Total Pancreatectomy for Ductal Cell Carcinoma of the Pancreas

An Update

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Forty-eight patients with ductal cell carcinoma of the pancreas underwent total pancreatectomy. During 1970–1976, there were four deaths (a mortality of 18%). During the last twenty-eight operations (1977–1986), there were no hospital deaths. Seventeen per cent of the patients suffered intraoperative complications involving the mesenteric vessels. Twenty-seven per cent suffered postoperative complications. Twenty-five per cent of the patients left the hospital within 2 weeks, 50% left within 4 weeks, and another 25% remained in the hospital for longer than 4 weeks. Thirty-five per cent of the patients have returned to their preoperative job or similar life activity. Another 35% were able to lead an active life but did not return to regular work, and 30% were to some degree incapacitated by their operative procedure and disease. Twenty-one per cent of the patients lived for 4 years, and 14% survived for 5 years.

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I N 1969, AFTER A REVIEW of the Brigham Hospital results with the Whipple procedure for ductal cell carcinoma of the head of the pancreas, it seemed clear that the survival rate was poor: there were no known survivors at 5 years after surgery. This dismal prognosis during the 1960s prompted some surgeons to suggest abandoning the Whipple procedure because of its operative mortality rate and lack of long-term survivors.[1]

At that time, a review of the pathology of this disease was undertaken at the Brigham Hospital. As a result of that review, it became apparent that in approximately 36% of the patients with carcinoma of the head of the pancreas, there was synchronous disease in the body and the tail.[2] This finding emphasized the fact that a Whipple procedure failed to remove all of the malignancy in that one third of the patients whose disease was multifocal, and it was theorized that this contributed to the low survival rate. Others have also reported multicentric disease.[3,4]

In evaluating the Whipple procedure,[3-5] it was also apparent that a significant number of patients developed pancreatic fistulae at the pancreaticojejunostomy anastomosis and that this was increasing the morbidity as well as the mortality of this operative procedure.

The first report of total pancreatectomy for carcinoma of the pancreas was made in 1954 by Ross[6] and in 1958 by Porter.[7] However, in 1960, Howard and Jordan[8] reported the mortality of total pancreatectomy in a collected series to be 37%, and the procedure was given up, at that time, for cancer of the head of the pancreas.

However, during the late 1960s and early 1970s, there was renewed enthusiasm for total pancreatectomy,[3-5] again because of poor results from the Whipple procedure and because of the theoretical advantages noted above (i.e., complete removal of the gland and absence of a pancreatic anastomosis). Advances in anesthesia technique, intensive care monitoring, and blood banking suggested that the procedure need not carry the prohibitively high complication rate noted by Howard and Jordan.

Coincident with the revival of interest in total pancreatectomy at the Brigham Hospital,[5,9,10] others also began to investigate this operative procedure for ductal carcinoma of the head of the pancreas.[3,4,11,12]

Since 1970, forty-eight patients have undergone total pancreatectomy at the Brigham Hospital for ductal cell carcinoma of the head of the pancreas. Another nine total pancreatectomies have been performed for other tumors or conditions of the pancreas (e.g., islet cell tumors, chronic pancreatitis). During these 16 years (1970–1986), the Whipple procedure has continued to be performed for tumors of the duodenum, common duct, and peri-

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TABLE 1. *Preoperative Findings: Carcinoma Pancreas*

Preoperative Findings	Percentage of Patients	
Age 30–77		
Sex		
Male	60%	
Female	40%	
Diabetic	25%	
History of pancreatitis	11%	
Cholelithiasis	17%	
Palpable gallbladder	23%	
Ultrasonographic performed	70%	
CAT scan performed	67%	
Liver function tests		
LDH		130–406 IU/l
SGOT		30–280 IU/l
Alkaline phosphatase		130–1028 IU/l
Bilirubin		3–22% mg

ampullary region. From 1970 to 1982, no patients underwent a Whipple procedure for ductal cell carcinoma of the head of the pancreas. During the last 5 years, a few Whipple procedures have been performed for ductal cell tumors. Also during this 16-year period, approximately 600 additional patients have undergone operations for tumors of the pancreas, at which time bypass procedures or simple biopsies were performed because of inoperability or unresectability. In this review, we report the results of total pancreatectomy for ductal cell carcinoma of the pancreas, with a follow-up ranging from 2.5 years to 16 years. This study pertains only to patients with ductal cell carcinoma.

Patient Material

Sixty per cent of the patients who underwent total pancreatectomy were men, and 40% were women (Table 1). Patient age ranged from 30 to 70 years. Twenty-five per cent of the patients had preoperative diabetes. Of this group, six patients developed diabetes shortly before they were discovered to have a tumor of the pancreas. Sixteen per cent of the patients had gallstones. Eleven per cent

TABLE 2. *Vessel Anomalies*

Vessel Anomalies	No. of Patients
Replaced hepatic artery coming off the superior mesenteric artery	3
Arcuate ligament obstruction of celiac axis with hepatic artery filling from gastroduodenal	1
Bifurcated hepatic artery	1
Celiac axis filling from superior mesenteric artery collaterals	1
Tumor encroachment producing displacement of gastroduodenal artery	1
Occlusion superior mesenteric vein	1

had a history of pancreatitis. Weight loss was common among these patients.

Sixteen per cent of the patients had previously undergone operation elsewhere, at which time the tumor of the head of the pancreas was discovered and the patient was referred to the Brigham and Women's Hosptial after either bypass or simple tumor biopsy. Seventeen per cent of the patients had had a previous cholecystectomy.

Physical Examination and Patient Evaluation

Ninety-five per cent of this patient group had visible jaundice, 23% had a palpable gallbladder, and 10% had a palpable mass in the epigastrium (Table 1). Chest x-rays were essentially normal in all patients. Liver function tests showed the bilirubin to range between 3 and 22 mgm % alkaline phosphatase ranged between 136 and 1028 IU/l; the lactic dehydrogenase (LDH) ranged between 130 and 406 IU/l; and the serum glutamic oxaloacetic transaminase (SGOT) ranged between 30 and 280 IU/l. Ultrasonographic studies revealed a mass and/or dilated common duct in 70% of the patients. Sixteen per cent of the patients did not have ultrasonographic studies performed, these patients having previously undergone operation elsewhere. A computerized axial tomography scan (CAT scan) was performed in 67% of the patients and showed a mass in 90%. Seven patients underwent endoscopic retrograde cholangiopancreatography (ERCP). Before the operation, angiography was performed in twenty-five patients, and anatomic vessel abnormality was noted in six (Table 2). These anomalies included: 1) a replaced hepatic artery coming off the superior mesenteric artery (in three patients), 2) arcuate ligament obstruction of the celiac axis with the hepatic artery filling from the gastroduodenal (in one patient), 3) a bifurcated hepatic artery (in one patient), 4) the celiac axis filling from superior mesenteric artery collaterals (in one patient), 5) tumor encroachment producing displacement of the gastroduodenal artery (in one patient), and 6) occlusion of the superior mesenteric vein (in one patient).

One patient underwent percutaneous biopsy of the tumor before operation. Three of the 48 patients underwent preoperative transhepatic common duct drainage. This procedure is no longer considered indicated. Although some surgeons disagree, preoperative transhepatic common duct drainage appears to add little to the postoperative course of patients undergoing pancreatic resection; we, as well as others,[13] believe that it delays the operative procedure and, in some instances, leads to cholangitis.

Operative Procedure

Preoperative cephalosporin antibiotic therapy was begun on the day of surgery and was continued, unless otherwise indicated, for the first 5 postoperative days. A
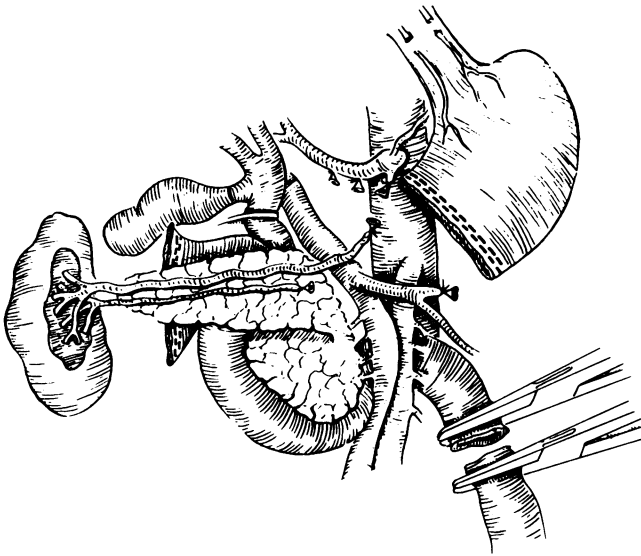
FIG. 1. Early stage in total pancreatectomy. (Reprinted with permission from *The Atlas of Advanced Surgery,* Yorke Medical Books.)

FIG. 3. Reconstruction stage. (Reprinted with permission from *The Atlas of Advanced Surgery,* Yorke Medical Books.)

transverse "rooftop" incision was used in all patients. On opening, the abdomen was surgically explored for gross liver or peritoneal metastases. The duodenum was Kocherized to evaluate the lower end of the portal vein, the lesser sac was entered, and the tumor was palpated. A Trucut needle biopsy of the tumor was obtained through
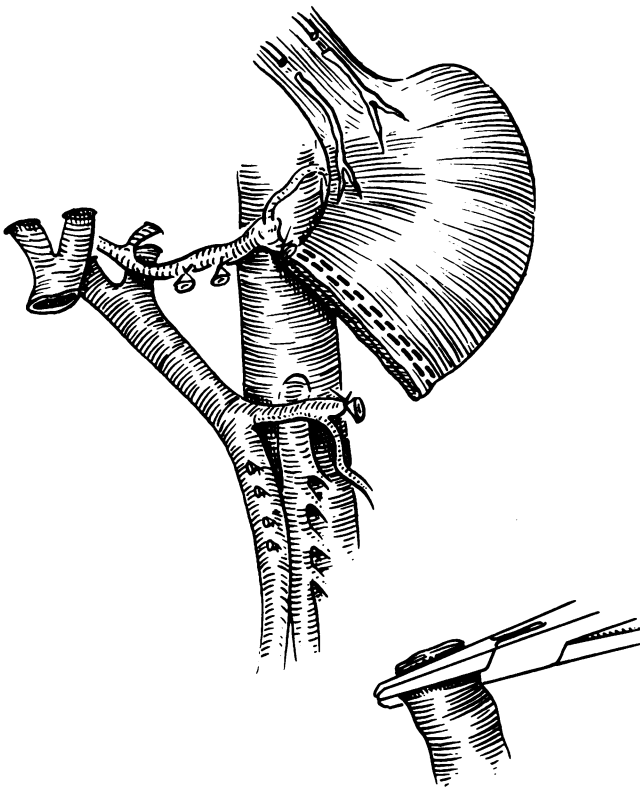
the duodenum, and sampling of lymph nodes was then performed in the celiac, superior mesenteric, and duodenal areas, as well as along the course of the common bile duct. If the biopsy was positive and lymph nodes were all negative, then total pancreatic resection was accomplished (Figs. 1–3). If a positive biopsy could not be obtained on two or three attempts, then resection was also accomplished if 1) the patient had significant jaundice, 2) the common duct was significantly dilated, 3) there were no gallstones, and 4) the patient was not alcoholic. In five cases, a positive biopsy could not be obtained before resection. In no instance was a pancreatectomy performed in which a malignant process was not found. After resection of the pancreas, spleen, duodenum, and antrum of the stomach, the jejunum was mobilized in retrocolic fashion, in most instances. Its end was turned in and an end-to-side choledochojejunostomy was performed. This anastomosis was stented with a rubber catheter that was brought out in Witzel fashion through the jejunum to the abdominal wall. A routine gastrojejunostomy was then performed. A gastrostomy was performed in 60% of the patients, and a vagotomy was performed in 57% of the patients; a cholecystectomy was performed in 53%, and a cholecystostomy was performed in 15%. No pylorus preservation was conducted. The operative time ranged between 6 and 10 hours, and the amount of blood given ranged from 4 to 17 units, with a mean of 6 units.

Intraoperative Complications

Three patients had trauma to the superior mesenteric artery (Table 3). Two of these instances of trauma were vessel wall tears that were controlled by sutures; one involved reimplantation of the superior mesenteric artery into the aorta.

FIG. 2. Postresection stage. (Reprinted with permission from *The Atlas of Advanced Surgery,* Yorke Medical Books.)

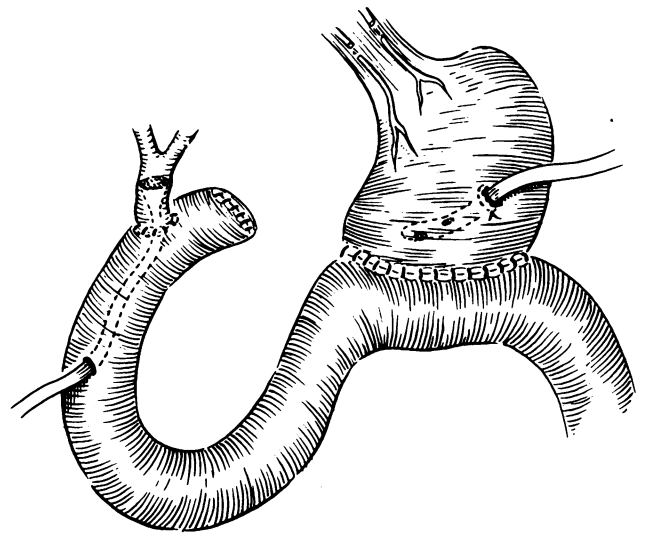TABLE 3. *Total Pancreatectomy For Pancreatic Carcinoma: Intraoperative Complications (17%)*

Complications	No. of Patients
Suturable mesenteric artery tears	2
Suturable mesenteric-portal vein tears	2
Need for major vascular reconstruction	4
Portal—superior mesenteric veins	3
Hepatic—Celiac axis	1

One patient had a vein patch graft repair to the hepatic artery performed while undergoing a Whipple procedure. He bled after the operation and required reoperation to control the bleeding. At that time, he underwent a completion total pancreatectomy (tumor was noted in the tail of the pancreas at pathologic examination).

Five patients had trauma to the portal-superior mesenteric vein venous system. Two of these instances of trauma consisted of tears that were suturable; two required autologous vein grafts, and one required plastic vascular reconstruction of the superior mesenteric venous portal vein junction.

Pathology

Tumor size ranged between 2 and 11 cm, with a mean of 4 cm (Table 4). Lymph nodes were found to be positive in 65% of the patients and were found to be negative in 35%. Multicentricity of tumor was noted in 36%. This multicentricity had various manifestations (Table 4): 1) widespread tumor in body and tail (in two patients), 2) tumor extending directly from the head into the central part of the body across the usual site of Whipple resection (in seven patients), 3) small tumor foci appearing in the pancreatic body and tail (in four patients), 4) carcinoma *in situ* separate from primary tumor in head (in two patients), 5) tumor cells in pancreatic ducts presumably washed back from the head (in one patient), and 6) tumor

TABLE 4. *Pathology: Pancreatic Carcinoma*

Pathology	No./% of Patients
Tumor size (2.0-11 cm)	
Postive nodes	65%–4 alive > 5 years
Negative nodes	35%–2 alive > 5 years
Multicentricity	36%–4 of 9 survivors > 4 years
Manifestations of multicentricity of tumor *Type*	
Widespread tumor in body and tail	2
Tumor extension into body	7
Small foci of carcinoma in body and tail	4
Carcinoma *in situ* in body and tail	2
Tumor cells free floating in pancreatic duct	1
Tumor extending up the common duct	4

TABLE 5. *Total Pancreatectomy For Pancreatic Carcinoma: Postoperative Complications (27%)*

Postoperative Complications	No. of Patients
Postoperative mortality 1970–1976	4 of 22 (18%)
Choledochojejunostomy leak and sepsis	1
Postoperative bleeding	1
Thrombosis superior mesenteric artery	1
Cardiopulmonary failure and abdominal sepsis (no leak)	1
Postoperative mortality 1977–1986	0 of 26 (0%)
Left pleural effusion	2
Postoperative bleeding (nonlethal) requiring reoperation to control bleeding	1
Tracheostomy	1
Postoperative gastric outlet obstruction requiring gastroenterostomy revision	1
Wound sepsis requiring wound drainage	3
Hepatic necrosis—sepsis that resolved	1

extending high up along the common duct (in four patients).

Postoperative Complications

Twenty-four patients had no intraoperative or postoperative complications (Table 5). Four patients died after operation in the hospital within 30 days of surgery. These deaths occurred early in the series, during the period of 1970–1976. There have been no postoperative in hospital deaths in the last 28 patients undergoing total pancreatectomy from 1977 to the present time. One of the above-mentioned patients died of bleeding during the postoperative period; one patient died of massive intra-abdominal sepsis secondary to a biliary fistula at the choledochojejunostomy anastomosis; one patient died of total superior mesenteric artery thrombosis due to arteriosclerotic plaque occlusion; and one patient died of a combination cardiopulmonary and septic death, but no anastomotic leak was found at postoperative exploration.

Nonlethal complications included left pleural effusions that resolved without treatment (two patients). Another patient developed postoperative gastric obstruction requiring gastroenterostomy revision. One patient developed purulent drainage from a sump tube placed at operation; one patient had postoperative bleeding requiring 6 units' transfusion (this patient also required a tracheostomy for postoperative respiratory support). Postoperative jaundice and areas (revealed on CAT scan) of liver necrosis-sepsis that eventually resolved developed in one patient. The etiology of this complication was not clear. Simple wound sepsis requiring wound drainage developed in three patients.

Postoperative Course

Of the 44 patients who survived operation, 25% were discharged from the hospital within 2 weeks (Table 6).

Fifty per cent of the patients remained in the hospital for 3–4 weeks; 25% of the patients remained for longer than 4 weeks. Insulin dosage was stabilized between 10 and 20 units of NPH in 17% of the patients, between 20 and 30 units of NPH in 72% of the patients; and between 30 and 40 units of NPH in 11% of the patients.

Major difficulty with diabetic control (hypoglycemia) occurred in 16% of the patients, requiring later hospitalization in some cases as well as more rigid control within the postoperative period to control blood glucose. In several cases, glucagon therapy was helpful in controlling the acute episodes. No patient died or developed severe complications from this brittle diabetes.

Gastrostomy tubes were removed at the time of discharge, and the indwelling choledochojejunostomy catheters were removed at varying times, in some cases at the time of discharge, and in other cases, 3–4 weeks after the operation. In all cases, contrast studies through the tube were obtained to delineate the status of the anastomosis and biliary radicals.

Patients remaining in the hospital for more than 4 weeks included those with intra-abdominal sepsis, those with postoperative bleeding, those whose postoperative jaundice subsided slowly, and those who failed to aliment properly.

Posthospital Course

After discharge from the hospital, most patients have been maintained on glucometer control of blood glucose levels. All patients have received six to twenty tablets of Pancrease (McNeil Pharmaceutical, Springhouse, PA) or Viokase (Robins, A.H. Co., Richmond, VA) per day. None of the patients gained significant weight, and the weight of all patients remained below their best preoperative weight. Varying degrees of stool looseness occurred in 48% of the patients. Thirty-five per cent of this patient population were able to resume their occupations and/or their preoperative level of life activity. One third of the patients were able to carry out restricted activity, whereas another one third never returned to work. Insulin requirements during the posthopsital period continued to show that 17% of patients were in the NPH range of 10–20 units, that 72% were in the NPH range of 20–30 units, and that 11% were in the NPH range of 30–40 units.

Long-term Survival

Of 44 patients who survived operation, one patient died of pulmonary complications 30 days after discharge from the hospital; 33 patients (75%) survived for more than 6 months; 23 patients (52%) survived for more than 1 year; 21 patients (48%) for survived more than 2 years; 15 patients (38%) survived for more than 3 years; and nine patients (21%) survived for more than 4 years (Fig. 4). Six

TABLE 6. Total Pancreatectomy For Pancreatic Carcinoma: Post-operative Course (44 Patients)

Postoperative Course	Percentage of Patients
Postoperative hospitalization	
<2 weeks	25%
3–4 weeks	50%
>4 weeks	25%
Insulin dosage	
NPH 10–20	17%
NPH 20–30	72%
NPH 30–40	11%
Pancreatic enzyme replacement—Viokase, Pancrease 4–20 tablets per day	
Major difficulty with diabetic control	16%
Work—active	35%

patients (14%) survived more than five years and three patients (7%) survived more than six years. Of nine patients who survived for more than 4 years, four revealed multicentric tumor at pathologic examination. Lymph node positivity appeared not to affect survival significantly, although patients who had positive lymph nodes and who survived longer had fewer positive nodes.

Discussion

As has been pointed out by others,[14,15,16,17,18] it appears that the surgical mortality of pancreatectomy has decreased significantly during the last 10 years. There have been no postoperative deaths in the recent group of 28 patients who underwent operations at the Brigham and Women's Hospital. There also appears to be increased improvement in the survival rate for both the Whipple procedure and total pancreatectomy.[15,17,18] This improvement appears not to be due to earlier diagnosis, better patient condition, smaller tumors, or other known factors. It is also interesting to note that in Cameron's recently reported series,[17] although pancreatic fistulae developed in 18% of the patients, there were no deaths as a result of the fistulae. Presumably, this is a function of better handling of the fistula and improved supportive
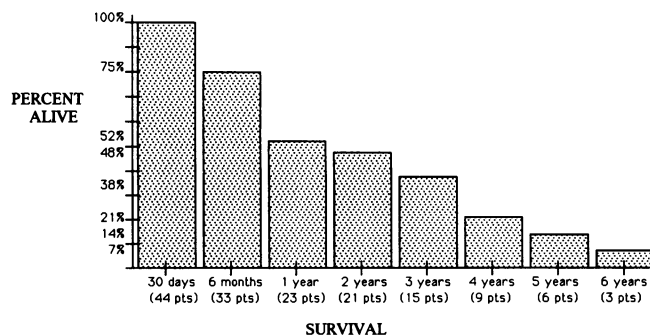

FIG. 4. Survival after total pancreatectomy.

therapy. Approximately 40% of the deaths resulting from pancreatectomy during previous years were due to pancreaticojejunostomy fistulae, and another 40% were due to cardiopulmomary complications. Clearly, the number of deaths resulting from both pancreatectomy and pancreaticojejunostomy have both decreased in frequency.

Overall long-term survival after the Whipple procedure and total pancreatectomy are similar despite the concepts of multicentricity noted previously.[17,18] If complications and death from pancreaticojejunostomy can be eradicated[17] and multicentricity of tumor can be shown not to affect survival, then the easier control of diabetes (which does occur in a significant percentage of patients after a Whipple procedure, albeit in a less brittle form) supports the concept of subtotal pancreatectomy. A point for discussion here relates to how much pancreatic tail need be left *in situ* in order to prevent diabetes. Obviously, the more pancreas that is removed, the lesser the likelihood of leaving multicentric tumor behind. Also, it is conceivable that by leaving a very small remnant of pancreatic tail *in situ*, one could avoid the major complications resulting from pancreaticojejunostomy as well as minimize the degree of diabetic complications that do occur.

Summary

The postoperative mortality (0%) and 5-year survival rate (14%) after total pancreatectomy for pancreatic cancer has improved significantly during the last 10 years. Although radiotherapy and/or chemotherapy have been used in treating some of these patients, their use has not been consistent enough to be evaluated properly in the present series.

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