factors (P = 0.007 and 0.017, OR = 11.87 and 15.45). Although anastomotic technique was not a significant factor, pancreatic leakage rate was much less in cases that underwent duct-to-mucosa pancreaticojejunostomy.

CONCLUSION: Pancreatic duct size and texture of the remnant pancreas are risk factors influencing pancreatic leakage after PD. Duct-to-mucosa pancreaticojejunostomy, as a safe and useful anastomotic technique, can reduce pancreatic leakage rate after PD.

INTRODUCTION

Pancreaticoduodenectomy (PD) is one of the standard treatments for various benign and malignant diseases of the pancreatic head and periampullary region. Recently, the

operative mortality rate after PD has significantly declined, while the incidence of postoperative morbidity remains high, from 40% to 50%[1-5]. Pancreatic fistula is the major source of complications, and leakage rate varies from 0% to 25%, according to recent reports[6-8]. Abdominal abscess and hemorrhage are common sequelae of pancreatic anastomotic leakage, which have been associated with a mortality rate of 40% or more. Subsequently, pancreatic fistula has become one of the major complications discouraging surgeons from performing PD[2,6,7,9]. Recent literature suggests that many factors influence pancreatic leakage after PD, including sex, age, jaundice, operation time, intraoperative blood loss, pancreaticojejunal anastomotic technique, texture of the remnant pancreas, pancreatic duct size, use of somatostatin, and surgeon experience. However, no definite factor has yet been identified. Some authors have compared the incidence of pancreatic leakage with various techniques of anastomosis, such as invagination pancreaticojejunal anasto-mosis, duct-to-mucosa pancreaticojejunal anastomosis, pancreaticogastrostomy, pancreatic duct ligation, and their modifications. No conclusions though can be drawn to demonstrate which technique is best and suitable for any particular case. To analyze perioperative risk factors for pancreatic leakage after PD and to compare duct-to-mucosa with invagination pancreaticojejunal anastomosis, we reviewed retrospectively 62 cases that underwent PD at our hospital.

MATERIALS AND METHODS

Between January 2000 and November 2003, 62 patients underwent PD at our hospital, including 38 men and 24 women. Patients' age ranged from 33 to 77 years, with a mean age of 57.53 years. Before surgery, jaundice was found in 30 cases and 3 cases had hypoproteinemia. The diagnoses are shown in Table 1. All of the diseases were confirmed by pathologic examinations.

Table 1 Diseases and surgical techniques

Diseases	No. of patients ($n = 62$)	Surgical techniques	
		PD ($n = 52$)	PPPD ($n = 10$)
Pancreas cancer	29	26	3
Ampullary cancer	14	10	4
Bile duct cancer	13	12	1
Islet cell cancer	2	1	1
Duodenal cancer	1	1	0
Chronic pancreatitis	1	1	0
Pancreatic cystadenoma	1	0	1
Gastric cancer	1	1	0

PD: pancreaticoduodenectomy; PPPD: pylorus-preserving pancreaticoduodenectomy.

Surgical techniques

In the 62 cases, standard PD was performed for 25 patients, PD with extended lymphadenectomy for 27 patients, and PPPD for 10 patients. One patient with gastric cancer invading the peripancreas region underwent radical gastrostomy and PD with extended lymphadenectomy. In all cases, two drainage tubes were placed posterior to the biliary and pancreatic anastomoses.

The selection of various pancreaticojejunal anastomotic

techniques was based on pancreatic duct size and texture of the remnant pancreas. A duct-to-mucosa pancreaticojejunostomy was performed for patients with a hard pancreas and a dilated pancreatic duct (diameter ≥ 3 mm) (Figure 1). Posterior suture was achieved with 3-0 silk sutures between the posterior capsular parenchyma of the pancreatic remnant and the seromuscular layer of the jejunum. At the site for anastomosis to the main pancreatic duct, a small opening was made on the antimesenteric side of the jejunal wall according to the site and diameter of the pancreatic duct. Then anastomosis between the pancreatic duct and jejunum (all layers) was performed with 6-0 Prolene interrupted sutures at intervals of approximately 1 mm, from the posterior layer to the anterior layer, with all knots out of the anastomosis. Next, suture of the anterior side of the anastomosis between the pancreatic capsular parenchyma and the jejunal seromuscular layer was made by the same technique as used for the posterior side. No pancreatic duct drainage was used in cases undergoing duct-to-mucosa anastomotic technique (Figure 2). A traditional end-to-end or end-to-side invagination pancreaticojejunostomy was performed for patients with a soft pancreas and a non-dilated duct. The pancreas remnant was invaginated into the jejunum by about 2 cm, and two-layer sutures were performed interruptedly, with an internal duct stent tube inserted in the pancreatic duct.

Prophylactic use of somatostatin after PD was based on the experience of the surgeon and satisfactory degree of the anastomosis. Octreotide was used for 5-7 d postoperatively, 0.3 mg per d by subcutaneous injection.
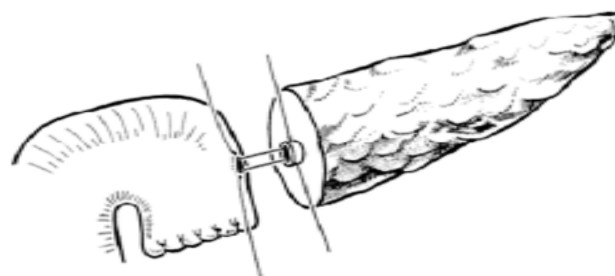

Figure 1 End-to-side duct-to-mucosa pancreaticojejunal anastomosis.

Study design and statistical analysis

Pancreaticojejunal anastomotic leakage was defined as: (1) discharge from the postpancreatic drain ≥ 50 mL/d after postoperative d 3, and (2) an amylase level of drainage fluid exceeding three times of the serum concentration.

Patients were divided into two groups according to the above criteria: 10 cases with postoperative pancreaticojejunal anastomotic leakage (leakage group) and 52 cases without leakage (nonleakage group). Seven general factors and six intraoperative clinical factors with the potential to affect the incidence of pancreaticojejunal anastomotic leakage were analyzed. Statistical computations were done with the SPSS10.0 software. Data were expressed as mean±SE, and percentage was used to express grouped data. The two groups were

first compared by the univariate statistical tests, t-test, rank sum test, χ^2 test or Fisher's exact test, when applicable (Tables 2 and 3). Logistic regression was then used to determine the effect of multiple factors on pancreatic leakage (Table 4). P less than 0.05 was considered statistically significant.

RESULTS

Complications
Of the 62 patients, 10 (16.1%) were identified as having pancreatic leakage after operation. Other major postoperative complications included delayed gastric emptying (eight patients), abdominal bleeding (four patients), abdominal abscess (three patients) and wound infection (two patients). Overall surgical morbidity was 43.5% (27/62). One patient died of massive abdominal hemorrhage associated with pancreatic fistula 10 d after operation, and two died of abdominal bleeding within 3 d after operation. The hospital mortality in this series was 4.84% (3/62), and the mortality associated with pancreatic fistula was 10% (1/10). One patient required reoperation because of abdominal bleeding, but no pancreaticojejunal anastomotic leakage was found in this patient.

Risk factors
General risk factors were compared for patients with or without pancreatic leakage (Table 2). Patient age, gender, history of jaundice, preoperative nutrition, pathological diagnosis and the length of postoperative stay were similar in the two groups. The incidence of pancreatic fistula was 20.7% (6/29) in the 29 patients who received the prophylactic use of octreotide treatment after surgery, compared to 12.1% (4/33) in the 33 patients who did not undergo somatostatin therapy, and no statistical difference was found in the two patient

groups. Moreover, multivariate logistic regression analysis showed that none of these factors seemed to be associated with pancreatic fistula.

Two intraoperative risk factors were found to be significantly associated with pancreatic leakage: pancreatic duct size and texture of the remnant pancreas. The incidence of pancreatic leakage was 4.88% in patients with a pancreatic duct size greater than or equal to 3 mm, and was 38.1% in those with ducts smaller than 3 mm ($P = 0.002$). The pancreatic leakage rate was 2.94% in patients with a hard pancreas, and was 32.1% in those with a soft pancreas ($P = 0.004$). Operative time, blood loss and type of resection were similar in the two patient groups. The incidence of pancreatic leakage was 6.25% (1/16) in patients with duct-to-mucosa anastomosis, and was 19.6% (9/46) in those with traditional invagination anastomosis. Although the difference of pancreatic leakage between the two groups was obvious, no statistical significance was found. This may be due to the small number of patients with duct-to-mucosa anastomosis.

The three factors affecting pancreatic leakage were further analyzed by multivariate logistic regression. Both pancreatic duct size and texture of the remnant pancreas were demonstrated to be independent risk factors (Table 3). Patients with a small pancreatic duct or a soft pancreas were at high risk of pancreatic leakage.

Table 2 General risk factors for pancreatic leakage [n (%)]

Parameters	Leakage group ($n = 12$)	Nonleakage group ($n = 45$)	P
Age (yr)	59.8±10.04	57.1±11.37	0.487
Gender			0.166
Male	4 (10.5)[1]	34 (89.5)[1]	
Female	6 (25)[1]	18 (75)[1]	
History of jaundice			0.733
Yes	4 (13.3)[1]	26 (86.7)[1]	
No	6 (18.8)[1]	26 (81.2)[1]	
Preoperative serum-albumin			>0.95
Normal	10 (16.9)[1]	49 (83.1)[1]	
Low	0 (0)[1]	3 (100)[1]	
Pathology			0.312[2]
Pancreas cancer	3 (10.3)[1]	26 (89.7)[1]	
Ampullary cancer	3 (21.4)[1]	11 (78.6)[1]	
Bile duct cancer	3 (23.1)[1]	10 (76.9)[1]	
Islet cell tumor	1 (50)[1]	1 (50)[1]	
Duodenal cancer	0 (0)[1]	1 (100)[1]	
Chronic pancreatitis	0 (0)[1]	1 (100)[1]	
Pancreatic cystadenoma	0 (0)[1]	1 (100)[1]	
Gastric cancer	0 (0)	1 (100)	
Octreotide			0.493
Used	6 (20.7)[1]	23 (79.3)[1]	
Non-used	4 (12.1)[1]	29 (87.9)[1]	
Postoperative stay (d)	32.7±12.37	26.4±13.51	0.177

[1]Values in parentheses are percentages. [2]Pancreatic cancer *vs* non-pancreatic cancer.

Table 3 Intraoperative risk factors for pancreatic leakage [n (%)]

Parameters	Leakage group ($n = 12$)	Nonleakage group ($n = 45$)	P
Type of resection			0.629
PD	8 (15.1)[1]	45 (84.9)[1]	
PPPD	2 (22.2)[1]	7 (87.8)[1]	
Anastomotic technique			0.43
Duct-to-mucosa	1 (6.25)[1]	15 (93.75)[1]	
Invagination	9 (19.6)[1]	37 (80.4)[1]	
Pancreatic size (mm)			0.002
⩾3	2 (4.88)[1]	39 (95.12)[1]	
<3	8 (38.1)[1]	13 (61.9)[1]	
Pancreatic texture			0.004
Hard	1 (2.94)[1]	33 (97.06)[1]	
Soft	9 (32.1)[1]	19 (67.9)[1]	
Operative time (h)	7.05±2.40	6.34±2.02	0.325
Intraoperative blood loss (mL)[2]	400 (0, 1 250)	350 (0, 1 200)	0.352

[1]Values in parentheses are percentages. [2]Median (minimum, maximum).

Table 4 Multivariate logistic regression for pancreatic leakage

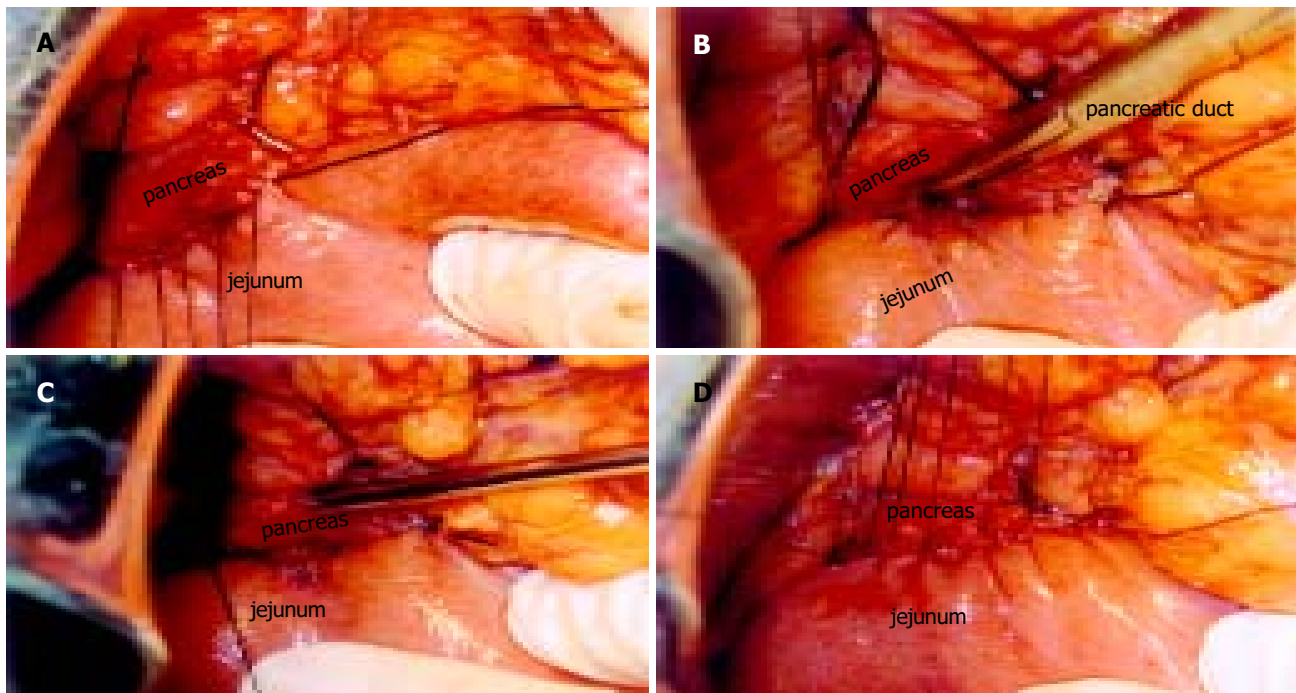| Parameters	P	Odds ratio	CI
Anastomotic technique			
Duct-to-mucosa	–	1	
Invagination	0.128	9.967	0.514-193.15
Pancreatic size (mm)			
⩾3	–	1	
<3	0.007	11.867	1.96-71.86
Pancreatic texture			
Hard	–	1	
Soft	0.017	15.445	1.629-146.46

CI: 95% confidence intervals.

Figure 2 Duct-to-mucosa pancreaticojejunal anastomosis. **A**: Posterior suture with 3-0 silk sutures between posterior capsular parenchyma of the pancreatic remnant and the seromuscular layer of the jejunum. **B**: Posterior layer anastomosis with 6-0 Prolene interrupted sutures between the pancreatic duct and jejunum (all layers). **C**: Anterior layer anastomosis with 6-0 Prolene interrupted sutures between the pancreatic duct and jejunum. **D**: Anterior suture with 3-0 silk sutures between anterior interrupted sutures between the pancreatic duct and capsular parenchyma of the pancreatic remnant and the seromuscular layer of the jejunum.

Treatment and outcome

All the 10 patients who developed pancreatic leakage were diagnosed on the basis of the total amount and concentration of amylase in postpancreatic drainage exudate. One patient had abdominal massive hemorrhage, and two had abdominal abscess, the rest were successfully managed by conservative treatment. In five patients, a prolonged drainage duration for 4 wk after surgery was required. Octreotide was administered to five patients, including two with ineffective drains requiring another percutaneous drainage.

DISCUSSION

In recent years, PD has been used increasingly as a safe method of resection in patients with malignant and benign disorders of the pancreas and periampullary region. Although postoperative mortality has decreased significantly, the incidence of postoperative morbidity is still high. The overall surgical morbidity after PD was 43.5% (27/62), and the incidence of pancreatic leakage was 16.1% (10/62), similar to recent literature reports[6].

Risk factors for pancreatic anastomotic leakage after PD

Risk factors for pancreatic leakage include general factors (age, gender, jaundice, malnutrition), disease factors (pancreatic pathology, pancreatic texture, pancreatic duct size, pancreatic juice output) and procedure-related factors (operative time, resection type, anastomotic technique, intraoperative blood loss). In addition, surgeon experience has been shown to correlate with pancreatic anastomotic leakage rate, and prophylactic use of somatostatin has also been reported in recent literature to influence pancreatic leakage.

It has been widely accepted that a fibrotic pancreatic remnant in patients with chronic pancreatitis facilitates the pancreaticoenteric anastomosis, whereas a soft and friable pancreatic parenchyma makes the anastomosis difficult to perform. Yeo *et al*.[10], found that there was a strong association between the pancreatic texture and pancreatic leakage. None of the 53 patients with hard pancreatic remnants developed pancreatic leakage, whereas 25% (19/75) of patients with soft pancreatic texture were complicated by pancreatic leakage. Hosotani *et al*.[11], reviewed 161 patients who had undergone PD and reported a fistula rate of 11% (17/161), finding that pancreaticojejunostomy anastomotic technique, pancreatic texture and pancreatic duct size were substantial risk factors for pancreatic leakage after PD. In a study by Marcus *et al*.[12], male sex was found to be a significant factor predisposing pancreatic fistula[15]. A recent study by Yeh *et al*.[13], identified jaundice, creatinine clearance abnormality, and intraoperative blood loss as significant risk factors for leakage. Matsusue *et al*.[14], found that advanced age (>70 years) was an adverse factor for pancreatic leakage.

Inhibition of exocrine pancreatic secretion may reduce the anastomotic fistula rate after PD. In recent years, more importance has been attached to prophylactic use of somatostatin after PD, but no consensus has been achieved. European studies found that prophylactic octreotide in pancreatic resection could reduce total morbidity rate or pancreatic fistula rate, though none of them demonstrated a decrease in the overall mortality rate[15-18]. In another report, a significantly lower pancreatic fistula rate was observed with the use of octreotide among patients who underwent distal pancreatectomy or local pancreatic resection, whereas no statistical difference was noted between octreotide and

placebo groups in patients who underwent PD[15]. Yeo et al.[10], recently randomized 211 patients who underwent PD into saline control and octreotide groups. The pancreatic fistula rate in the octreotide group was 11%, and 9% in the control group. The authors concluded that prophylactic use of octreotide after PD could not reduce the pancreatic fistula rate[10]. Poon et al.[19], studied the meta-analysis of six prospective randomized trials on the prophylactic use of octreotide in pancreatic resection and published them as full reports in the literature from January 1990 to December 2000. The meta-analysis did not show any beneficial effect of octreotide on pancreatic anastomotic leakage rate.

In this study, we analyzed 13 general or intraoperative factors. Two intraoperative factors were significantly associated with the risk of pancreatic leakage: pancreatic duct size and texture of the remnant pancreas. Multivariate analysis also revealed that the two factors turned out to be independent risk factors. Prophylactic use of octreotide after PD did not result in a decline of the pancreatic fistula rate.

Anastomotic techniques and pancreatic leakage

Management of the pancreatic remnant after PD is regarded as the key point to reduce pancreatic leakage. Various reconstruction techniques have been developed to diminish pancreatic fistulae, such as duct-to-mucosa pancreaticojejunostomy, invagination pancreaticojejunostomy, pancreaticogastrostomy, use of a transanastomotic stenting tube, and their modifications. Ligation or obliteration of the pancreatic duct has not been popularized as they abolish the pancreatic exocrine secretion, with still a high incidence of pancreatic leakage[20-22].

Reviewing various techniques of pancreaticojejunal anastomosis in the literatures published over the last decade, Poon et al.[19], found that duct-to-mucosa anastomosis was a safer technique than invagination anastomosis. Marcus et al.[12], found that duct-to-mucosa anastomosis was associated with a low pancreatic fistula rate in low-risk patients with a dilated pancreatic duct or a fibrotic pancreas, whereas end-to-end invagination technique was safer in high-risk patients with small ducts or a soft friable pancreas. Suzuki et al.[23], selected various pancreaticojejunostomy techniques according to the pancreatic texture and duct size, and obtained an overall pancreatic leakage rate of 8% (4/50). All of the patients who developed pancreatic fistulae were all with a small duct and a soft pancreas. In that series, the incidence of pancreatic leakage rate was 6.25% in patients who underwent a duct-to-mucosa pancreaticojejunal anastomosis, compared to 19.6% in invagination group. The difference, of course, resulted from the variation of anastomotic techniques; while all of the patients who received the duct-to-mucosa anastomosis, on the other hand, were with a dilated pancreatic duct ($\geq$3 mm) or a soft pancreas. Therefore, both of the two factors might be associated with the discrepancy of the pancreatic leakage rate in the two groups.

There has been no conclusion as to whether a pancreatic duct stent for internal or external drainage can reduce the pancreatic leakage rate after PD. According to the authors who recommended it, a stent might help drain the pancreatic secretion juice from the anastomosis, and allow a more precise placement of sutures, thus protecting the pancreatic

duct from injury and reducing fistula rate[24-27]. Some investigators found a few drawbacks to this method, such as accidental removal of the stent, obstruction or bending of the stenting tube, which might increase the incidence of pancreatic leakage. However, the overall pancreatic leakage rate in patients with a pancreatic stent was found to be similar to that in patients without a stent[28]. Therefore, as far as invagination anastomosis is concerned, it is safer to use an internal drainage stent for patients with a small pancreatic duct and a soft pancreas.

Appraisal of duct-to-mucosa pancreaticojejunal anastomosis

Duct-to-mucosa pancreaticojejunal anastomosis was first used by Cattel in 1943. This technique allows direct contact of the pancreatic duct with jejunal mucosa, preventing direct contact of pancreatic juice with the cut end of the pancreas and thus helping healing of the mucosa, protecting the anastomosis by embedding the pancreatic remnant under jejunal serosa. Therefore, duct-to-mucosa anastomosis is a theoretically more rational technique to avoid pancreatic fistulae. Since it is technically difficult to perform, duct-to-mucosa pancreaticojejunal anastomosis was previously recommended for patients with a dilated pancreatic duct, whereas in recent years this technique has been preferred regardless of the diameter of the pancreatic duct[11,29]. Hosotani et al.[11], using multivariate analysis found that only pancreaticojejunal anastomosis technique turned out to be an independent risk factor and duct-to-mucosa anastomosis pancreaticojejunostomy reduced the risk of pancreatic leakage after PD (odds ratio = 4.15). In our hospital, invagination pancreaticojejunal anastomosis was performed for patients with either a dilated or a non-dilated pancreatic duct before 2000, with a consistent high pancreatic leakage rate. From 2000, duct-to-mucosa pancreaticojejunal anastomosis has been performed for patients with a dilated pancreatic duct, and the pancreaticojejunal anastomotic leakage rate has declined significantly when compared with previous invagination anastomosis, though no statistical difference was found in the present study.

Based on accumulated evidence so far, no conclusion could be drawn to appraise various anastomotic techniques, since most pertinent articles were retrospective studies. In prospective studies, most were not randomized controlled trials. On the other hand, anastomotic leakage rate is greatly related to the surgery technique and experience, which cannot be easily compared among different institutions. The need for a prospective randomized controlled trial by the same surgeons to evaluate various anastomotic techniques is highlighted. In conclusion, anastomotic techniques should be selected based on the status of the remnant pancreas intraoperatively: duct-to-mucosa anastomosis without a pancreatic duct stent for patients with a dilated pancreatic duct ($\geq$3 mm), and invagination anastomosis with an internal drainage stent for patients with a small pancreatic duct and a soft pancreas.

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