ANNALS OF SURGERY
Vol. 221, No. 6, 635–648

Optimal Management of the Pancreatic Remnant After Pancreaticoduodenectomy

Stuart G. Marcus, M.D.,* Henry Cohen, M.P.H.,† and John H. C. Ranson, B.M., B.Ch., M.A.*

From the Departments of Surgery and Environmental Medicine,† New York University School of Medicine, New York, New York*

Objective

The authors evaluated methods of operative management of the pancreatic remnant after pancreaticoduodenectomy.

Summary Background Data

Despite reductions in mortality after pancreaticoduodenectomy, leakage from the pancreatic remnant still may cause significant morbidity. Patients with small, unobstructed pancreatic ducts or soft, friable pancreata are at particularly high risk. Although numerous surgical techniques have been described to avoid such complications, no single method is suitable for all patients.

Methods

The authors retrospectively reviewed the medical records of 114 consecutive patients who underwent pancreaticoduodenectomy. Sixty-nine patients were men (61%) and 45 were women (39%), with median age 66 years. Underlying disease was malignant in 87 (76%) and benign in 27 (24%). Patients were divided into groups based on risk for postoperative pancreatic fistula and on the operative management of the pancreatic remnant. Sixty-eight patients underwent end-to-side pancreaticojejunostomy, 13 of whom were high risk (group 1A) and 55 of whom were low risk (group 1B). Thirty-seven patients, all high risk, had either pancreatic duct closure by oversewing (N = 19, group 2) or end-to-end pancreaticojejunal invagination (N = 18, group 3). Nine patients underwent total pancreatectomy (group 4). Morbidity related to prolonged pancreatic drainage (PPD) of greater than 20 days was determined.

Results

Overall incidence of PPD was 17% and caused the only death. Patients considered high risk for postoperative pancreatic fistula had a 36% incidence of PPD compared with 2% in patients considered low risk ($p < 0.0001$). Prolonged pancreatic drainage frequency related to the method of pancreatic remnant management was as follows: group 1A, 15%; group 1B, 2%; group 2, 79%; and group 3, 6% ($p < 0.001$ for group 2 *vs.* other groups). No serious sequelae followed PPD in 15 patients (79%); however, 4 patients required reoperation for pseudocyst or abscess drainage; one in group 1A (who died) and three in group 2. Multivariate analysis revealed that operative technique (oversewing of the pancreatic duct) and male sex were significant factors predisposing a patient to the development of PPD.

Conclusions

After pancreaticoduodenectomy, pancreatic remnant management by end-to-side pancreaticojejunostomy appeared safe in low-risk patients. In high-risk patients, end-to-end

pancreaticojejunal invagination was the safest option. Morbidity was greatest after pancreatic duct closure without anastomosis.

The reported operative mortality after pancreaticoduodenectomy has decreased dramatically in several recently published reports,[1-8] but complications arising from the pancreatic anastomosis remain a major source of morbidity. In eight large studies during the past 5 years, including 1865 patients, the overall mortality averaged 6.0% (range 0–8.9%). Postoperative pancreatic fistula or leakage occurred in 13.5% (range 6–25%) of patients and was a contributing factor to at least 25% of postoperative deaths. It is believed that patients with a nondilated pancreatic duct and a soft, friable pancreas are especially susceptible to this complication.

Several techniques have been advocated for management of the pancreatic remnant after pancreaticoduodenectomy, in an attempt to decrease the incidence of postoperative pancreatic fistula and its associated morbidity. These include end-to-side pancreaticojejunostomy,[9] pancreaticojejunal invagination,[10] total pancreatectomy,[11] pancreaticogastrostomy,[12-14] pancreatic ductal ligation,[15,16] and pancreatic ductal occlusion.[17] No single method has proven to be satisfactory for all patients. In the current study, we retrospectively reviewed our patient population and our methods of pancreaticoduodenectomy to identify factors predisposing to the development of pancreatic fistula.

PATIENTS AND METHODS

The medical records of 114 consecutive patients undergoing pancreaticoduodenectomies between July 1977 and December 1993 by the senior author (JHCR) and by residents under his direct supervision were retrospectively reviewed. Ninety-seven procedures (85%) were performed after 1986. All clinical, operative, and pathologic data were obtained from treatment records at our institution. The following data were abstracted from each chart: 1) patient characteristics—age, sex, race, and histopathologic diagnosis; 2) clinical presentation—past medical and surgical history, predominant symptoms, physical examination findings and laboratory values at the time of hospital admission for surgical therapy; 3) operative details—time, estimated blood loss, intraoperative transfusions, operative technique; 4) postoperative recovery—early and late complications, time to resumption of regular diet, to removal of operative drains, and to hospital discharge; and 5) follow-up information—presence of postoperative diabetes mellitus, diarrhea or steatorrhea, current disease status, date and cause of death.

All follow-up data are from the time of pancreaticoduodenectomy. If current follow-up data were not available from the hospital chart or office records, attempts were made to contact patients or their referring physician by telephone. Follow-up data on 109 patients (96%) were current as of January 1994, with a median potential follow-up time of 2.3 years (0.08–16.9 years) from the time of surgical therapy.

Patients were categorized as being either high risk or low risk for postoperative pancreatic fistula. High-risk patients had small, unobstructed pancreatic ducts or soft, friable pancreata. Patients with dilated pancreatic ducts or firm, fibrotic pancreata were considered low risk for postoperative pancreatic fistula. Patients with small ducts but established pancreatic fibrosis were judged to be low risk.

Four variations of pancreaticoduodenectomies were performed (Fig. 1). End-to-side pancreaticojejunostomies were undertaken in 68 patients. Thirteen of these 68 patients were considered high risk for postoperative pancreatic fistula (group 1A) and 55 patients were considered low risk (group 1B). Thirty-seven additional patients, all high risk, had either ligation of the pancreatic duct with oversewing of the transected pancreas (N = 19, group 2) or end-to-end pancreaticojejunal invagination of the remnant (N = 18, group 3). Nine patients underwent total pancreatectomies (group 4). One patient in group 4 was high risk and one was low risk for postoperative pancreatic fistula. Seven patients in group 4 were not applicable for risk classification because involvement of the entire pancreas by their disease process necessitated total pancreatectomy for pathologic reasons.

Patients in group 1 underwent end-to-side pancreaticojejunostomies by a technique similar to that described by Cattell[9] (Fig. 1A). After excision of the specimen, the end of the jejunum was closed in two layers. The jejunal limb was then brought up to the pancreatic remnant, usually in an anticolic position. The transected end of the pancreas was closed with interrupted simple silk sutures, except for the pancreatic duct. The posterior pancreatic capsule was sewn to the seromuscular jejunal wall with interrupted silk sutures. A full-thickness stab incision was then made in the jejunal wall, corresponding in size and position to the pancreatic duct. The jejunal

Presented at the 106th Annual Session of the Southern Surgical Association, December 4–7, 1994, Palm Beach, Florida.

Address reprint requests to John H.C. Ranson, B.M., B.Ch., M.A., S. Arthur Localio Professor of Surgery, New York University Medical Center, 530 First Ave, Suite 6B, New York, NY 10016.

Accepted for publication January 18, 1995.

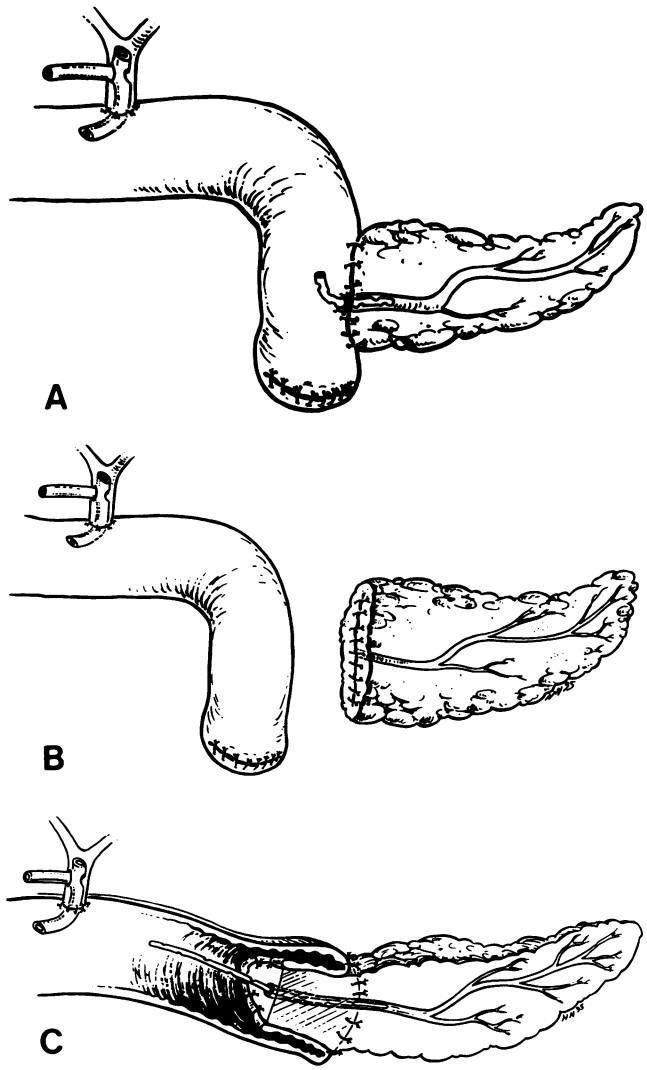

Figure 1. Diagrammatic representation of three methods of pancreatic remnant management after pancreaticoduodenectomy: (A) end-to-side pancreaticojejunostomy (groups 1A and 1B); (B) oversewing of the transected pancreatic remnant (group 2); and (C) end-to-end pancreaticojejunal invagination (group 3).

mucosa was sutured circumferentially to the pancreatic ductal mucosa with fine interrupted polyglycolic acid sutures. Before completing the mucosa-to-mucosa anastomosis, a short (6 cm) silastic catheter was introduced into the jejunum and pancreatic duct as an anastomotic stent and sutured in place with a polyglycolic acid stitch. The anastomosis was completed by a layer of interrupted silk sutures between the anterior pancreatic capsule and the seromuscular jejunum.

For patients in group 2 (Fig. 1B), the end of the pancreatic remnant was closed with interrupted silk sutures. The pancreatic duct was identified and oversewn with a polypropylene suture. The duct was further occluded by a suture that encircled it through the pancreatic parenchyma approximately 5 mm from the transected margin.

In patients undergoing pancreaticojejunal invagination (group 3; Fig. 1C), the end of the jejunum was not closed. The width of the pancreatic remnant was evaluated relative to that of the jejunum. A bulky pancreatic remnant sometimes required further pancreatic resection to yield a remnant that could be invaginated into the jejunum. In one patient who had an unusually bulky pancreatic remnant infiltrated with fat, attempted invagination was abandoned in favor of pancreatic ductal closure. Once the jejunum and pancreas were prepared, a layer of interrupted fine silk sutures was placed between the posterior pancreatic capsule and the seromuscular layer of the jejunum. These sutures were placed approximately 2 cm from the cut end of each organ. The capsular edge of the transected pancreas and the free end of the jejunum were then sewn to each other circumferentially. Before completion of this layer, a silastic catheter was introduced into the pancreatic duct and secured with polyglycolic acid sutures. In addition, the sutures between the pancreas and the jejunum included the pancreatic ductal wall at the appropriate points. Finally, an anterior outer layer of interrupted silk sutures was placed in a manner similar to the outer posterior layer and the pancreas was thus invaginated into the free end of the jejunum.

The final group of patients underwent total pancreatic resection (group 4). In four cases, the spleen was preserved and in another four, it was resected. One patient in group 4 had a previous distal pancreatectomy and splenectomy. No pancreatic drains were left in these nine patients. In all other cases, the pancreatic anastomosis or the oversewn remnant was drained by two silastic closed suction drains placed anteriorly and posteriorly to the pancreatic stump.

For the purpose of this report, prolonged pancreatic drainage (PPD) is defined as drainage that required the presence of pancreatic drains for more than 20 days. Prolonged pancreatic drainage is used synonomously with pancreatic fistula. The timing of pancreatic drain removal was based on the judgment of the senior surgeon (JHCR). Factors such as intraoperative findings, the quantity of drainage, and the drainage amylase were considered before drain removal. Octreotide was not used in any patients.

Differences between medians were compared by Wilcoxon's rank sum test. Differences in proportions were determined by the Fisher exact test. Multivariate analysis of factors that significantly affected the presence of PPD was performed using nominal logistic regression.[18] The McNemar test was used to evaluate the significance of changes between preoperative and postoperative symptoms.[19] The Kaplan-Meier method was used to cal-

Table 1. CHARACTERISTICS OF 114 PATIENTS UNDERGOING PANCREATICODUODENECTOMY*

	High Risk (n = 51)	Low Risk (n = 56)	Risk N/A (n = 7)	Total (n = 114)
Age (yrs)				
Median	62	68†	67	66
Range	18–82	30–84	34–74	18–84
Sex				
Male	32 (63)	32 (57)	5 (71)	69 (61)
Female	19 (37)	24 (43)	2 (29)	45 (39)
Race				
White	45 (88)	51 (91)	7 (100)	103 (90)
Other	6 (12)	5 (9)	0 (0)	11 (10)
Final histology				
Malignant	37 (73)	46 (82)	4 (57)	87 (76)
Benign	14 (27)	10 (18)	3 (43)	27 (24)
Final pathology				
Pancreatic cancer	9 (18)	20 (36)‡	3 (43)	32 (28)
Ampullary cancer	11 (22)	11 (20)	0 (0)	22 (19)
Cystic neoplasm	5 (10)	8 (14)	0 (0)	13 (11)
Chronic pancreatitis	3 (6)	7 (12)	3 (43)	13 (11)
Bile duct cancer	7 (13)	3 (5)	0 (0)	10 (9)
Duodenal tumor	9 (18)	1 (2)§	0 (0)	10 (9)
Islet cell tumor	3 (6)	4 (7)	1 (14)	8 (7)
Miscellaneous	4 (8)	2 (4)	0 (0)	6 (6)

* N/A = not applicable.
At the time of pancreaticoduodenectomy.
† p = 0.0004.
‡ p = 0.05.
§ p = 0.006.
Numbers in parenthesis are percentages.

culate the probability of overall survival as a function of time at risk.[20] The log-rank test was used to evaluate the significance of survival by histologic type. All p values were two-tailed, and a value of less than 0.05 was considered statistically significant.

RESULTS

The clinical characteristics of the 114 patients included in this study are presented in Table 1. Patients considered high risk for postoperative pancreatic fistula were compared with patients considered low risk to define factors that may preoperatively identify patients at high risk for pancreatic fistula. Seven patients undergoing total pancreatectomies for pathologic reasons could not be classified by risk and were excluded from this comparison.

Overall, the median age of all 114 patients was 66 (range, 18–84 years) at the time of pancreaticoduodenectomy. High-risk patients were significantly younger than patients considered low risk (Table 1; p = 0.0004). Sixty-nine patients were men (61%), and 45 patients were women (39%). Malignant disease was ultimately diagnosed in 87 patients (76%), and benign disease was diagnosed in 27 patients (24%). High-risk and low-risk patients were well matched for sex, race, and incidence of malignant disease.

Carcinoma of the head of the pancreas was the most common histopathologic diagnosis, accounting for 28% of patients. Patients with pancreatic cancer were more likely to be considered low risk for postoperative pancreatic fistula compared with patients with other pathologies (p = 0.05). Conversely, patients with duodenal cancer were more likely to be considered high risk (p = 0.006). There was no other significant association between risk for postoperative pancreatic fistula and any other pathology. Six patients are listed as having miscellaneous conditions. One patient each was identified with intraductal papillary adenomatosis, leiomyoma obstructing the ampulla of Vater, pancreaticoblastoma, bleeding duodenal hemangiomas, papillary solid epithelial tumor, and duodenal carcinoid. Three of these conditions were malignant.

Predominant signs and symptoms and abnormal laboratory values are summarized in Table 2. Pain, jaundice, and weight loss were the most common presenting symptoms. Although the majority of patients had nor-

Table 2. CLINICAL PRESENTATION OF 114 PATIENTS UNDERGOING PANCREATICODUODENECTOMY*

	High Risk (n = 51)	Low Risk (n = 56)	Risk N/A (n = 7)	Total (n = 114)
Signs and symptoms				
Pain	27 (53)	32 (57)	4 (57)	63 (55)
Jaundice	26 (51)	32 (57)	2 (29)	60 (53)
Weight loss	19 (37)	29 (52)	4 (57)	52 (46)
Pruritus	14 (27)	16 (29)	0 (0)	30 (26)
Diarrhea	7 (14)	17 (30)†	1 (14)	25 (22)
Diabetes mellitus	2 (4)	16 (29)‡	5 (71)	23 (20)
Nausea	11 (22)	10 (18)	2 (29)	23 (20)
Vomiting	9 (18)	5 (9)	2 (29)	16 (14)
Anorexia	9 (18)	7 (12)	2 (29)	18 (16)
Abnormal serum chemistries				
Alkaline phosphatase	24 (47)	31 (55)	4 (57)	59 (52)
Total bilirubin	21 (41)	25 (45)	2 (29)	48 (42)
SGOT	15 (29)	19 (34)	3 (43)	37 (32)
Glucose	5 (10)	21 (38)‡	2 (29)	28 (25)
Amylase	8 (16)	14 (25)	1 (14)	23 (20)

* At the time of hospital admission for pancreaticoduodenectomy.
† p = 0.06.
‡ p ≤ 0.001.
N/A = not applicable; SGOT = serum glutamic oxaloacetic transaminase.
Numbers in parentheses are percentages.

Table 3. OPERATIVE TECHNIQUE IN 114 PATIENTS UNDERGOING PANCREATICODUODENECTOMY

	High Risk (n = 51)	Low Risk (n = 56)	Risk N/A* (n = 7)	Total (n = 114)
Management of pancreatic remnant				
End-to-side PJ	13 (26)	55 (98)	N/A	68 (59)
Oversew	19 (37)	0 (0)	N/A	19 (17)
Invagination	18 (35)	0 (0)	N/A	18 (16)
Total pancreatectomy	1 (2)	1 (2)	7 (100)	9 (8)
Pylorus sparing				
Yes	35 (69)	38 (68)	0 (0)	73 (64)
No	16 (31)	18 (32)	7 (100)	41 (36)

N/A = not applicable; PJ = pancreaticojejunostomy.
Numbers in parentheses are percentages.

mal glucose tolerance at presentation, patients with diabetes mellitus and hyperglycemia were more likely to be considered low risk than patients without these findings ($p \leq 0.001$). Patients with diarrhea also tended to be considered low risk ($p = 0.06$). Otherwise, the clinical presentation of high- and low-risk patients was comparable.

After pancreaticoduodenal resection, four methods of pancreatic remnant management were used as summarized in Table 3. End-to-side pancreaticojejunostomy was preferentially performed in patients considered low risk for postoperative pancreatic fistula. High-risk patients underwent a variety of procedures, as shown. Seventy-three patients (64%) underwent pylorus-sparing pancreaticoduodenectomies. All seven patients undergoing total pancreatectomy for pathologic reasons had pylorus-resecting surgery.

Operative characteristics and postoperative recovery were analyzed according to the intraoperative method of pancreatic remnant management. Operative time and estimated blood loss were similar between the various methods (Table 4). Patients undergoing pancreaticojejunal invagination (group 3) tended to have the least number of intraoperative blood transfusions, and patients undergoing total pancreatectomies (group 4) had the most.

Prolonged pancreatic drainage of >20 days, indicative of pancreatic fistula, occurred postoperatively in 19 of the 114 patients (17%). Because patients undergoing total pancreatectomies were not at risk for PPD, they were excluded from additional analysis. The average duration of pancreatic drainage for the whole group of patients undergoing pancreatic ductal ligation with oversewing of the transected pancreas (group 2) was 58.6 days compared with 17.8 days of drainage for all patients in group 1A, 12.9 days in group 1B, and 15.8 days in group 3 ($p \leq 0.0001$).

Early and late morbidity in 105 patients at risk for pancreatic fistula are summarized in Table 5. Patients considered high risk for postoperative pancreatic fistula had a 36% incidence of PPD compared with 2% in patients considered low risk ($p < 0.0001$). Prolonged pancreatic drainage frequency by group was as follows: group 1A, 15%; group 1B, 2%; group 2, 79%; group 3, 6% ($p < 0.001$ for group 2 *vs.* all other groups). No serious sequelae followed PPD in 15 patients (79%); however, 4 patients had major complications as a result of PPD. The characteristics of these four patients are shown in Table 6. Two patients, one each in group 1A and group 2, developed intra-abdominal abscesses postoperatively, requiring early operative drainage. The patient in group 1A also had undergone reoperation on postoperative day 1 for control of hemorrhage. He went on to develop

Table 4. OPERATIVE CHARACTERISTICS OF 114 PATIENTS UNDERGOING PANCREATICODUODENECTOMY

	Group 1A (n = 13)	Group 1B (n = 55)	Group 2 (n = 19)	Group 3 (n = 18)	Group 4 (n = 9)
Time for pancreaticoduodenectomy (min)					
Median	360	360	360	345	390
Range	(300–420)	(300–540)	(330–480)	(300–420)	(300–600)
Estimated blood loss (mL)					
Median	750	700	800	700	800
Range	(250–1300)	(200–5000)	(350–3000)	(200–1200)	(500–6000)
Intraoperative transfusions (units)					
Median	2	1	1	0*	3†
Range	(0–4)	(0–12)	(0–7)	(0–4)	(0–8)

* $p = 0.009$ *vs.* group 1A; $p = 0.01$ *vs.* group 4.
† $p = 0.01$ *vs.* group 3; $p = 0.04$ *vs.* group 1B.

Table 5. MORBIDITY RELATED TO PANCREATIC REMNANT STATUS

	Group	No	PPD (%)	Complications		Reoperations		Death
				Early	Late	Early	Late	
Overall*		105	19 (18)	9	7	3	6	1
High risk								
End-to-side PJ	1A	13	2 (15)	3	0	1‡	0	1
No anastomosis	2	19	15 (79)†	2	4	1	3	0
Invagination	3	18	1 (6)	1	1	0	1	0
Totals		50	18 (36)	6	5	2	4	1
Low risk								
End-to-side PJ	1B	55	1 (2)§	3	2	1	2	0

PPD = prolonged pancreatic drainage; PJ = pancreaticojejunostomy; numbers refer to number of patients.
* excludes nine patients undergoing total pancreatectomy.
† $p < 0.001$ *vs.* groups 1A, 1B, and 3.
‡ One patient underwent reoperation on postoperative day 1 for hemorrhage, reoperation on postoperative day 16 for abscess drainage. Patient died of sepsis on postoperative day 30.
§ $p < 0.0001$ *vs.* high-risk patients.

multi-organ system failure and died of sepsis on postoperative day 30. This patient represents the one postoperative death in this series (0.8%). Two patients in group 2 required cystgastrostomies for pseudocyst formation, which followed PPD.

Overall, there were nine early and seven late major complications (Table 5). Nine complications required reoperation—three early and six late. Other than complications related to PPD, five additional operative procedures for complications of pancreaticoduodenectomy were required. One patient in group 1B underwent early reoperation for control of postoperative hemorrhage; late revision of the hepaticojejunostomy for stricture was required in three patients—at 1 year in two patients (one each in group 1B and 3) and at 3 years in one patient (group 2); one patient in group 1B underwent lysis of an adhesive small bowel obstruction at 3 months. Early complications that did not require operative intervention were as follows: one patient in group 1B had a postoperative myocardial infarction; four patients (two in group 1A, one each in groups 1B and 2) developed bile leaks at the hepaticojejunostomy, which resolved with conservative treatment; and one patient with an intra-abdominal abscess after pancreaticojejunal invagination (group 3) was successfully treated with percutaneous drainage and intravenous antibiotics. The position of this abscess did not suggest a relationship to the pancreatic anastomosis. The one late complication that did not require operative intervention was a patient in group 2 whose postoperative course was complicated by PPD and has had a stable asymptomatic 4 × 7-cm pseudocyst for 2.5 years. In addition, one 74-year-old patient who

Table 6. CHARACTERISTICS OF PATIENTS UNDERGOING REOPERATION FOR COMPLICATIONS OF PPD

Patient No	Age (yrs)/ Race/Sex	Group	Pathology	Days of Drainage	Complication	Time to Reoperation	Procedure Performed	Outcome
1	67/W/M	2	Ampullary cancer	60	Abscess	34 days	Drainage	Alive, NRD at 3.6 yrs
2*	68/W/M	1A	Ampullary cancer	30	Abscess	16 days	Drainage	Dead of sepsis at 30 days
3	50/W/F	2	Cystic neoplasm	120	Pseudocyst	7 mos	Cystgastrostomy	Alive, NRD at 4.5 yrs
4	41/W/M	2	Islet cell tumor	54	Pseudocyst	4.5 mos	Cystgastrostomy	Alive, NRD at 4.5 yrs

PPD = prolonged pancreatic drainage; NRD = no residual disease.
* Patient also underwent reoperation on postoperative day 1 for hemorrhage.

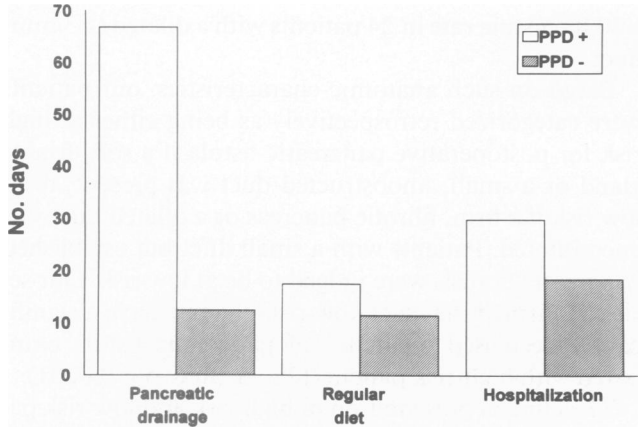

Figure 2. Postoperative recovery of patients with PPD *vs.* patients without PPD. Patients with PPD had a significantly longer period of time of pancreatic drainage ($p < 0.0001$), to resumption of regular diet ($p = 0.02$), and to hospital discharge ($p < 0.0001$) compared with patients without PPD.

underwent total pancreatectomy died of diabetic ketoacidosis at 3 months.

Figure 2 compares the recovery of patients whose hospital course was complicated by PPD *versus* those without PPD. Patients with PPD had their drains in place an average of 66.8 days compared with 12.4 days for those without PPD ($p < 0.0001$). An average of 17.4 days elapsed between pancreaticoduodenectomy and resumption of regular diet in patients whose postoperative recovery was complicated by PPD, compared with 11.4 days for patients without PPD ($p = 0.02$). Hospital length of stay was 29.7 days for patients with PPD compared with 18.3 days for those without PPD ($p < 0.0001$).

Age, sex, risk classification, operative technique and characteristics, pathology, histology, presenting signs and symptoms, and laboratory values were all considered potential influences for the development of PPD. Multivariate analysis revealed that male sex ($p = 0.03$) and operative technique, specifically ligation of the pancreatic duct with oversewing of the transected pancreas ($p = 0.0004$), were the only significant factors predisposing a patient to the development of PPD.

The pre- and postoperative incidence of diabetes mellitus and diarrhea or steatorrhea was examined for all 114 patients. There was no statistically significant difference in the incidence of diabetes mellitus postoperatively as compared with preoperatively in any group (Fig. 3). Patients undergoing pancreatic transection without anastomosis (group 2) had significant increases in diarrhea or steatorrhea postoperatively compared with preoperatively (Fig. 4, $p = 0.03$), as did patients undergoing total pancreatectomies (group 4, $p = 0.004$). Although 18 of 55 low-risk patients (35%) undergoing end-to-side pancreaticojejunostomies (group 1B) required postoperative supplemental pancreatic digestive enzymes, 31% of patients in this group had diarrhea at presentation. Likewise, analysis of patients in groups 1A and 3 revealed that the postoperative incidence of diarrhea or steatorrhea was not significantly different from the preoperative incidence.

Survival curves are shown in Figure 5. Overall actuarial survival rate for all 114 patients undergoing pancreaticoduodenectomies was 56% at 5 years (Fig. 5A). Patients with benign disease had a 92% 5-year survival rate compared with 44% for those with malignant disease (Fig. 5B, $p = 0.0001$). When survival by pathologic diagnosis was analyzed, patients with pancreatic adenocarcinoma had the poorest results, with a median survival of approximately 15 months and only 1 of 32 patients alive at 5 years (data not shown).

DISCUSSION

Failure of any surgical anastomosis may have devastating consequences. Anastomosis of the pancreas to the small bowel presents special hazards because of the digestive capacities of activated pancreatic secretions and also, perhaps, because the anastomosis usually involves not only the pancreatic duct, but also pancreatic parenchyma. In the current series, overall 30-day mortality was 0.8%, confirming the acceptable mortality rate now associated with pancreaticoduodenectomy.[3] Prolonged pancreatic drainage of >20 days indicative of pancreatic fistula, occurred in 19 of 114 patients (17%) after pancreaticoduodenectomy and directly contributed to the one postoperative death. This is comparable to the reported incidence of pancreatic fistula in other series.[1-8,21-25] Although 79% of our patients with PPD had no serious sequelae, morbidity was not inconsequential. Postoperative recovery in these patients was complicated by a significantly longer period of time to resumption of regular

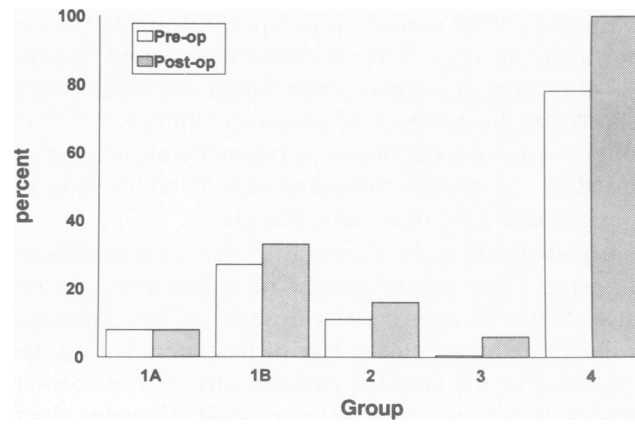

Figure 3. Incidence of preoperative and postoperative diabetes mellitus related to method of pancreatic remnant management. There was no statistically significant difference in any group.

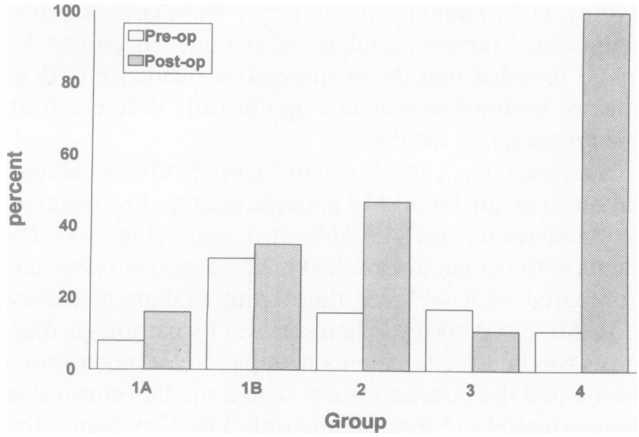

Figure 4. Incidence of preoperative and postoperative diarrhea or steatorrhea related to method of pancreatic remnant management. These symptoms were significantly increased postoperatively compared with preoperatively for patients in group 2 ($p = 0.03$) and in group 4 ($p = 0.004$).

diet and a significantly longer hospitalization. Also, most patients with PPD were discharged home with their pancreatic drains in place, necessitating more frequent outpatient office visits.

The most important factor in the prevention of pancreatic fistula after pancreaticoduodenectomy is technical precision and gentleness in construction of the pancreatic anastomosis. Several other factors predisposing to the development of postoperative pancreatic fistula have been suggested in earlier studies. Age of patients older than 65 years, hyperbilirubinemia, urgent operation, increased operative blood loss, and failure to stent the pancreaticojejunal anastomosis all have been reported to be associated with pancreatic fistula.[22,23,25] Additional considerations influencing the safety of the pancreatic anastomosis are related to the pancreas itself and may be broadly characterized as anatomic and functional. The most significant anatomic features are the consistency of the pancreatic parenchyma and the size of the pancreatic duct. Several studies have found that the risk of postoperative pancreatic fistula was significantly reduced by the presence of pancreatic fibrosis.[1,5,22,25] In patients with normal pancreatic parenchyma, fistulae occurred in 12% to 28% compared with 5% to 9% in those considered to have pancreatic fibrosis.

A dilated pancreatic duct may decrease the possibility of postoperative fistula because of technical factors because dilated ducts are easier to sew.[26–28] The influence of ductal diameter on the risk of postoperative fistulae is clouded by the fact that patients with chronic benign pancreatic fibrosis may have a small diameter duct. Nonetheless, Kojima[28] reported a 44.4% pancreatic fistula rate after pancreaticojejunostomy in 18 patients with a normal (≤2 mm) pancreatic duct, compared with a 20.8% fistula rate in 24 patients with a dilated (≥3 mm) duct.

Based on such anatomic characteristics, our patients were categorized retrospectively as being either at high risk for postoperative pancreatic fistula if a soft, friable gland or a small, unobstructed duct was present; or at low risk if a firm, fibrotic pancreas or a dilated duct was encountered. Patients with a small duct but established pancreatic fibrosis were judged to be at low risk. Our series confirmed that such low-risk patients have a significantly decreased incidence of pancreatic fistula compared with high-risk patients (2% *vs.* 36%, $p < 0.0001$).

The clinical presentation of high-risk and low-risk patients were compared to identify characteristics predictive of risk for postoperative pancreatic fistula. Older patients and those with evidence of diabetes mellitus or diarrhea were more likely to be considered low risk. These symptoms may be reflective of pancreatic fibrosis and associated pancreatic insufficiency. Patients with pancreatic cancer were more likely to be considered low risk

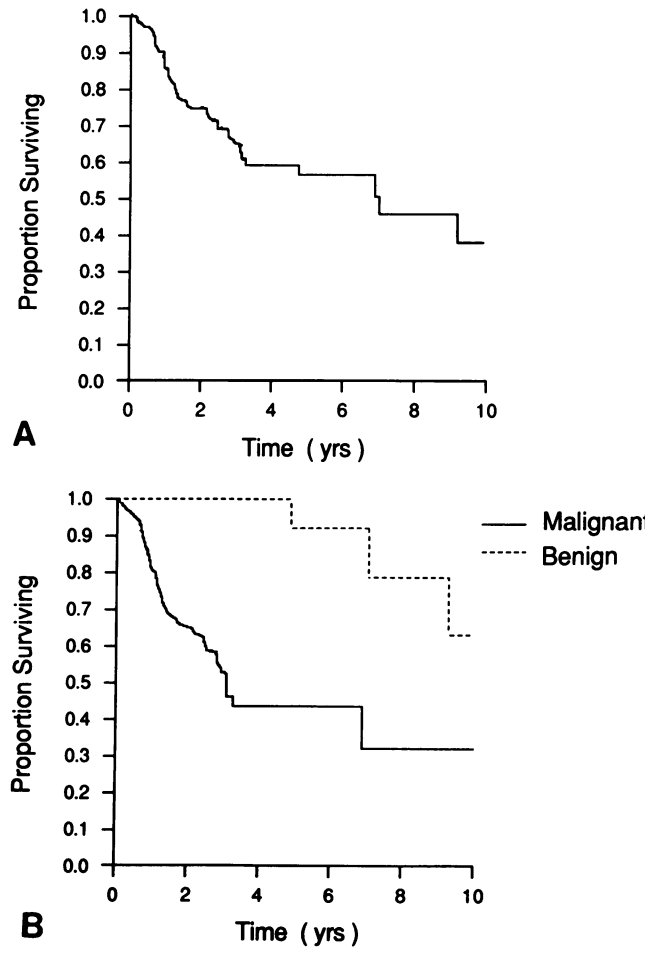

Figure 5. Overall actuarial survival of all 114 patients after pancreaticoduodenectomy: (A) all patients; (B) malignant histology *vs.* benign histology ($p = 0.0005$).

and those with duodenal tumors were more likely to be considered high risk. This was probably because of the frequent presence of pancreatic ductal obstruction found in patients with pancreatic cancer. This was a rare anatomic finding in those with duodenal cancer. Unfortunately, the pathologic process is not always known with certainty before surgical resection. In a recent review and meta-analysis of pancreatic fistula after pancreaticoduodenectomy for malignant tumors, Bartoli et al. found that patients with pancreatic malignancies and ampullary malignancies had a significantly lower incidence of pancreatic fistula than patients with bile duct tumors.[29] We were not able to confirm this finding; although pancreatic cancer correlated with low risk for pancreatic fistula, our sample size was small, and multivariate analysis did not reveal any pathology to be either predictive or protective of postoperative pancreatic fistula formation. Likewise, no presenting characteristic except male sex was predictive of pancreatic fistula in our series. We know of no plausible explanation for why male sex should be an independent predictor of pancreatic fistula formation, and this may reflect a sampling error in our series.

The functional factor affecting the safety of pancreatic surgery is the digestive activity of the pancreas, which also may be related to the anatomic findings. First, in the presence of established pancreatic ductal obstruction or in patients with firm, fibrotic glands (i.e., chronic pancreatitis), the exocrine secretory capacity of the pancreas is sharply reduced. Second, the capacity of the pancreas to destroy itself through acute pancreatitis also is related to the functional integrity of the gland. Mild pancreatic inflammation may occur in a fibrotic gland, but severe postoperative pancreatitis involving the pancreatic remnant almost always occurs in a relatively normal gland. Finally, most of the pancreatic digestive secretions are produced in inactive forms. To destroy adjacent tissue, activation of pancreatic secretions is required, in most instances by succus entericus. Accordingly, leakage of pancreatic juice, which is inactive, rarely causes extensive tissue damage. By contrast, leakage of pancreatic secretions that are activated may lead to far more dire consequences. Thus, it is theoretically possible that the avoidance of the pancreaticojejunal anastomosis may be safer for the patient, although a higher risk of pancreatic fistula would be present.

It has been proposed that the perioperative administration of octreotide may reduce the incidence of postoperative pancreatic fistula by pharmacologically inhibiting exocrine pancreatic secretion. A controlled clinical trial appeared to support this proposal.[30] Unfortunately, that study was multi-institutional and thus, surgical technique was not standardized. In addition, the definition of a pancreatic fistula was so wide that a 27% incidence of pancreatic fistula was reported. It is not clear how clinically significant these fistulae were and how they contributed to overall morbidity and mortality; thus, their results were difficult to interpret. Further studies investigating the use of octreotide are warranted. We did not use octreotide in patients in the current study.

The operative management of the pancreatic remnant also has been shown to be an important factor influencing the development of pancreatic fistulae.[1,23,27] This is confirmed in the current series. Multivariate analysis revealed that operative technique, specifically ligation of the pancreatic duct with oversewing of the transected pancreas, was the most significant factor predisposing a patient to the development of postoperative pancreatic fistula. Four methods of pancreatic remnant management were used in our series. One method for avoiding any problem with the pancreatic remnant is to remove all pancreatic tissue. An "alleged total pancreatectomy for cancer of the pancreas" was undertaken in 1900 by Franke, with survival for 5½ months.[31] More recently, there was a period of interest in total pancreatic resection for all cases of suspected carcinoma of the head of the pancreas.[11] This eliminated the risk of pancreatic fistula and it was hoped that better cancer control may be achieved through wider resection margins, a more adequate lymph node resection, and resection of possible multicentric tumors within the gland. At this time, reported experience does not indicate any improvement in overall short or long-term results of total pancreatectomy compared with pancreaticoduodenectomy.[32–35] The potential advantages are offset by the endocrine and exocrine consequences of removal of all pancreatic tissue. This is supported by our findings. Nine patients in the current series underwent total pancreatectomy. All nine patients required supplemental pancreatic enzymes postoperatively for control of diarrhea or steatorrhea. In addition, all nine patients required insulin postoperatively for glucose control. One patient who was 74 years old was readmitted 3 months postoperatively with uncontrolled diabetic ketoacidosis, which resulted in death. Unless indicated by the extent of disease, total pancreatectomy is not recommended.

Oversewing of the transected pancreas without anastomosis has the advantage of avoiding activation of pancreatic enzymes. Thus, a pancreatic fistula from the oversewn pancreatic remnant would be less dangerous than one from a pancreaticojejunal anastomosis. In 1971, Goldsmith reported similar morbidity and mortality in 45 patients undergoing ductal ligation compared with 34 patients who had their pancreatic duct reimplanted into the gastrointestinal tract.[16] However, subsequent reports[23,27,36,37] have reported pancreatic fistula rates of 50% to 100%, without any subsequent mortality. There appears to be no difference in fistula rate between glands

ligated with sutures or with staples.[27] In the current series, 79% of patients with oversewing of the transected pancreas developed pancreatic fistula. Although there were no deaths in these 15 patients, reoperation was required in three patients (20%) for abscess or pseudocyst drainage. In addition, diarrhea or steatorrhea was significantly increased in this group of patients postoperatively *versus* preoperatively. The high incidence of PPD and its subsequent complications make this method unacceptable.

Occlusion of the pancreatic stump with synthetic or biologic substances to suppress exocrine pancreatic secretion also has been proposed as a safe alternative to pancreaticojejunal anastomosis. Di Carlo et al. reported two fistulas occurring in 51 patients (4%) after Neoprene injection in the Wirsung duct.[17] Both fistulae resolved spontaneously without complications. With limited postoperative follow-up, there did not appear to be an adverse effect on glucose tolerance, however all patients in their study required supplemental pancreatic digestive enzymes. Although we have no personal experience with this technique, the low rate of postoperative pancreatic fistula appears to be offset by the total loss of pancreatic exocrine function.

Most patients in our study underwent end-to-side pancreaticojejunostomy by a technique similar to that described by Cattell.[9] In our series, this method appeared safe in selected patients; only 1 of 55 low-risk patients developed a postoperative pancreatic fistula, and no serious complications arose as a result. In addition, pancreatic exocrine function did not appear to be adversely affected in these patients. On the other hand, 2 of 13 high-risk patients developed pancreatic fistulae after end-to-side pancreaticojejunostomies, and one of these resulted in death. Thus, although end-to-side pancreaticojejunostomy is acceptable for low-risk patients, in our experience, it does not appear safe for high-risk patients.

End-to-end pancreaticojejunal invagination was used in 18 high-risk patients. Only one patient developed PPD postoperatively, and this resolved spontaneously. The overall complication rate in this group, including the incidence of postoperative diarrhea or steatorrhea, compared favorably to high-risk patients undergoing ductal ligations or end-to-side pancreaticojejunostomies. For patients considered high risk for pancreatic fistula, jejunal invagination of the pancreatic remnant appears to be a safe technique. It is possible that this method should be applied to all patients undergoing pancreaticoduodenectomies. However, the end-to-side pancreaticojejunostomy avoids problems of discrepancy in size between the pancreatic remnant and the jejunum, and we believe that the end-to-side technique is simpler to perform.

Pancreaticogastrostomy is another procedure that has been proposed as a safe and effective method of pancreatic drainage after pancreaticoduodenectomy. Using this technique, pancreatic fistula rates of 0% have been reported in three separate series.[12–14] Theoretical advantages of this technique include the acid pH of the stomach, which inhibits the activation of pancreatic enzymes; the thickness of the gastric wall, which facilitates suturing; and the anatomic proximity of the two organs. A theoretical disadvantage is an anastomosis in direct continuity with the functioning gastrointestinal tract as opposed to the use of a defunctionalized intestinal limb. Although this method of reconstruction was not used in our patients, we believe that further investigation is warranted, based on the excellent results reported.

No single method of pancreatic remnant management after pancreaticoduodenectomy is suitable for all patients. The pancreatic surgeon must have more than one technique for managing the pancreatic remnant in his/her armamentarium. This is especially true for patients with small, unobstructed pancreatic ducts or soft, friable pancreata. Such high-risk patients should undergo alternative procedures to end-to-side pancreaticojejunostomies to restore pancreaticointestinal continuity. In our hands, pancreaticojejunal invagination appears to be a safe and effective alternative.

Acknowledgments

The authors thank Helena Logan for her help in editing this manuscript and Russell Crosbie for his help with medical records.

References

1. Matsumoto Y, Fujii H, Miura K, et al. Successful pancreaticojejunal anastomosis for pancreaticoduodenectomy. Surg Gynecol Obstet 1992; 175:555–562.
2. Roder JD, Stein HJ, Huttl W, et al. Pylorus-preserving *versus* standard pancreaticoduodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. Br J Surg 1992; 79:152–155.
3. Cameron JL, Pitt HA, Yeo CJ, at al. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993; 217:430–438.
4. Hannoun L, Christophe M, Ribeiro J, et al. A report of forty-four instances of pancreaticoduodenal resection in patients more than seventy years of age. Surg Gynecol Obstet 1993; 177:556–560.
5. Baumel H, Huguier M, Manderscheid JC, at al. Results of resection for cancer of the exocrine pancreas: a study from the French Association of Surgery. Br J Surg 1994; 81:102–107.
6. Cullen JJ, Sarr MJ, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: incidence, significance, and management. Am J Surg 1994; 168:295–298.
7. Tsao JI, Rossi RL, Lowell JA. Pylorus-preserving pancreaticoduodenectomy: is it an adequate cancer operation? Arch Surg 1994; 129:405–412.
8. Wade TP, Radford DM, Virgo KS, et al. Complications and outcomes in the treatment of pancreatic adenocarcinoma in the United States veteran. J Am Coll Surg 1994; 179:38–48.
9. Cattell RB. A technic for pancreatoduodenal resection. Surg Clin North Am 1948; 28:761–775.

10. Jordan GL Jr. Pancreatic resection for pancreatic cancer. Surg Clin North Am 1989; 69:569–597.
11. Brooks JR, Culebras JM. Cancer of the pancreas: Palliative operation, Whipple procedure, or total pancreatectomy? Am J Surg 1976; 131:516–520.
12. Icard P, Dubois F. Pancreaticogastrostomy following pancreatoduodenectomy. Ann Surg 1988; 207:253–256.
13. Delcore R, Thomas JH, Pierce GE, et al. Pancreaticogastrostomy: a safe drainage procedure after pancreatoduodenectomy. Surgery 1990; 108:641–647.
14. Takao S, Shimazu H, Maenohara S, et al. Modified pancreaticogastrostomy following pancreaticoduodenectomy. Am J Surg 1993; 165:317–321.
15. Brunschwig A. Resection of head of pancreas and duodenum for carcinoma-pancreatoduodenectomy. Surg Gynecol Obstet 1937; 65:681–685.
16. Goldsmith HS, Ghosh BC, Huvos AG. Ligation *versus* implantation of the pancreatic duct after pancreaticoduodenectomy. Surg Gynecol Obstet 1971; 132:87–92.
17. DiCarlo VD, Chiesa R, Pontiroli AE, et al. Pancreaticoduodenectomy with occlusion of the residual stump by Neoprene injection. World J Surg 1989; 13:105–111.
18. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: Jon Wiley and Sons, 1989.
19. Siegel S, Castellan N. Non-Parametric Statistics for the Behavioral Sciences. New York: McGraw-Hill, 1988.
20. Kaplan E, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–481.
21. Trede M, Schwall G. The complications of pancreatectomy. Ann Surg 1988; 207:39–47.
22. Lerut JP, Gianello PR, Otte JB, et al. Pancreaticoduodenal resection: surgical experience and evaluation of risk factors in 103 patients. Ann Surg 1984; 199:432–437.
23. Grace PA, Pitt HA, Tompkins RK, et al. Decreased morbidity and mortality after pancreaticoduodenectomy. Am J Surg 1986; 151: 141–149.
24. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. Ann Surg 1987; 206:358–365.
25. Miedema BW, Sarr MG, van Heerden JA, et al. Complications following pancreaticoduodenectomy: current management. Arch Surg 1992; 127:945–950.
26. Braasch JW, Gray BN. Considerations that lower pancreatoduodenectomy mortality. Am J Surg 1977; 133:480–484.
27. Papachristou DM, Fortner JG. Pancreatic fistula complicating pancreatectomy for malignant disease. Br J Surg 1981; 68:238–240.
28. Kojima Y, Katayama K, Note M, et al. Pancreaticojejunostomy and pancreatic leakage after pancreaticoduodenectomy. Int Surg 1992; 77:80–83.
29. Bartoli FG, Arnone GB, Ravera G, et al. Pancreatic fistula and relative mortality in malignant disease after pancreaticoduodenectomy: review and statistical meta-analysis regarding 15 years of literature. Anticancer Research 1991; 11:1831–1848.
30. Buchler M, Freiss H, Klempa I, et al. Role of octreotide in the prevention of postoperative complications following pancreatic resection. Am J Surg 1992; 163:125–131.
31. Brunschwig A. The Surgery of Pancreatic Tumors. St. Louis: CV Mosby Co, 1942:274.
32. Warshaw AL, Swanson RS. Pancreatic cancer in 1988: possibilities and probabilities. Ann Surg 1988; 208:541–553.
33. van Heerden JA, McIlrath DC, Ilstrup DM, et al. Total pancreatectomy for ductal adenocarcinoma of the pancreas: an update. World J Surg 1988; 12:658–662.
34. Brooks JR, Brooks DC, Levine JD. Total pancreatectomy for ductal cell carcinoma of the pancreas. Ann Surg 1989; 209:405–410.
35. Sarr MG, Behrns KE, van Heerden JA. Total pancreatectomy: an objective analysis of its use in pancreatic cancer. Hepatogastroenterology 1993; 40:418–421.
36. Aston SJ, Longmire WP. Management of the pancreas after pancreaticoduodenectomy. Ann Surg 1974; 179:322–327.
37. Williams JA, Cubilla A, Maclean BJ, et al. Twenty-two year experience with periampullary carcinoma at Memorial Sloan-Kettering Cancer Center. Am J Surg 1979; 138:662–665.

Discussion

DR. MCHENRY S. BREWER (Louisville, Kentucky): Dr. McDonald, Dr. Copeland. First I want to congratulate Dr. Ranson and his able substitute and Dr. Marcus on their excellent presentation of their experience with the management of the pancreatic stump during the Whipple operation. I hate to admit it, and I'm a little humiliated to do so, but it's one of the few papers presented this morning that I have understood.

This is a serious problem, and I want to show one slide briefly which illustrates a method which, in my hands, has been free of pancreatic complications. (Slide) The sutures taken with 30 silk superiorly and inferiorly across the cut edge of pancreas and each of these sutures is passed into the lumen of the jejunum and brought out through the wall of the jejunum 4 cm or so downstream from the cut edge of the jejunum. Then with gentle traction on the strands of these two sutures, it's possible to pull the pancreas into the open end of the jejunum, at the same time pulling the cut edge of the open jejunum in the opposite direction. And by so doing, you can very nicely invaginate a very significant length of pancreas into the open end of jejunum. These traction sutures are then anchored to the wall of the jejunum. The cut edge of the jejunum is then simply tacked down to the pancreas, and no attempt is made to invert any tissue with these sutures. You will notice that no stent is used in the pancreatic duct, and we also did not use a T tube in the common duct.

Now my experience with the Whipple procedure is somewhat limited. I actually have only used this in about 12 patients, but I have been impressed with the fact that we have had no pancreatic leaks and no pancreatic complications in any of these patients. There were no postoperative deaths. One very long-term survivor, 15 years, has had no symptoms of pancreatic insufficiency and does not take any pancreatic supplements.

Now I hasten to add that this method is not original with me. I really cannot remember where I saw this described many, many years ago. Some of you may be using it, but I haven't seen it described in any atlases on surgical technique. I strongly recommend it.

DR. CHARLES YEO (Baltimore, Maryland): Thank you Mr. President, Mr. Secretary, Members and Guests. I'd like to congratulate the authors on a very well-done study and pray for the speedy recovery of Dr. Ranson who has made major contributions in the field of pancreatic surgery and also saved the life of