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Incidence, Risk Factors, and Treatment of Pancreatic Leakage After Pancreaticoduodenectomy: Drainage versus Resection of the Pancreatic Remnant

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- BACKGROUND:** Pancreatic leakage is a major cause of morbidity and mortality after pancreaticoduodenectomy, with incidences varying between 6–24% and a mortality rate up to 40%. Treatment is an issue of controversy. In this study we analyzed risk factors for pancreatic leakage and the results of early resection of the pancreatic remnant versus drainage procedures for leakage of the pancreaticojejunostomy.
- STUDY DESIGN:** From 1983 to 1995, 269 patients underwent pancreaticoduodenectomy, with pancreaticojejunostomy. Patients with manifestations of pancreatic leakage were compared with nonleakage patients to evaluate risk factors. Patients with leakage were divided into two treatment groups. One group comprised patients undergoing percutaneous or surgical drainage procedures; the other had patients undergoing resection of the pancreatic remnant.
- RESULTS:** Twenty-nine patients (11%) had clinical manifestations of pancreatic leakage, and the mortality in these patients was 28% (overall mortality: 3.7%). Leakage occurred after a median of 5 days (range 1–20). Age, preoperative bilirubin level, and albumin counts were not risk factors for pancreatic leakage. Small pancreatic duct size (< 2 mm) ($p < 0.01$) and ampullary carcinoma as histopathologic diagnosis ($p < 0.05$) were risk factors. The median number of relaparotomies was two (range 0–4) in the drainage group ($n = 21$), versus 1.5 (range 1–5) in patients who underwent resection ($n = 8$). The median hospital stay was 74 days (range 36–219), versus 55 days (range 22–107) for the drainage and resection groups, respectively ($p < 0.05$). Mortality was lower in patients who underwent resection, 38 versus 0% ($p < 0.05$).
- CONCLUSIONS:** Leakage of the pancreatic anastomosis is a severe complication after pancreaticoduodenectomy and carries a high mortality rate (28%). Completion pancreatectomy could be performed without additional mortality. In patients with severe and persistent leakage of the anastomosis, early completion pancreatectomy is the treatment of choice. (J Am Coll Surg 1997;185:18–25. © 1997 by the American College of Surgeons)
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Mortality after pancreaticoduodenectomy has decreased dramatically in centers with experience, and has recently been reported between 0–5%.^{1–10} Morbidity, however, is still substantial, varying between 32–52%.^{4,5,7,9,11} Common complications include hemorrhage in 3–16%,^{1,5–7,9,12} intra-abdominal abscesses in 2–9%,^{4,6,7,9,11} and leak-

age of the pancreaticojejunostomy in 6–24%.^{1,2,4–7,9,11–16} Leakage can be associated with additional complications such as gastrointestinal or intra-abdominal hemorrhage, and intra-abdominal abscesses^{2,11,17,18} and leads to a prolonged hospital stay.¹¹ Mortality in patients with pancreatic anastomotic leakage is reported between 8–40%.^{2,7,9,15,16}

Treatment of anastomotic leakage depends on the definition of pancreatic leakage, severity of leakage, and personal experience. When leakage is minimal, treatment is generally possible with antibiotics or octreotide combined with percutaneous drainage of fluid collections. Operative interventions include relaparotomy

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with surgical drainage of the anastomotic area, disconnection of the pancreaticojejunal anastomosis, combined with pancreatic duct occlusion using neoprene or suture ligation of the pancreatic duct. This procedure is associated with a high incidence of fistula formation.^{19,20}

As a last and most radical option, resection of the pancreatic remnant, or completion pancreatectomy, might be performed. This intervention is reported to carry a mortality rate of 17–71%.^{2,9,21,22} Completion pancreatectomy is most often performed as a last resort in severely septic patients after multiple other interventions. The reticence to perform completion pancreatectomy is probably related to the major disadvantage of the resulting insulin-dependent diabetes mellitus. Farley and associates suggest that resection of the pancreatic remnant at an earlier phase after detection of leakage would lead to a lower mortality.²² The treatment protocol for pancreatic anastomotic leakage in our department was changed from a rather conservative approach favoring drainage procedures, toward a more aggressive approach in 1993, inducing early resection of the pancreatic remnant in patients with severe leakage or dehiscence of the pancreatic anastomosis. In this retrospective study we analyzed risk factors for pancreatic leakage, the outcome of treatment of anastomotic leakage after pancreaticoduodenectomy, and the effect of the change in policy toward early completion pancreatectomy.

METHODS

Incidence. From 1983 to 1995, 269 consecutive patients underwent a pancreaticoduodenectomy. Pancreaticojejunostomy was used as reconstruction. The charts of patients with postoperative pancreatic leakage were selected. Criteria for pancreatic leakage were defined as high amylase level (>3 times serum amylase) in the abdominal drain fluid; pancreatic anastomotic leakage proved radiologically, at relaparotomy, in combination with one or more clinical signs such as peritoneal tenderness, progressive abdominal pain, temperature rise above 38.5°C , or leucocytosis above $15 \times 10^9/\text{L}$. Because of a number of changes in the reconstruction and the treatment protocol for leakage in 1993, pancreatic leakage rate was analyzed for two periods from 1983 to 1992, and from 1993 to 1995.

Risk factors. Patients with anastomotic dehiscence were compared with patients without leakage, with respect to pre- and peroperative factors. The following factors were analyzed: patients' characteristics (eg, age,

gender, preoperative bilirubin level, and serum albumin); type of resection (pylorus preserving pancreaticoduodenectomy or standard pancreaticoduodenectomy); type of reconstruction (one or two jejunal loops); technique of pancreatic resection (surgical knife or linear stapler); type of anastomosis (end-to-end or end-to-side, in one or two layers); drainage of the hepatic or the pancreatic duct; diameter of the pancreatic duct; temporary duct occlusion with fibrin glue; use of octreotide or somatostatin (in a limited series²³); operative time and blood loss; pathology of the tumor; and (microscopic) completeness of the resection. A microscopically radical resection was defined as tumor-free resection margins and free dissection margins of the resectional specimen.

Diagnosis. Onset of pancreatic leakage after initial resection and clinical signs of pancreatic leakage were studied. The following diagnostic procedures were analyzed: abdominal ultrasonography, computed tomography, chest x-ray, and pancreatography via an indwelling, transanastomotic drain.

Treatment of leakage. Patients with leakage were divided into two groups. In group 1 patients were treated conservatively or by surgical and nonsurgical drainage, or both. In group 2 patients eventually underwent resection of the pancreatic remnant. These groups were analyzed with respect to the risk factors already mentioned, parameters of leakage, diagnostic and therapeutic interventions, hospital stay, and mortality. Therapeutic interventions also were evaluated, including conservative treatment (octreotide, antibiotics, percutaneous drainage), surgical drainage, dismantling of the anastomosis, and resection of the pancreatic remnant. The number of surgical interventions, postoperative day of resection, and mortality were analyzed. Mortality was defined as death during hospital stay.

Statistical analysis. Statistical analysis was performed using the chi-square test, two-tailed Fischer's exact test, and the Mann-Whitney *U* test, where applicable. A *p* value below 0.05 was considered significant.

RESULTS

Incidence. Of 269 patients who underwent pancreaticoduodenectomy 29 (11%) were identified with leakage of the pancreatic anastomosis. The incidence of pancreatic leakage during the periods from 1983 to 1992 and 1993 to 1995 was not significantly different: 10%, and 12%, respectively. The overall mortality was 3.7%.

Table 1. Preoperative Risk Factors for Pancreatic Leakage

Risk factors	Nonleakage* (n = 240)	Leakage* (n = 29)	p value
Age† (years)	62, 25–79	64, 48–75	ns
< 65 years	152 (91)	15 (9)	ns
≥ 65 years	88 (84)	14 (16)	
Sex (M/F)	137/103	18/11	ns
Preoperative bilirubin (mg/dL)†	1.5, 0.2–41.8	1.4, 0.2–4.5	ns
< 10 mg/dL	217 (87)	29 (13)	ns
≥ 10 mg/dL	23 (10)	0	
Preoperative albumin (g/dL)†	4.2, 2.1–5.4	4.3, 3.2–5.2	ns
< 3.0 g/dL	12 (100)	0	ns
≥ 3.0 g/dL	228 (87)	29 (13)	

*Numbers in parentheses represent percentages.

†Median, range.

ns, not significant.

Risk factors. Preoperative risk factors were compared for patients with anastomotic leakage versus nonleakage patients (Table 1). Age, gender, and preoperative bilirubin and albumin levels were similar in both groups. Preoperative bilirubin exceeding 10 mg/dL and preoperative albumin below 3.0 g/dL did not cause a higher incidence of postoperative anastomotic leakage.

Peroperative risk factors are listed in Table 2. The diameter of the pancreatic duct was significantly different between the two groups. In patients with a dilated (more than 2 mm) pancreatic duct, 7% experienced leakage versus 22% of the patients with a small pancreatic duct ($p < 0.01$). There was no difference in treatment with fibrin glue or octreotide between the two groups. The incidence of benign or malignant pathology was not different in the two groups, but there was a higher incidence of ampullary carcinoma in patients with pancreatic leakage ($p < 0.05$). There was a trend toward a larger number of microscopically radical resections in patients with anastomotic leakage, but this did not reach statistical significance ($p < 0.09$).

Because only two factors were significantly different in patients with leakage compared with patients without pancreatic leakage, a multivariate analysis was not considered suitable. Instead, a subanalysis of those patients with a pancreatic duct size smaller than 2 mm ($n = 65$) was performed (Table 3). The use of a stapler to transect the pancreas provided no significant difference between the nonleakage and leakage patients; treatment with fibrin glue also produced no difference. Of high-risk pa-

Table 2. Preoperative Risk Factors for Pancreatic Leakage

Risk factors	Nonleakage* (n = 240)	Leakage* (n = 29)	p value
Type of resection			
Pylorus-preserving	66 (88)	9 (12)	ns
Classic Whipple's resection	174 (90)	20 (10)	
Reconstruction			
1 jejunal loop	74 (90)	8 (10)	ns
2 jejunal loops	166 (89)	21 (11)	
Transection pancreas			
Surgical knife	206 (91)	21 (9)	ns
Linear stapler	34 (81)	8 (19)	
Pancreatic anastomosis			
End-to-side	237 (89)	29 (11)	ns
End-to-end	3 (100)	0	
1 layer	82 (87)	12 (13)	ns
2 layers	158 (90)	17 (10)	
Pancreatic duct			
Drainage	136 (89)	16 (11)	ns
No drainage	104 (89)	13 (11)	
Pancreatic duct size			
> 2 mm	189 (93)	15 (7)	0.001
≤ 2 mm	51 (78)	14 (22)	
Fibrin glue			
Yes	16 (84)	3 (16)	ns
No	224 (90)	26 (10)	
Octreotide			
Yes	50 (91)	5 (9)	ns
No	190 (89)	24 (11)	
Hepatic duct			
Drainage	81 (89)	10 (11)	ns
No drainage	159 (89)	19 (11)	
Operative time/blood loss			
Operative time (hr)	5.6 ± 0.11	5.9 ± 0.25	ns
Blood loss (L)	1.6 ± 0.09	1.4 ± 0.16	ns
Transfusion (units of PCs)	2.8 ± 0.16	2.5 ± 0.35	ns
Pathology			
Pancreatic head carcinoma	93 (92)	8 (8)	ns
Ampullary carcinoma	72 (83)	15 (17)	0.02
Distal bile duct carcinoma	44 (90)	5 (10)	ns
Other malignant	11 (100)	0	ns
Chronic pancreatitis	15 (95)	1 (5)	ns
Other benign	5 (100)	0	ns
Resection margins (microscopically)			
Negative	160 (87)	24 (13)	ns
Positive	80 (94)	5 (6)	

*Numbers in parentheses represent percentages.

ns, not significant.

Table 3. Patients at High Risk for Pancreatic Leakage*: Transection Using a Linear Stapler and Treatment with Octreotide or Fibrin Glue

	Non-leakage† (n = 51)	Leakage† (n = 14)	p value
Stapler			
Yes	10 (67)	5 (33)	ns
No	41 (82)	9 (18)	
Fibrin glue			
Yes	12 (92)	1 (8)	ns
No	39 (75)	13 (25)	
Octreotide			
Yes	12 (86)	2 (14)	ns
No	39 (76)	12 (24)	

*Ductal size of ≤ 2 mm. n = 65.

†Numbers in parenthesis represent percentages.

ns, not significant.

tients treated with octreotide, 14% experienced leakage versus 24% of patients not treated by octreotide (not significant).

Diagnosis. The first clinical signs of pancreatic leakage started after a median of 5 days after surgery. The clinical signs of pancreatic leakage were not different for the two treatment groups (data not shown) and are summarized in Table 4. Sixty-nine percent of patients had leucocytosis, and 72% had high amylase levels in the abdominal drain fluid. Pancreatography was used in 8 patients to identify anastomotic dehiscence (Fig. 1); ul-

Table 4. Clinical Signs of Pancreatic Leakage; Diagnostic Procedures and Their Success Rates

	Leakage* (n = 29)
Days after surgery (median, range)	5, range 1–20
Sign	
Temperature rise $> 38.5^{\circ}\text{C}$	18 (62)
Tachycardia	15 (52)
Peritoneal tenderness	19 (66)
Abdominal pain	12 (41)
Dyspnea	10 (34)
Laboratory	
Leucocytosis $> 15 \times 10^9/\text{L}$	20 (69)
Drain amylase $> 3 \times$ serum amylase	21 (72)
Diagnostic procedure	
Pancreatography†	8 of 8 (100)
Ultrasound†	18 of 20 (90)
Computed tomography†	8 of 9 (89)
Chest x-ray (pleural effusion)†	14 of 19 (74)
Proved intra-abdominal fluid collection	29 (100)

*Numbers in parenthesis represent percentages.

†Number positive of number performed.

Figure 1(A) AND (B). Leakage of the pancreatic anastomosis (black arrowheads), diagnosed by pancreatography via indwelling transanastomotic canula. The pancreatic duct is indicated by the white, open arrows.

trasonography was used in 20 patients, and computed tomography scanning was used in 9 patients. In 14 patients, pleural effusion was noted on the thoracic x-ray. All patients had proved intra-abdominal fluid collections.

Treatment of leakage. Patient characteristics, preoperative bilirubin levels, pancreas characteristics, and pathology were similar in both treatment groups (Table 5). Patients undergoing drainage procedures underwent a

Table 5. Pre- and Preoperative Parameters of the Primary Resection of Patients Who Had Leakage of the Pancreatic Anastomosis: Comparison of the Two Treatment Groups

Patient characteristics	Drainage group (n = 21)	Resection group (n = 8)	p value
Age* (years)	65 (48–75)	61 (50–68)	ns
Gender (M/F)	13/8	5/3	ns
Preoperative bilirubin (mg/dL)*	1.4 (0.4–4.3)	1.4 (0.2–4.5)	ns
Pancreatic duct size			
> 2 mm	12	3	ns
≤ 2 mm	9	5	
Consistency of pancreas			
Soft gland	6	4	
Normal gland	14	4	ns
Firm gland	1	0	
Pathology			
Malignant	20	8	ns
Benign	1	0	

*Median, range.

ns, not significant.

median of 2 relaparotomies (range 0–4) (Table 6). Two patients did not undergo relaparotomy and were treated with percutaneous drainage only. Patients who underwent resection of the pancreatic remnant underwent 1.5 relaparotomies (range 1–5), including the resection. Four patients had one or more surgical drainage procedures before the resection. Resection of the pancreatic remnant was performed after a median of 5.5 days (mean 5.1, range 1–8 days). Median postoperative hos-

Table 6. Number of Relaparotomies, Postoperative Hospital Stay, and Mortality

	Drainage group (n = 21)	Resection group (n = 8)	p value
Number of relaparotomies*	2 (0–4) [†]	1.5 (1–5) [‡]	ns
Number of days until resection*		5.5 (1–9)	
Postoperative hospital stay (days)*	74 (36–219)	55 (22–107)	0.04
Mortality	8 (38%)	0	0.04

*Median, range.

[†]Two patients did not undergo relaparotomy and had percutaneous drainage only.[‡]Four patients had one or more surgical drainage procedures before resection. One patient underwent four operative drainage procedures before resection; one patient had two earlier drainage procedures, and two patients had one prior drainage procedure.

ns, not significant.

pital stay was shorter for patients undergoing resection than it was for patients undergoing drainage procedures: median 74 days versus 55 days, respectively ($p < 0.05$). Overall mortality among patients with pancreatic leakage was 28%. Part of total mortality from pancreatic leakage was 80% (8 of 10 patients). Mortality was higher in the drainage group: 8 patients (38%) versus 0 patients in the resection group ($p < 0.05$).

DISCUSSION

In our study only patients with clinically manifest leakage of the pancreaticojejunostomy after pancreaticoduodenectomy were defined as having pancreatic leakage. Patients with prolonged drainage of amylase-rich fluid without any clinical signs of illness were not classified as having pancreatic leakage. An incidence of leakage of 11% in this series is in accordance with the figures reported in the literature. The wide range between 6–24% reported in the literature^{1,2,4-7,9,11-16} could be a result of different criteria for pancreatic leakage, subjectively arrived at by each author.

In our series, elevated preoperative serum bilirubin levels, low preoperative albumin concentrations, and patients in higher age groups were not risk factors for postoperative leakage of the pancreatic anastomosis, contrary to other studies.¹⁵ Consistency of the pancreatic tissue was not reported in the operative report in all patients. Pancreatic duct size was also used as a risk factor for pancreatic leakage, and the incidence of leakage was higher in patients with a small pancreatic duct size. Several risk factors for pancreatic leakage have been reported in the literature. The most frequently reported are the surgeon's patient/operating volume and the degree of fibrosis of the pancreas.^{11,19,24,25}

The effect of the type of pancreatic anastomosis on prevention of postoperative dehiscence of the anastomosis has been the subject of many publications, and many surgeons favor their own modification of a pancreaticoenteric anastomosis and report excellent results.²⁶⁻³¹ In retrospective studies, a decreased incidence of pancreatic leakage has been reported after pancreaticogastrostomy, compared with pancreaticojejunostomy,^{26,32-35} although this was not confirmed in a recent prospective randomized trial.¹¹ In a recent review article, the incidence of anastomotic leakage after anastomosis by invagination was the same as after duct-to-mucosa anastomosis. Furthermore, no difference was found between end-to-end and end-to-side reconstruction.³⁶

Temporary occlusion of the pancreatic duct with fibrin glue can reduce leakage after pancreaticoduodenectomy.^{37,38} Our study revealed no significant advantage for patients treated with fibrin glue; this was true also in patients with a small duct.

In four randomized trials, the use of octreotide reduced overall postoperative complications after elective pancreatic surgery for pancreatic or periampullary cancer and benign disease.³⁹⁻⁴² In all studies, fistula rate decreased after treatment with octreotide, although the incidence of evidenced pancreatic anastomotic leakage was not affected,³⁹⁻⁴² as our study documents.

Transection of the pancreas with a linear stapler to enable easier hemostasis of the pancreatic remnant for anastomosis^{43,44} did not decrease the incidence of leakage in this series. This could be related to the fact that staplers were more commonly used to transect a soft pancreas, providing a higher risk of postoperative leakage.^{19,24,25} In our series a stapler was used in 23% of patients with a small duct and in 13% of other patients.

Some reports show that external drainage of the pancreatic duct decreases the incidence of pancreatic anastomotic leakage and fistula formation after pancreaticoduodenectomy.^{27,28} It is hypothesized that pancreatic fluid does not leak into the abdominal cavity by postoperative ductal drainage and therefore leads to less serious symptoms.²⁸ In our series, no difference was seen in anastomotic leakage in patients with or without external duct drainage. External drainage of the pancreatic duct facilitates diagnosis of pancreatic leakage, because the transanastomotic drain gives direct access for pancreatography.^{24,45}

We found the same incidence of pancreatic leakage after pancreaticoduodenectomy for malignant and benign disease. The higher incidence of leakage in patients with ampullary tumors may exist because jaundice is an early symptom in these patients. Therefore, obstruction of the pancreatic duct is of shorter duration, and hence, obstructive pancreatitis has less time to develop, leaving the pancreas relatively soft. These results are in accordance with the literature, that the structure of the pancreas is an established risk factor for anastomotic leakage after pancreatoduodenectomy.^{19,24,25}

Postoperative leakage of the pancreaticojejunal anastomosis became evident after a median of 5 days in our series. The most common clinical signs included a rise of temperature, tachycardia, peritoneal irritation, abdominal pain, and dyspnea. Farley and colleagues²², who

discussed 17 completion pancreatectomies for anastomotic leakage, found tachycardia, peritoneal irritation, and fever the most important bedside findings, crucial for the decision to use relaparotomy. Apart from similar clinical findings, we found peritoneal irritation and, especially, pleural effusion and secondary pneumonia ominous signs for leakage of the pancreaticojejunal anastomosis. The pancreatic fluid originating from the anastomotic leakage irritates the pleural viscera directly above the diaphragm. Pleural effusion on the thoracic x-ray was seen in 74% of patients with pancreatic leakage.

In both treatment groups a similar number of relaparotomies was performed. This indicates that in a number of patients, an attempt was made to treat these patients with a drainage procedure, eventually leading to completion pancreatectomy. Nevertheless, this procedure, although not immediately performed in half of the patients, probably has reduced morbidity and even mortality. The postoperative hospital stay was reduced from 74 to 55 days, and no patients died after completion pancreatectomy. In the present study, however, comparison of both treatment procedures was not randomized, and pancreatic remnant resection was performed later in the study period, suggesting that part of the reduction in mortality and hospitalization could be a result of their surgeon's improved experience and improved care. The advantageous results for completion pancreatectomy in our study contradict reports in the literature that document mortality as high as 64–71%.^{2,21} This difference could result from the fact that completion pancreatectomy was performed in a relatively early stage of deterioration in this series. Completion pancreatectomy was performed after a mean of 5 days after the initial resection. In two other studies, resection of the remnant was performed after 6 and 18 days, respectively, after the initial resection.^{21,22}

Induction of insulin-dependent diabetes mellitus is a major disadvantage of completion pancreatectomy. This apocrine diabetes can lead to severe episodes of hypoglycemia that can be very difficult to manage and can even lead to death.^{12,46} In our series, none of the patients died from postresection diabetes during follow-up. In seven of the eight patients, diabetes was controlled with insulin treatment. In one patient this proved very difficult because of the patient's active life.

The 5-year survival after completion pancreatectomy depends on histopathologic diagnosis and is reported to

be 24% in a small patient group.²² We did not address the possibility of preserving a 3–5 cm section of the pancreas. This is a procedure that might be considered because it can improve glucose tolerance after resection, and it might prevent the postoperative diabetes seen after total pancreatectomy.^{46,47}

Patients with severe and persistent pancreatic leakage can receive completion pancreatectomy without additional morbidity and mortality. Completion pancreatectomy for leakage is a very aggressive treatment and is not the first step in treatment of pancreatic leakage. It should be performed only in cases of severe leakage, in which other (surgical) interventions have failed or when patient condition deteriorates. In these cases it is especially important to perform completion pancreatectomy in an early phase. Postoperative hospital stay and mortality might be reduced with this procedure.

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