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Total Pancreatectomy: Indications, Operative Technique, and Postoperative Sequelae

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Abstract Total pancreatectomy has been used to treat both benign and malignant disease of the pancreas, but its use has been limited by concerns about management of the apancreatic state with its attendant total endocrine and exocrine insufficiency. Here, we review the indications for total pancreatectomy, operative technique, and improvements in the postoperative management of patients. Total pancreatectomy remains a viable option in the treatment of intractable pain associated with chronic pancreatitis, multicentric or extensive neuroendocrine tumors, patients with familial pancreatic cancer with premalignant lesions, and in patients with intraductal papillary mucinous neoplasia with diffuse ductal involvement or invasive disease. Improvements in postoperative management include auto-islet cell transplantation, advances in insulin formulations, and the use of glucagon rescue therapy which allow much tighter control of blood glucose than previously possible. This markedly lessens the risk of life-threatening hypoglycemia and decreases the risk of long-term complications, resulting in improved quality of life for these patients.

Keywords Pancreatic neoplasms · Chronic pancreatitis · Pancreatectomy · Diabetes

Abbreviations
IPMN intraductal papillary mucinous neoplasia

Billroth performed the first reported total pancreatectomy for pancreatic cancer in 1884[1]. This patient was said to have done well postoperatively, which would be questionable in the pre-insulin era. The first modern report of total pancreatectomy for pancreatic adenocarcinoma was by Rockey in 1943, with early patient death in the perioperative period from a bile duct leak[2]. Priestley performed the first successful total pancreatic resection in a hypoglycemic patient with a non-palpable 8×5 mm islet cell tumor in 1944[2]. As reports of long-term metabolic complications of the apancreatic state have accumulated, total pancreatectomy for benign, premalignant, and malignant disease has generally been avoided because of the perceived difficulty of managing the associated brittle diabetes. However, new formulations of long-acting insulin and improvements in the use of autologous islet cell transplantation have made total pancreatectomy an increasingly viable option in the treatment of both benign and selected malignant pancreatic diseases. Here, we will review the indications for total pancreatectomy, technical considerations, and postoperative management strategy for the apancreatic state.

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Indications

Chronic Pancreatitis

Warren first performed total pancreatectomy in patients with recurrent pancreatitis, proposing at that time that the

Table 1 Possible Indications for Total Pancreatectomy

Intractable pain of chronic pancreatitis
Neoplasm
Sporadic adenocarcinoma
Familial pancreatic cancer
Neuroendocrine tumors

procedure should be limited to patients with intractable pain and intraductal obstruction not amenable to a drainage procedure (Table 1)[3]. He theorized that if the pain associated with end-stage chronic pancreatitis arose from the inflamed pancreatic parenchyma, then total pancreatectomy should result in complete relief of symptoms. Initial experiences did not bear out this theory (Table 2). Several large retrospective studies showed that only 30 to 60% of patients undergoing total pancreatectomy experienced significant pain relief, and a large percentage of patients were readmitted for diabetic complications[4–7]. The Lahey Clinic's experience with total pancreatectomy, reported in 1978, showed that of the 25 patients studied, 12 had late deaths secondary to diabetic complications[6]. Many of these patients who died suffered from substance abuse, highlighting that this subset of patients was poorly suited for the intensive patient involvement required for the maintenance of normoglycemia following total pancreatectomy and were more likely to complain of continued pain postoperatively[8].

Advancements in the use of autologous islet cell transplantation have led to renewed interest in the use of total pancreatectomy for relief of the pain associated with chronic pancreatitis. The University of Minnesota has the largest experience with the use of total pancreatectomy and autologous islet transplantation in the current era, as described by Gruessner and colleagues[9]. The records of 112 patients were reviewed, with follow-up ranging from 4 months to 26 years. Islets were isolated following pancreatectomy using the semiautomated technique originally described by Ricordi, followed by intraoperative infusion into the portal venous system[10]. Of 112 patients, 70% experienced significant pain relief based on comparison of pre- and postoperative narcotic requirements. Importantly, 72% of patients who had not undergone previous pancreatic resection did not require insulin postoperatively. Those with previous pancreatic resection (and thus, with fewer islets available for autotransplantation) fared worse, with only about 20% of patients achieving insulin independence. Patients actively abusing alcohol were not enrolled in the study. Two additional reports from the University of Cincinnati and University of Leicester (with patient follow-up between 3 months–3 years and 7 months- –6 years, respectively) show similarly excellent pain control in patients who were not actively abusing alcohol. The University of Cincinnati group reported that 82% of the 22 patients in their series were able to be weaned entirely from narcotics. At both centers, approximately 40–50% of patients became insulin independent following the procedure[11,12]. The need for insulin postoperatively following this procedure appears to be due to a number of factors, including number of islets transplanted, similar to that observed with non-autologous transplantation used to treat type 1 diabetes[13]. There is evidence that maintenance of normoglycemia in the immediate postoperative period is necessary to insure recovery of transplanted islet cell function, which can occur as late as 1 year following transplantation[12]. Because higher islet recovery rates translate into better outcomes, proponents of this approach argue for early pancreatectomy in patients with chronic pancreatitis before they develop glucose intolerance due to loss of β-cell mass.

Pancreatic allotransplantation has also been used as an alternative approach in patients with previous total pancreatectomy for chronic pancreatitis; long-term results in the small number of patients[14] who have undergone this procedure at the University of Minnesota show a 3-year graft survival of 77% in the tacrolimus era[9]. There were no transplant-related deaths in this group. With total organ transplantation, these patients benefit from restoration of exocrine and endocrine function if enteric rather than bladder drainage is provided. The potential benefits of the procedure must be balanced with the need for lifelong immunosuppression and the resultant morbidity and mortality associated with rejection, infection, and malignancy.

Table 2 Review of Series of Total Pancreatectomy for Chronic Pancreatitis

Author	Year	Number of patients	Median follow-up	Percentage of pain improvement	Autotransplant	Percentage of nondiabetic
Gruessner, et al.[9]	2004	132	0.3–26 yr	72	Yes	33
Clayton, et al.[12]	2003	31	2–6 yr	50	Yes	0
Rodríguez-Rilo, et al.[11]	2003	19	19 mos (3 to 41)	94	Yes	40
Easter, et al.[66]	1991	8	29 mos (8 to 51)	75	No	0
Stone, et al.[4]	1988	15	9.1 yr (2.1 to 13.1)	67	No	0
Braasch, et al.[6]	1978	26	Unknown	78	No	0

Sporadic Pancreatic Adenocarcinoma

Historically, the rationale for total pancreatectomy for the treatment of pancreatic adenocarcinoma stems from: (1) the desire to avoid the complications of pancreatic fistula; (2) the belief that the disease is frequently multicentric; and (3) the view that total pancreatectomy represents a more definitive oncologic resection than a partial pancreatic resection, with greater lymph node clearance and an increase in the percentage of R0 resections. Approaching these arguments point by point: (1) Recent retrospective reviews of the complications of pancreatic resection show pancreatic fistula rates between 3 and 11% at high volume centers[14,15]. More than 90% of those patients who develop pancreatic fistulas are now managed successfully with percutaneous drainage, without the relatively high mortality rate (up to 40%) previously reported with this complication[16]. (2) Brooks et. al. in the 1960s reported that up to 34% of patients with pancreatic adenocarcinoma undergoing resection had multicentric disease[17]. This view was supported by data in two other reports[18,19]. More recent studies using immunohistochemistry and PCR have found multicentricity to be much less prevalent, ranging between 0 and 6%[20,21]. The prevalence of multicentric disease in earlier studies may have been due to sampling error, or operator bias, in the identification of truly discontinuous lesions. It could also be due to the inclusion of a disproportionate number of cases of familial pancreatic cancer[3]. Regarding the efficacy of total pancreatectomy as an oncologic operation, large retrospective series have shown no long-term survival benefit. In fact, several studies show that perioperative mortality is higher with total pancreatectomy than with subtotal pancreatectomy. Ihse, et al. reported an in-hospital mortality of 27% of their 89 patients undergoing total pancreatectomy for cancer[22]. In a more recent report from Memorial Sloan Kettering Hospital, 28 patients who underwent total pancreatectomy for adenocarcinoma had a 5-year survival rate of 9%, no better than that seen in patients undergoing partial pancreatectomy for adenocarcinoma[24]. Given the fact that pancreatic fistulas are now better managed, most tumors are not multicentric and that total pancreatectomy results in higher perioperative morbidity and mortality with no increased long-term survival, there is no role for routine consideration of total pancreatectomy in the management of sporadic pancreatic adenocarcinoma.

Familial Pancreatic Adenocarcinoma

In families affected by this condition, first degree relatives with three or more affected family members have up to a 57-fold increase in the risk of developing pancreatic cancer[25]. The susceptibility to pancreatic cancer is inherited in an autosomal dominant fashion[26]. Germline mutations in BRCA2 have been identified in up to 20% of affected families, and recently, a susceptibility locus has been mapped to chromosome 4q32–34[27–29]. In patients with familial pancreatic cancer, there is often an early age of onset, and some question of anticipation (i.e., the disease presents earlier with a more aggressive clinical course in succeeding generations)[30–32]. Other familial cancer syndromes also predispose to pancreatic cancer, most notably Peutz–Jegher syndrome, familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal carcinoma (HNPCC), familial breast–ovarian cancer, and familial atypical multiple mole melanoma (FAMMM). Hereditary pancreatitis, a result of either a mutation in the cationic trypsinogen gene (PRSS1) or in the serine protease inhibitor (SPINK1), also results in increased susceptibility to pancreatic cancer. Screening with endoscopic ultrasound has been recommended in asymptomatic patients with two or more first-degree relatives with pancreatic cancer, one first-degree relative with cancer diagnosed before the age of 50, or with two or more second-degree relatives, one of whom was diagnosed before the age of 50[33]. The exact timing for initiating surveillance is up to some debate, with experts agreeing that surveillance should begin somewhere between 5 to 10 years before the onset of pancreatic cancer in the youngest affected relative or by the age of 40 or 50, or at the onset of symptoms (including the development of diabetes or weight loss)[25,33]. In a study by Rulyak and colleagues of 35 family members undergoing surveillance, 12 had positive findings of a mass lesion on endoscopic ultrasound (EUS) and/or endoscopic retrograde cholangiopancreatography (ERCP)[35]. These patients underwent either total or partial pancreatectomy and all 12 had pancreatic dysplasia on histological examination without invasive adenocarcinoma. These patients were found to have extensive, multicentric lesions. A larger group of 50 kindreds has been followed at the University of Washington, of which 10 patients have undergone total pancreatectomy. All were found to have Pan IN-3 lesions (carcinoma in situ). One patient with postoperative hypoglycemic unawareness underwent solid organ pancreas transplantation and had normal glucose homeostasis 1-year post-transplant[35]. Clearly, surveillance and total pancreatectomy have the potential to avert the development of invasive pancreatic adenocarcinoma in the setting of familial pancreatic cancer and should be considered as a prophylactic procedure in some patients.

Neuroendocrine Tumors

In 1993, a large retrospective study from the Mayo Clinic showed completion pancreatectomy for recurrent insulinoma to be associated with 10 year decrease in mean survival when

compared to patients undergoing repeat partial pancreatectomy[36]. It should be noted that all of these patients underwent resection before 1977. More recent analysis suggests that endocrine tumors do not have as benign a course as previously thought, and that aggressive resection might be warranted, including total pancreatectomy. Doherty et al. examined a group of 34 distinct kindreds of multiple endocrine neoplasia type I (MEN-I) syndrome with 1,838 members and found that 46% of MEN-I patients died as a result of their endocrine tumors at a median age of 47 years[37]. These patients succumbed to metastatic islet cell or carcinoid tumors, ulcer disease, or complications of hypercalcemia. Aggressive screening of MEN-I patients using endoscopic ultrasound was therefore suggested[38]. In 2003, Norton et al. reported three patients who had undergone total pancreatectomy for locally advanced neuroendocrine tumors without postoperative complications[39]. As our understanding of the natural history of pancreatic neuroendocrine tumors has evolved, it is clear that a place remains for completion pancreatectomy in the endocrine surgeon's armamentarium.

Intraductal Papillary Mucinous Neoplasm (IPMN)

Ohhashi et al. first described IPMN of the pancreas in 1982; initially, it was thought to be an indolent disease with a favorable prognosis[40,41]. It is now widely recognized to be a premalignant lesion with between 30 and 72% of patients having invasive or noninvasive carcinoma at the time of presentation[42,43]. Those patients found to have invasive carcinoma after resection have a poor prognosis, with a 5-year survival ranging from 24–60%[42,44–46]. The distribution of IPMN has been proposed as a predictor of progression: lesions involving the main pancreatic duct have a higher rate of malignancy discovered at the time of resection than lesions arising from a branch duct[47]. Intraoperative frozen sections following planned partial resection for localized lesions are necessary to assure negative margins. If there is evidence of severe dysplasia or invasive cancer at the resection margin, the resection should be extended, up to and including total pancreatectomy. In patients with diffuse noninvasive disease, total pancreatectomy should be considered in select patients to minimize the chance of recurrent, invasive disease.

Operative Technique

The operative technique utilized for total pancreatectomy depends upon whether the patient has undergone previous pancreatic resection. Distal pancreatectomy can be performed in patients who had a previous pancreatoduodenectomy. Patients with a previous distal pancreatectomy are candidates for either duodenum-preserving pancreatectomy or completion pancreaticoduodenectomy. Preservation of the spleen should be considered whenever possible if it is felt not to compromise the oncologic nature of the operation. In cases when accompanying splenectomy is planned, the patient should be vaccinated 2 weeks preoperatively against pneumococcus, Hemophilus influenza group B, and meningiococcus group C to minimize the likelihood of developing potentially lethal post-splenectomy sepsis.

The operative procedure begins with a thorough exploration to evaluate the presence of extra-pancreatic disease. The right colon and hepatic flexure of the colon are mobilized to provide access to the second part of the duodenum. A wide Kocher maneuver is performed, and the duodenum and pancreas are elevated off the inferior vena cava until the left border of the abdominal aorta can be palpated. The Kocher maneuver is extended by continuing mobilization of the third portion of the duodenum until the superior mesenteric vein is encountered. The gastrocolic ligament is widely divided to allow access to the body of the pancreas. The anterior surface of the superior mesenteric vein is identified and dissected under direct vision. Using a Cushing vein retractor, the neck of the pancreas is lifted, and entering this avascular plane, the superior mesenteric vein is traced proximally to its confluence with the portal vein. Following cholecystectomy, the peritoneal reflection over the hepatoduodenal ligament is carefully opened, and the common bile duct and common hepatic artery are carefully dissected, and vessel loops are placed around them. The gastroduodenal artery is identified and ligated in continuity to facilitate access to the portal vein at the superior aspect of the pancreas. The splenorenal ligament is divided, and the spleen is drawn medially together with the tail of the pancreas, thus, opening the retropancreatic plane. The splenic vein and artery are ligated. Next, the distal part of the stomach is mobilized and transected. The duodenojejunal flexure is located and dissected free from the retroperitoneum by dividing the ligament of Treitz. Approximately 10 to 15 cm distal to the duodenojejunal flexure, the vessels within the mesentery and subsequently the small bowel are divided. The pancreas, distal stomach, duodenum, and spleen are removed en bloc (Fig. 1). To restore gastrointestinal continuity, an end-to-side choledochojejunal anastomosis is performed. The stomach is then anastomosed to the jejunum in two layers.

Metabolic Consequences of Total Pancreatectomy

Endocrine Insufficiency

The diabetic state induced by total pancreatectomy is characterized by complete insulin deficiency (as confirmed

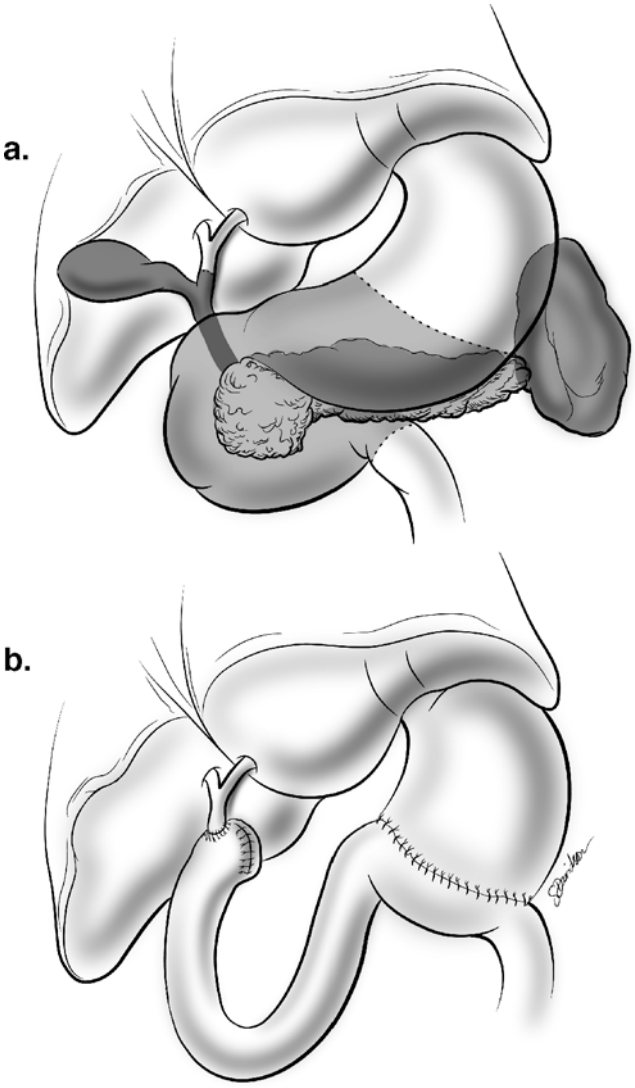

Figure 1 Total pancreatectomy with partial gastrectomy, duodenectomy, cholecystectomy, and splenectomy with choledochojejeunostomy and gastrojejeunostomy.

by the absence of C-peptide in the serum), pancreatic polypeptide deficiency, and an absence of functional glucagon[48,49]. Because the apancreatic state is characterized by a defect in gluconeogenesis secondary to hypoglucagonemia, daily insulin requirements in these patients are typically lower than in type I or type II diabetics[50,51]. However, the therapeutic window is narrowed, resulting in frequent episodes of mild to severe postprandial hypoglycemia following insulin administration (Table 3)[52]. Patients who are chronically hypoglycemic have been shown to upregulate cerebral endothelial glucose transporters which are responsible for the initiation of the autonomic response to hypoglycemia[53]. This results in an attenuation of epinephrine secretion and may account for episodes of diabetic unawareness in pancreatectomized individuals[54,55]. Reductions in the adrenal secretion of epinephrine also decrease hepatic glucose production[56]. The combination of insulin sensitivity and hypoglycemic unawareness was termed "brittle" diabetes by R.T. Woodyatt in the 1930s[57].

Insulin therapy for the apancreatic patient has been simplified by the availability of the long-acting insulin, glargine, a recombinant human insulin analogue which can be dosed once or twice daily. Because glargine is less soluble than native human insulin at physiological pH, there is a delayed absorption, resulting in a relatively 'peakless' insulin profile. The combined use of glargine with supplemental short-acting insulins such as insulin lispro or insulin aspart at mealtimes helps to prevent postprandial hypoglycemia after intestinal carbohydrate absorption has been completed. Most patients are able to achieve adequate glycemic control using these insulin preparations. However, continuous subcutaneous insulin infusion pumps have also been used to simplify dosing for patients[58]. The use of insulin lispro or insulin aspart via continuous infusion has been shown in several open-label, randomized, crossover trials in type I and type II diabetic patients to provide better control of postprandial hyperglycemia and a significantly lower glycosylated hemoglobin level, with lower daily insulin requirements and less hypoglycemic episodes than with the use of regular insulin in the pump[58].

Current clinical work in patients with type I diabetes suggests that glucagon rescue injections can help prevent late postprandial hypoglycemia[59]. Glucagon replacement therapy has been attempted in small numbers of apancreatic patients[60,61]. Tankjoh et al., reported that when a physiological dose of glucagon is given proportional to the amount of insulin administered, the utilization of glycogenic amino acids and lipids increased along with a marked improvement in the utilization of carbohydrates.

Exocrine Insufficiency

Exocrine insufficiency also complicates postoperative management following total pancreatectomy. Even with aggressive pancreatic enzyme replacement (up to 120,000 IU of lipase per meal taken in conjunction with a proton pump

Table 3 Clinical Differences Between Type I Diabetes and the Apancreatic State

Conditions	Type I	Apancreatic diabetes
Glycemic instability	++	+++
Insulin requirement	+++	+
Hypoglycemia	++	+++
Ketoacidosis	+++	+
Vascular complications	+++	+

inhibitor to prevent early inactivation of the enzymes by gastric acid), patients continue to have moderate steatorrhea which causes glucose malabsorption and further complicates diabetic management[62,63]. Because of fat and glucose malabsorption, these patients can require an intake of up to 5,000 k/cal per day to maintain their body weight[64]. High-calorie/complex carbohydrate diets with aggressive vitamin and calcium supplementation can help prevent weight loss, control postprandial glycemic shift, and prevent the osteoporosis associated with the apancreatic state. Some simple sugars should be taken at the beginning of a meal following the injection of short acting insulin because of its rapid onset of action. In some patients, it will be necessary to delay insulin injection until after the meal to reduce the risk of hypoglycemia.

Maintenance of continuity of the upper gastrointestinal tract has been proposed as a mechanism to improve absorption following total pancreatectomy. Buchler et al. have reported improved glucose tolerance following duodenum-preserving pancreatic head resection when compared to pylorous-preserving pancreaticoduodenectomy, leading some to speculate that patients undergoing total pancreatectomy might also benefit from more conservative resection[65,66]. Easter in 1991 reported that of eight patients undergoing duodenum-sparing total pancreatectomy for the pain of chronic pancreatitis, none experienced problems with the control of diabetes or any hypoglycemic attacks requiring medical treatment[66]. Proposed mechanisms include improved intestinal transit, improved oral intake, and maintenance of sufficient insulin- and pancreatic polypeptide-secreting tissue to ameliorate the effects of pancreatic resection. However, more recent series of patients undergoing duodenum-sparing total pancreatectomy for chronic pancreatitis reported no statistically significant differences in diabetic complications[67].

Steatohepatitis and Liver Failure

Another metabolic consequence of the apancreatic state is the development of steatohepatitis with progressive liver failure. Dressler, et al. noted that three of the patients in their series of 49 followed at Memorial Sloan-Kettering died of complications of hepatic failure, only one of whom had significant preoperative alcohol abuse[64]. Centrilobular steatosis was documented in two of these patients. All 49 patients demonstrated a durable elevation in levels of serum aspartate aminotransferase and alkaline phosphatase, but the degree of elevation did not correlate with an increased risk for the development of steatohepatitis. It has been hypothesized that decreased hepatic stimulation by glucagon results in progressive fatty deposition in the liver[69]. Periodic evaluation of hepatic aminotransferases, serum bilirubin, and prothrombin time are recommended to evaluate hepatic function in pancreatectomized patients. These patients are also at increased risk for the development of marginal ulcers or peptic ulcer disease secondary to lack of bicarbonate secretion, mandating proton pump inhibitor therapy[63].

Quality of Life Following Total Pancreatectomy

A relative paucity of data exist on quality of life following total pancreatectomy in the current era. In 2004, 20 patients who had undergone total pancreatectomy at the University of Verona, a mean of 34 months earlier (range, 1.5–112 months), were surveyed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ). They were found to have a median insulin requirement of 30.5 IU/day with one patient requiring subcutaneous insulin infusion. Among the patients, 88% had a normal HbA1C level, while 72% patients claimed to have hypoglycemic episodes at least weekly. The median QOL score was 5.5 (range, 3–7) and the median health status score was 5 (range, 3–7), similar to age-matched patients with type II diabetes[69]. More recently, 34 patients who had undergone total pancreatectomy at the Mayo Clinic were surveyed with multiple quality-of-life instruments (SF-36, Audit of Diabetes Dependent Quality of Life, EORTC PAN26) and were found to have quality of life scores equivalent to age- and sex-matched diabetics[70]. Three alcoholic patients died of late hypoglycemic episodes, emphasizing the importance of screening for substance abuse before performing total pancreatectomy. The authors concluded that in appropriately selected patients, total pancreatectomy can provide an acceptable quality of life.

Conclusions

In conclusion, total pancreatectomy remains a viable option in the treatment of (1) intractable pain associated with chronic pancreatitis, (2) multicentric or extensive neuroendocrine tumors, (3) patients with familial pancreatic cancer with premalignant lesions, and (4) in patients with IPMT with diffuse ductal involvement or invasive disease. The use of islet autotransplantation in selected patients with chronic pancreatitis and pancreatic allografts in young patients with premalignant disease can also be included in the armamentarium of treatment options for pancreatectomized patients. In patients who are not candidates for transplantation, advances in insulin formulations and the use of glucagon rescue therapy allow much tighter control of blood glucose than previously possible, markedly lessening the risk of life-threatening hypoglycemia and

decreasing the risk of long-term complications, resulting in improved quality of life for these patients.

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