How Durable Is Total Pancreatectomy and Intraportal Islet Cell Transplantation for Treatment of Chronic Pancreatitis?

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BACKGROUND: A total pancreatectomy and intraportal islet cell autotransplant (TPIAT) is increasingly being offered to patients with chronic pancreatitis (CP). The benefits include removal of the root cause of pain and amelioration of diabetes. However, the long-term durability of this operation remains unclear.

STUDY DESIGN: Of the 742 patients who have undergone a TPIAT at our center, 215 who did so between 1998 and 2008 now have at least 10 years of follow-up time and were eligible for this single-center observational study. Our outcomes measures included abdominal pain relief, narcotic use, islet graft function (subdivided into 3 groups: insulin independence; partial graft function, defined by C-peptide level $>$ 0.6 mg/dL; and no function, defined by C-peptide level $<$ 0.6 mg/dL), and health-related quality of life.

RESULTS: The 10-year actuarial survival rate was 72%. A BMI $>$ 30 kg/m^2 ($p = 0.04$) predicted 10-year mortality. The rates of pain relief were 82% at 10 years and 90% at 15 years. Narcotic use declined with time: the rates were 50% at 5 years and 37% at 10 years. At 10 years, the rate of insulin independence was 20%; the rate of partial graft function, 32%. Transplantation of islet equivalents/kg $>$ 4,000 was the strongest predictor of islet graft function at 10 years. Pediatric patients were more likely to have islet function than adults ($p = 0.01$). Health-related quality of life continued to improve at 10 years, even in patients on narcotics.

CONCLUSIONS: This represents the first and largest series to examine long-term outcomes (10 years or more) in TPIAT patients. In our series, this dual procedure produced durable pain relief and sustained islet graft function, even past 10 years postoperatively. (J Am Coll Surg 2019;228:329–339.
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Chronic pancreatitis is challenging to patients and physicians alike. A major public health concern, its annual incidence in the United States alone is 5 to 12 new cases per 100,000, with an estimated prevalence of 0.05%.[1,2] Its economic impact is notable: the estimated annual health care expenditure for chronic pancreatitis is $3.7 billion—a burden compounded by the costs of workers' disability and lost workdays.[3,4] Initial treatment is directed at relieving pain and restoring quality of life, including narcotic analgesics, pancreatic enzymes (to reduce pancreatic stimulation and to treat pancreatic exocrine insufficiency), nerve block procedures (eg celiac plexus blocks), and endoscopic decompression (whether by pancreatic sphincterotomy, stone extraction, stricture dilation, or stent placement).[5-7] Patients for whom those medical and endoscopic interventions fail may be candidates for surgery.[8]

The role of surgery for patients with chronic pancreatitis is not clear; A number of surgical techniques have been used in an attempt to ameliorate pain and restore quality of life, including partial resection, drainage

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Abbreviations and Acronyms

IAT = islet autotransplant
IEQs = islet equivalents
OR = odds ratio
SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey
TP = total pancreatectomy
TPIAT = total pancreatectomy and intraportal islet cell autotransplant

procedures (eg Puestow lateral pancreaticojejunostomy), and combined resection/drainage variants (eg Frey procedure, Beger procedure).[9,10] These techniques often lead to transient pain relief. But given the disease's diffuse nature and its involvement of the entire pancreas, pain eventually recurs in up to 50% of patients,[11-16] and, over time, exocrine and endocrine insufficiency often develops.[17,18]

Total pancreatectomy (TP) completely removes the root cause of pain. However, TP alone, in the absence of preservation of any beta-cell function, results in diabetes that is often difficult to manage, similar to type 1 diabetes but with added exocrine pancreatic insufficiency. But combining TP with an intraportal islet autotransplant (IAT)—a dual procedure known as TPIAT—preserves as much beta-cell mass with insulin secretory capacity as possible, thereby mitigating diabetic complications.[19]

The TPIAT procedure was first performed at the University of Minnesota in 1977 to treat patients with chronic painful pancreatitis.[20] The rationale was, and is, this: removing the inciting organ and the associated inflammation should confer long-term pain relief. Since 1977, a growing number of centers have devoted considerable resources to developing TPIAT programs; worldwide, more than 1,500 TPIATs have now been performed.[21-27] Many centers, including ours, have reported outcomes data at 5 years, yet very few centers have follow-up data past 10 years. We undertook this study to specifically evaluate the outcomes in our cohort of patients past 10 years to determine whether TPIATs are indeed durable and stand the test of time.

METHODS

For this single-center study, we used our prospectively maintained database. Of the 742 patients who, so far, have undergone TPIAT at our center, 215 from our 1998 to 2008 cohort are now $\geq$10 years post-TPIAT. We collected data under 2 consecutive research protocols, both approved by the University of Minnesota institutional review board. We collected data on pancreatitis, surgical history, and pain and diabetes outcomes after TPIAT. We collected additional data on pain, pain medications, insulin dosing, and quality of life from participant-completed questionnaires. For all patients who completed questionnaires, we obtained informed consent (or, if appropriate, parental consent).

Pre-TPIAT, all patients and families were counseled about the risks and benefits of this dual procedure, including the risks of insulin-dependent diabetes, the need for pancreatic enzyme supplementation, the risks of infection associated with a splenectomy, the likelihood of long-term pain relief, the expected long-term outcomes, and other surgical options or therapeutic approaches. Patients also underwent a psychological and pain evaluation; those with complex substance abuse issues or with difficult pain management regimens were offered additional approaches for anxiety and pain management.

Surgical technique

Our surgical technique has been described elsewhere.[28,29] Total pancreatectomy is performed in such a way that the blood supply to the pancreas is preserved until just before its removal, therefore minimizing warm ischemia time and maximizing islet preservation. In the early years of our TPIAT series, we restored gastrointestinal continuity by anastomosing the first portion of the duodenum to the fourth portion of the duodenum and then performing a choledochoduodenostomy to the first portion of the duodenum. Because of a significant number of patients with bile reflux gastritis and ascending cholangitis, we modified the typical resection to preserve the pylorus, to resect most of the duodenum with the pancreas, and to create a Roux-en-Y biliary drainage (entering the enteric stream 40 cm distal to a duodenojejunostomy). We routinely placed a gastrojejunostomy feeding tube in the stomach, using the Stamm technique, with the tip of the jejunal limb in the jejunum. In addition, in all patients, we performed a cholecystectomy and, if not previously done, an appendectomy.

Islet isolation

For our 1998 to 2008 cohort, the basic method of islet isolation remained the same, even though modifications have been introduced throughout the years. The process consisted of dispersion of the pancreas in a stepwise fashion, first by intraductal injection of collagenase solution under pressure to enzymatically disrupt the exocrine pancreas (sparing the islets) and then by digestion at 34° to 37°C in (since 1991) a shaking (Ricordi) chamber to mechanically facilitate dispersion.[30,31] Enzymatic digestion was performed with Liberase HI (Roche Molecular

Biochemicals) and subsequently, with Serva GMP or Premium (SERVA). After digestion, the islets were generally infused as an unpurified preparation, but could be wholly or partially purified by either a gradient separation or a manual gravity-based method.

The final islet tissue preparation was suspended in 200 mL CMRL (originally developed by Connaught Medical Research Laboratories) culture medium (Mediatech, Inc) per infusion bag, with human serum albumin added to a final concentration of 2.5%, HEPES (4-[2-hydroxyethyl]-1-piperazineethanesulfonic acid) at 25 mM, and ciprofloxacin at 20 μg/mL. To protect against aggregation before infusion, we added heparin at 35 U/kg to the final islet preparation. We permitted a maximum of 10 mL of settled tissue per infusion bag. The total islet isolation and preparation time ranged from 3.5 to 6.5 hours (median 4.5 hours).

Islet infusion

All patients received at least 70 U/kg of heparin (35 U/kg added to the final islet preparation plus another 35 U/kg given directly). Additional heparin (beyond the 70 U/kg) was administered to individual patients at the surgeon's discretion. Then, over a period of 30 to 60 minutes, we infused the islets intraportally (typically, through a cannula inserted through the splenic vein stump), with hemodynamic portal monitoring. After islet infusion, all patients were placed on a heparin drip or Lovenox (Sanofi-Aventis) to minimize the risk of portal vein thrombosis.

Postoperative care

In most of our patients, immediate extubation was possible. Some, however, required overnight mechanical ventilation to ensure airway safety (because of edema or the effects of narcotic analgesia after protracted operative time). Postoperatively, return of gastrointestinal motility and function was often quite delayed. To normalize glycemia, we promptly started insulin infusion (on the day of surgery, during the TPIAT procedure) and then continued it postoperatively. As gastrointestinal function returned, oral or tube narcotics were started.

During the first 3 postoperative months, use of exogenous insulin was nearly universal in our TPIAT patients in order to maintain euglycemia and reduce beta-cell functional stress during the engraftment (neovascularization) stage.[32] Thereafter, patients were weaned off insulin, as long as blood glucose levels remained in a near-normal target range (fasting, <125 mg/dL; postprandial, <180 mg/dL; glycosylated hemoglobin, ≤6.5%). Outside of those ranges, patients were maintained on insulin.

When patients were able to tolerate adequate oral intake, calories, and protein, we advanced their diet and reduced their tube feeding. When patients were able to resume an oral diet, we educated them on the use of pancreatic enzymes, recommending an initial dose of 1,000 lipase units/kg/meal (500 for snacks) and a goal dose of 1,500, with adjustments as necessary. Their diet was supplemented with fat-soluble vitamins and other elemental nutrients as needed.

For postoperative pain management, we started patients on intravenous dexmedetomidine and narcotics. After extubation and basic control of pain, they were weaned off dexmedetomidine; note that we did not attempt to wean patients off narcotics until perioperative pain management was achieved. As a result, all patients were weaned off narcotics in the outpatient setting, often in collaboration with their local providers.

Follow-up was scheduled per our clinical protocol for assessing pancreatectomy outcomes and islet function. Patients were seen postoperatively in outpatient clinics at 3 months, 6 months, 1 year, and then annually. At each clinic visit, we assessed pancreatic pain, its severity (ie better, same, or worse, as compared with pre-TPIAT pain), and narcotic use (any reason, including nonpancreatic pain), and we compared all postoperative and pre-TPIAT assessments.

To assess metabolic control and islet graft function, we also assessed insulin use at each clinic visit. Beginning in September 2006, we added routine laboratory follow-up, once C-peptide testing became more routinely clinically available. Therefore, from September 2006 on, we assessed levels of fasting glucose and C-peptide, stimulated glucose and C-peptide (after a Boost High Protein drink, 6 mL/kg to a maximum of 360 mL), and hemoglobin A_{1c}.

In our overall analysis of islet graft outcomes for all 215 patients, we classified graft function into 3 categories: insulin independence (full islet graft function); partial graft function (C-peptide $\geq$ 0.6 ng/dL; or, if C-peptide level unknown, maintenance of near-normal glucose and glycosylated hemoglobin levels either on once-daily long-acting insulin alone or with occasional supplementation [less than daily] with short-acting insulin); and insulin dependence (islet graft failure) (C-peptide $<$ 0.6 ng/dL; or, if C-peptide level unknown, maintenance of glycemic control on both long- and short-acting insulin [basal-bolus regimen][29]).

Also beginning in September 2006, we administered questionnaires to consenting patients undergoing TPIAT at our center.[33] Specifically, to measure generic health-related quality of life, we asked them to complete the RAND Corporation's Medical Outcomes Study

36-Item Short Form Health Survey (SF-36) before surgery and again at 3 months, 6 months, 1 year, and then annually. We asked additional questions about any narcotic use, pain symptoms, "pancreatic pain" (whether or not similar to preoperative levels), and insulin requirements.[33,34]

Statistical analyses

Data are presented as mean (standard deviation). We defined long-term follow-up intervals as 1 year (range 6 months to 2 years), 5 years (±1 year), 10 years (±2 years), and 15 years (±3 years). To analyze potential patient and disease predictors of pain, narcotic use, and graft function at 10 years post-TPIAT, we used univariate and multivariate analyses. A Kaplan-Meier estimate of overall patient survival through the first 15 years after TPIAT was produced, and a multivariate analysis of mortality focused on the 10-year visit window with logistic regression. Graft function at 10 years was also analyzed by multivariate logistic regression. Confidence intervals for proportions of patients reporting pain or narcotic use at 10 years are "exact."

RESULTS

Baseline patient characteristics

Our study group of 215 patients included 185 adults and 30 children (<18 years old at the time of their TPIAT, Table 1). Mean age was 35.7 years; most were female. Adults and children differed in terms of their primary cause of chronic pancreatitis: idiopathic in nearly half (45.6%) of the adults vs familial or hereditary in most of the children. The mean BMI was 24.6 kg/m^2.

For all 215 patients, medical management and any feasible endoscopic management had failed. For the 148 patients who underwent endoscopy, the mean number of stents was 2.4 ± 3.4. For 63 patients, previous (ie pre-TPIAT) pancreatic surgery was unsuccessful. All 215 patients were on narcotics pre-TPIAT. The mean duration of diagnosed pancreatitis was 6.5 ± 6.2 years; narcotic use, 3.6 ± 2.5 years. Of the 215 patients, 16 (7.4%) patients were diabetic and received insulin pre-TPIAT.

The mean islet mass transplanted was 220,270 ± 127,743 islet equivalents (IEQs), or 3,462 ± 2,261 IEQs per kilogram of body weight. For 187 patients, all islets were infused intraportally into the liver. For 26 patients, islets were primarily infused into the liver, with a small portion placed elsewhere because of concern about portal hypertension (14 peritoneal, 6 stomach subserosa, 4 kidney capsule, 2 omentum). For 2 patients, in the early years of our series, all islets were transplanted under Gerota's fascia of the kidney capsule.

Survival rates

The 1-year patient survival rate was 95%; 10-year survival was 72% (Fig. 1). The causes of death are listed in Table 2. Sepsis was the most common cause. Predictors of mortality at 10 years are shown in Figure 2. The strongest risk factor for mortality was obesity. Obese patients (defined by a BMI > 30 kg/m^2) had a 9-fold increased odds of mortality (odds ratio [OR] 9.26; 95% CI 2.49 to 34.48; p = 0.001), as compared with patients whose BMI was normal (20 through 24 kg/m^2). Patients who had had pancreatitis for 5 to 10 years (vs <5 years) had a lower mortality rate (OR 0.06; 95% CI 0.01 to 0.36; p = 0.002).

We had follow-up up data on pain and/or islet graft function for 140 of patients who remained alive at 10 years post-TPIAT.

Post-total pancreatectomy and intraportal islet cell autotransplant pain and narcotic use

Postoperatively, most patients reported a sustained benefit in pain reduction. Overall pain symptoms were perceived as better or improved in 77.1% of patients at 1 year; 75% at 5 years; and 81.5% at 10 years; in contrast, overall pain symptoms were perceived as the same or worse in 5.6% of patients at 1 year; 8.3% at 5 years; and 6.8% at 10 years (Fig. 3). Any type of abdominal pain was common post-TPIAT, reported by 61% of patients at 1 year, 67% at 5 years, and 62% at 10 years. Yet pancreatitis-type pain was less common, reported by only 6% at 1 year, 19% at 5 years, and 18% at 10 years. Narcotic use for any reason, including intermittent use for causes other than abdominal pain, was reported by 54% of patients at 1 year and declined over time to 37% at 10 years (Fig. 4).

Per our univariate analysis, we found that, at 10 years post-TPIAT, the overall prevalence of pancreatic pain varied by age at surgery: 11.8% for patients less than 18 years old, 17.9% for those 18 to 34 years old, 23.5% for those 35 to 49 years old, and 12.5% for those older than 50 years, but was not significantly different by patient age (p = 0.75). The overall prevalence of narcotic use was 16.7% for patients less than 18 years old, 41.9% for those 18 to 34 years old, 50% for those 35 to 49 years old, and 18.8% for those more than 50 years old (p = 0.034); therefore, narcotic use was significantly lower in the youngest and oldest age groups. However, in a multivariate logistic regression analysis, age as a continuous variable was not significantly associated with narcotic use at 10 years post-TPIAT (OR 1.01; 95% CI 0.98 to 1.04).

Besides age at surgery, none of the other preoperative variables that we assessed (namely, sex, BMI, duration of pancreatitis, duration of narcotic use, previous endoscopy and stenting, or era of surgery) predicted persistent pancreatic pain or narcotic use at 10 years.

Table 1. Baseline Patient Characteristics (n = 215)

Characteristic	Data
Age, y, mean (SD)	35.7 (13.8)
Sex, n	
Female	159
Male	56
Cause of chronic pancreatitis, n (%)	
Idiopathic	98 (45.6)
Hereditary	31 (14.4)
Alcohol	17 (7.9)
Other	69 (32.1)
BMI, kg/m^2, mean (SD)	24.6 (5.6)
Duration of pancreatitis before TPIAT, y, mean (SD)	6.5 (6.2)
Duration of narcotic use before TPIAT, y, mean (SD)	3.6 (3.2)
Insulin use before TPIAT, n (%)	16 (7.4%)
Prior intervention, endoscopic stenting, missing data = 47, n (%)	148 (88.1)
Celiac nerve block, n (%)	53 (24.7)
Previous pancreas operation, n (%)	63 (29.3)
Puestow, n	17
Beger, n	3
Duval, n	1
Distal pancreatectomy, n	1
Frey, n	11
Open sphincteroplasty, n	18
Whipple, n	12

TPIAT, total pancreatectomy and islet autotransplant.

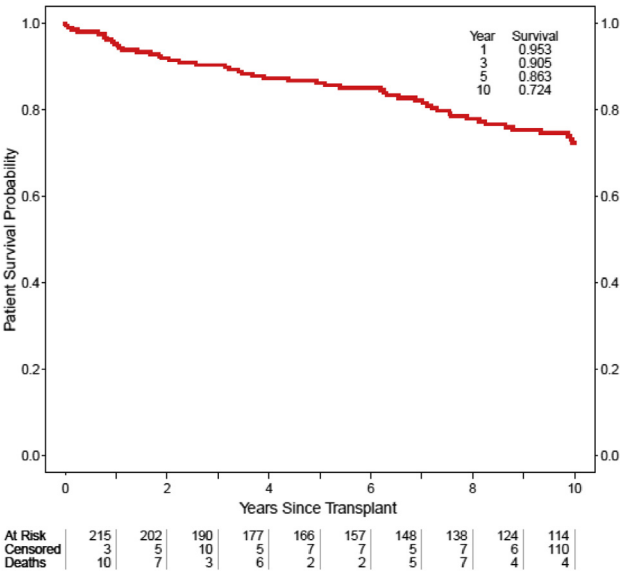

Figure 1. Patient survival from 1998 to 2008, Kaplan-Meier curve (n = 215). Kaplan-Meier based on patient survival times censored at last available follow-up. TPIAT, total pancreatectomy and islet autotransplant.

Islet graft function

Islet graft outcomes (including graft loss due to death) are summarized in Table 3. Among our 215 patients, insulin independence (full islet graft function) was documented for 58 (27.0%) at 1 year post-TPIAT, for 48 (22.3%) at 5 years, and for 28 (13.0%) at 10 years. For patients with known graft status, either insulin independence or partial graft function was documented for 77.3% at 1 year post-TPIAT, for 60% at 5 years, and for 47.1% at 10 years (Fig. 5).

Per our multivariate logistic regression analysis, insulin independence at 10 years was positively associated with age less than 18 years at surgery and with a higher islet mass transplanted (Fig. 6). For that youngest age group (vs the combined reference group of patients 35 to 49 years old), the OR was 9.39 (95% CI 1.0 to 88; p = 0.05). The odds of insulin independence increased progressively with a higher islet mass transplanted: for patients with >4,000 (vs <2,000) IEQs/kg, the OR was 44.6; 95% CI, 6.7 to 296.9; p <0.001.

Among patients with insulin independence at 5 years post-TPIAT, older age was significantly associated with a decline in islet graft function at 10 years. For each 1-year increase in age, the OR for decline in function was 1.09; (95% CI 1.02 to 1.16; p = 0.015). Islet mass (IEQ/kg) transplanted was not significantly associated with change in graft status from full to partial/failed. Neither age nor IEQ/kg transplanted was associated with decline from any graft function (full/partial) at 5 years to a failed graft at 10 years.

Health-related quality of life

Health-related quality of life (HRQoL) assessments with the SF-36 were introduced in late 2006 and therefore are represented for only a subset of patients. We analyzed

Table 2. Post-Total Pancreatectomy and Islet Autotransplant Causes of Death

Cause	n	%
Unknown	29	58
Sepsis	8	16
Pneumonia	2	4
Enterocutaneous fistula	2	4
Cerebrovascular accident	2	4
Cancer	1	2
Kidney failure	1	2
Liver failure	1	2
Diabetic complication	1	2
Sudden death	1	2
Suicide	1	2
Other	1	2

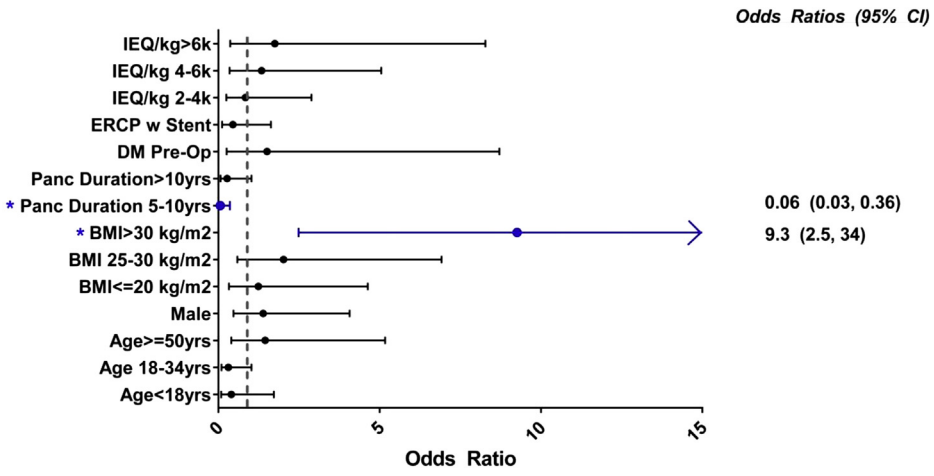

Figure 2. Predictors of mortality at 10 years. *Significant associations. Reference standards for categorical variables are: <2,000 islet equivalents (IEQ)/kg; no ERCP stenting procedures, no diagnosis of diabetes before surgery, pancreatitis duration < 5 years, BMI 20 to 25 kg/m^2, female sex, age 35 to 50 years. DM, diabetes mellitus; ERCP, endoscopic retrograde cholangiopancreatography; panc, pancreatitis.

scores from the SF-36 completed by 59 patients before surgery and by 65 patients $\geq$ 5 years after surgery (mean [SD] time post-TPIAT, 9.97 [3.48] years). The mean (SD) SF-36 physical component summary (PCS) score was 36.4 (11.6) $\geq$ 5 years after surgery vs 26.6 (6.5) before surgery (Student's *t*-test, p = 0.0001). The mean (SD) mental component summary (MCS) score was 41.6 (11.4) $\geq$ 5 years after surgery vs 30.0 (7.9) before surgery (p = 0.0001). Overall raw scores from the 8 subscales of the SF-36 were significantly higher after surgery vs before (p < 0.01 for all); notable findings included a higher bodily pain score (ie indicating less pain) of 53.2 (26.7) after surgery vs 25.0 (19.0) before (p = 0.0001).

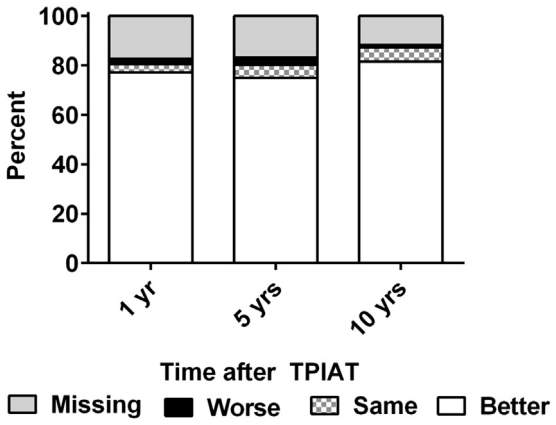

Figure 3. Pain improvement post-total pancreatectomy and islet autotransplant (TPIAT), per patients' perception.

DISCUSSION

Total pancreatectomy and intraportal islet cell autotransplant is most often performed in patients with painful and debilitating chronic pancreatitis who have not responded to medical endoscopy or to previous surgery; their impairment and quality of life due to pain needs to be substantial enough to warrant acceptance of the risk of developing postoperative insulin-dependent diabetes and a lifelong commitment to pancreatic enzyme replacement therapy.[34] In the mid-1990s, TPIAT began to gain acceptance, with several centers performing relatively large series by early 2000.[21-29] We previously reported the early outcomes of the Minnesota series at the Southern Surgical Association's 123rd Annual Meeting in 2011.[29] At that meeting, we reported pain improvement in 94% of our TPIAT patients at 1 year, with pancreatic pain present for only 15% at 1 year and 23% at 2 years; we also reported a decline in narcotic use to 54% of patients at 1 year and 51% at 2 years. But at that time, longer-term data were lacking. In this study, we evaluated pain outcomes and islet function long-term, at 5, 10, and 15 years post-TPIAT, with a focus on the 10-year outcomes. By 10 years post-TPIAT, 82% of our patients experienced sustained relief of pancreatic pain, 63% used no narcotic pain medications (for any cause), nearly 50% had at least partial graft function, and 13% remained insulin independent. These results highlight the potential for long-term benefit in pain relief for islet longevity with TPIAT.

Most of the larger series previously reported in the literature included up to only 5 years of follow-up, with very

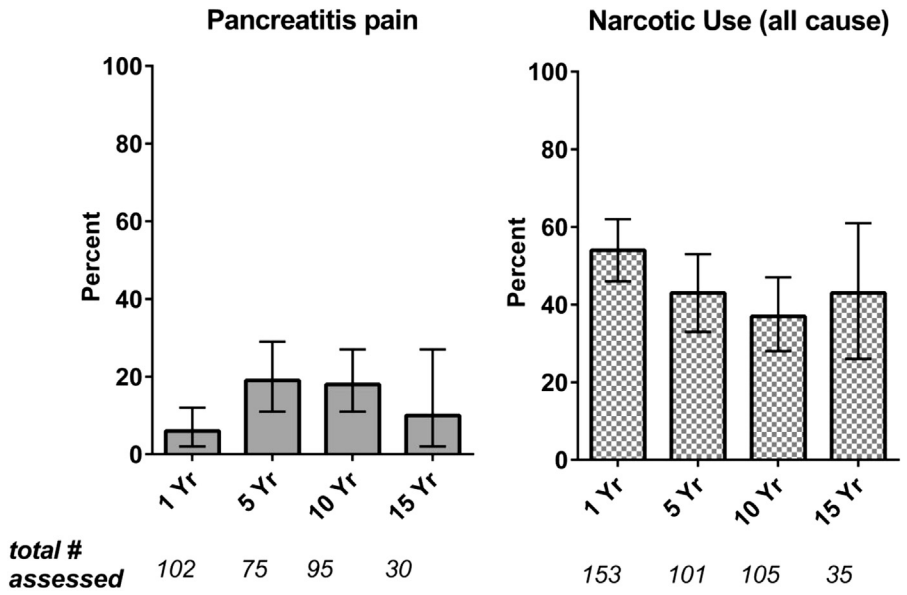

Figure 4. Percent of patients with pancreatic pain and on narcotics (for any reason) post-total pancreatectomy and islet autotransplant.

few results beyond 5 years.[21-26] The Leicester General Hospital group presented their long-term data of 50 patients; follow-up time ranged from 6 months to 10 years.[23] Of the Leicester patients, 25 had >5 years of follow-up; only 2 had >10 years. Over time, those patients had increased insulin requirements and higher glycosylated hemoglobin levels, but all patients tested at 5 and 10 years demonstrated stimulated C-peptide activity, suggesting significant long-term islet graft function. Unfortunately, long-term data (10 years or more) on narcotic independence were available for only 4 of those patients, with no long-term data on quality of life.[23]

Morgan and colleagues,[21] from the Medical University of South Carolina group, reported their series of 195 TPIAT patients, noting improvement in quality of life scores and in pain that persisted at 5 years. Insulin independence was reported for 29% of their patients at 1 year, for 28% at 2 years, and for 23% at 5 years. In addition, Morgan and colleagues[21] observed that patients with hereditary pancreatitis more often were narcotic-free and had better quality of life than patients with pancreatitis due to other causes.

The Cincinnati group reported a series of 112 patients who had at least 5 years of follow-up. The narcotic-free rate at 1 year was 55% and continued to improve, to 73%, at 5 years.[22] The insulin independence rate was 38% at 1 year and declined over time to 27% at 5 years. All patients had stable glycemic control (median hemoglobin A_{1c}, 6.9%). Of a subset of patients who completed the SF-36, 34 demonstrated persistent improvements in all subscales from baseline values; 85% of them continued to report improved health beyond 5 years post-TPIAT.[22]

Our study is the first and largest to focus on long-term outcomes of patients >10 years post-TPIAT. Our findings are consistent with those of the Leicester, South Carolina, and Cincinnati groups, confirming the durability of TPIAT at an even longer follow-up time. At >10 years, we found that relief from pancreatic pain was sustained, with 82% of our patients reporting improvement. Narcotic use continued to decline after the first year, with fewer than 40% of our patients reporting any narcotic use at 10 years, as compared with 100% of our 215 patients using narcotics, either continuously or intermittently, before TPIAT.

Of note, 37% of our patients were taking narcotics at 10 years post-TPIAT, a somewhat higher percentage than in other reports. One potential reason for this higher prevalence is that we included narcotic use for any indication, including, for example, back pain or arthritis. From our patients' medical records or questionnaires, it was often not feasible to discern the indication for narcotic

Table 3. Islet Graft Outcomes

	1 y		5 y		10 y	
Outcome	**n**	**%**	**n**	**%**	**n**	**%**
Patient death						
With graft failure	2	1	9	4.2	14	6.5
Without graft failure	2	1	17	7.9	28	13.0
Graft failure	45	20.9	68	31.6	74	34.4
Partial graft function	95	44.2	52	24.2	38	17.7
Insulin independence	58	27.0	48	22.3	28	13.0
Graft status unavailable	13	6.0	21	9.8	33	15.3

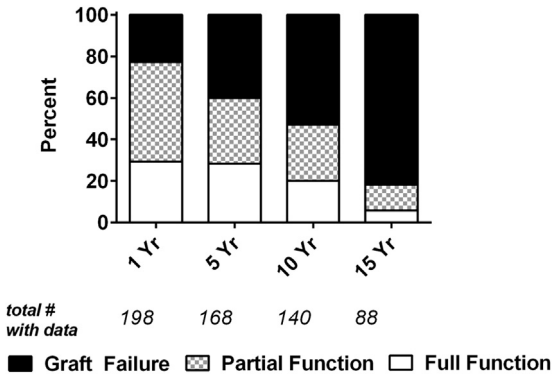

Figure 5. Percent of patients with islet graft function. Graft function defined as: graft failure if stimulated C-peptide < 0.6 ng/mL, or in absence of C-peptide testing patient, requires basal-bolus insulin (multiple daily injections); partial function if on insulin therapy with C-peptide ≥ 0.6 ng/mL, or in the absence of C-peptide data, requires only once daily basal insulin or occasional (less than daily) supplemental insulin; and full function if insulin independent.

use; therefore, our finding of 37% likely overestimates the proportion of our patients on narcotics for abdominal pain. Nonetheless, these patients may be physiologically predisposed to chronic pain issues from the long duration of pancreatitis pain (mean 6.5 years in our cohort) and of narcotic use before surgery. Prolonged exposure to chronic pain, with repetitive acute exacerbations, has the potential to produce central sensitization. Ultimately, neuroplastic changes can lead to complex behavioral responses that contribute to persistent pain, such as muscle memory encoding responses.[35,36] In addition, TPIAT patients can have other complex medical complications that contribute to abdominal pain symptoms, including gastrointestinal dysmotility, narcotic bowel syndrome, and chronic postsurgical pain that may be difficult to diagnose or treat.[36] All of these factors could have contributed to the long-term narcotic use in our patients.

Our findings also highlight the need to improve long-term pain management post-TPIAT. A small proportion of patients may continue to need narcotic medications for other unrelated conditions, yet narcotic use can ultimately worsen central sensitization, opioid-induced hyperalgesia, and gastrointestinal dysmotility. Therefore, comprehensive pain management programs that address alternative pharmacologic and nonpharmacologic approaches may enhance long-term pain relief.

More important than changes in narcotic use, however, is the issue of whether patients are able return to a functional lifestyle with improved quality of life. Our SF-36 results suggest that our TPIAT patients enjoyed improved quality of life, even those who were unable to be completely weaned off narcotics. Therefore, when quality of life improves, the inability to be weaned off narcotics is not necessarily a treatment failure.

We previously reported that patients from our center with prolonged narcotic use (>5 years), repetitive stenting (>3 stents), and lower SF-36 scores preoperatively, were more likely to have persistent pain or prolonged narcotic use postoperatively.[27] In this cohort, only pediatric patients (<18 years at surgery) and older patients (>50 years at surgery) had a lower prevalence of narcotic use at 10 years, per our univariate analysis. We found no statistically significant predictors of narcotic use or of persistent pancreatic pain past 10 years, per our multivariate logistic regression analysis—perhaps because of the

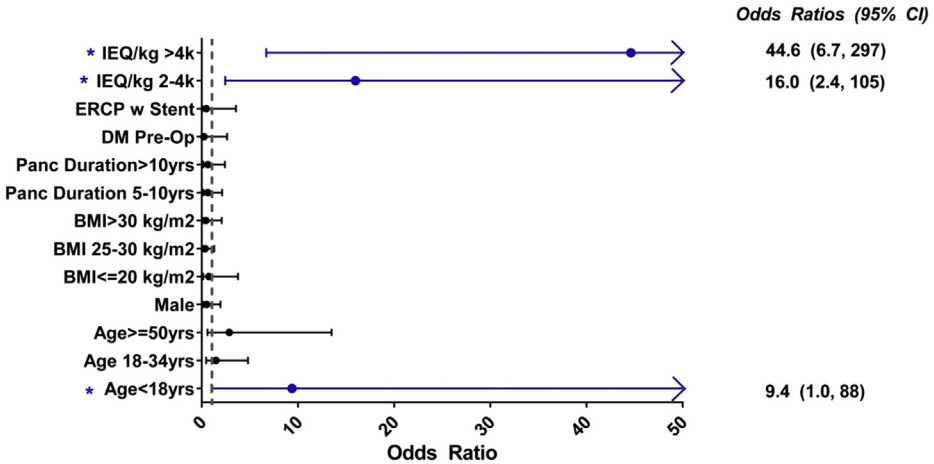

Figure 6. Predictors of islet graft function. *Significant associations. Reference standards for categorical variables are: <2,000 islet equivalents (IEQ)/kg; no ERCP stenting procedures, no diagnosis of diabetes before surgery, pancreatitis duration < 5 years, BMI 20 to 25 kg/m^2, Female sex, Age 35 to 50 years. DM, diabetes mellitus; ERCP, endoscopic retrograde cholangiopancreatography; panc, pancreatitis.

small number of patients with >10 years of follow-up. In particular, we lacked data on the duration of preoperative narcotic use for many patients in the early years of our series (those predating the advent of detailed electronic medical records), which limited our analysis.

Among the known causes of mortality, infection accounted for 8 deaths in our cohort. In addition, 1 of our patients presented to an outside emergency room with abdominal pain and fever 8 years post-TPIAT; laboratory testing showed a white blood cell count of 25,000/mm^3, and the patient suddenly died within 24 hours after admission. An autopsy was not performed, so post-splenectomy sepsis as the cause could not be ruled out. Another of our patients died, 7 years post-TPIAT, from a complication with placement of the spinal rod, also at an outside hospital; this patient had been ventilator-dependent for 3 months post-TPIAT, and the cause of death was listed as acute respiratory distress syndrome. In both of these patients, splenectomy during their TPIAT could have increased the possibility of sepsis. Since those 2 deaths, we now include splenectomy prophylaxis in our TPIAT protocol, as follows. All children are fully immunized against *Haemophilus influenzae* type b, meningococcus, and pneumococcus before TP IAT; they are also given antibiotic prophylaxis for 1 year post-TPIAT.[28]

One patient in this series died from a diabetes-related complication. Chronic pancreatitis is associated with significant increased mortality, even in the absence of surgery. Data from Olmsted County in southeastern Minnesota suggest that age- and sex-matched standardized mortality increases nearly 2-fold in patients with chronic pancreatitis, and 3.4-fold specifically in females with chronic pancreatitis, which is notable because females made up 74% of our cohort.[1]

With regard to islet graft function, we confirmed insulin independence in 13% of our 215 patients at 10 years post-TPIAT. Of those patients who were alive and had data available for islet graft function at 10 years, 47% had a functioning graft and 53% were considered to have a failed graft. In many patients in the early years of our series, islet graft failure was defined by insulin use (ie multiple daily injections), which may overestimate islet graft failure as compared with the more recent advent of more sensitive C-peptide testing. The most important predictors of a functioning graft at 10 years were age less than 18 years at surgery and a higher islet mass transplanted (ie >4,000 IEQs/kg), which is similar to what we previously reported for patients 1 to 3 years post-TPIAT.[27-29]

Over time, we observed an overall decline in the proportion of patients with either insulin independence or partial graft function post-TPIAT. Worsening function has previously been reported for both islet autografts and islet allografts.[37] The reasons are not fully understood, but nonimmune mechanisms likely contribute to a slow loss of viable islet mass post-TPIAT, including the repeated metabolic strain on a borderline islet mass (glucotoxicity), exposure to portal toxins or beta cell-toxic drugs, and inability of the body to replace or regenerate islets in the liver (via processes that may be present in a normal pancreas, such as islet neogenesis).[38-41] In our series, age was an important factor: between 5 and 10 years post-TPIAT, changes from insulin independence were more likely if patients were older at time of surgery, with risk for resumption of insulin increasing by 9% for each year of age. Islet mass, however, was not significantly associated with changes in graft function between 5 to 10 years. However, only a few patients had a decline in graft function between 5 and 10 years. Larger series may be required to adequately understand factors that mediate islet attrition over time.

Also of note, although only a small proportion of our patients appeared to retain graft function at 15 years, our 15-year data are more limited: fewer of our patients have yet reached that follow-up time. There is also a potential bias toward overestimating islet graft failure, because once an islet graft has failed, it is always failed. In contrast, partial or full graft function requires current data on insulin use and/or C-peptide levels to confirm persistent function. More complete follow-up data will be required to make firm conclusions on diabetes outcomes at 15 years and beyond.

CONCLUSIONS

In summary, in our cohort of 215 patients, we showed that TPIAT effectively alleviated pain due to chronic pancreatitis. The benefits of pain relief remained durable even at 10 years or more after surgery. Narcotic use continued to decline after surgery and remained at about 40% at 10 years; even the patients still on narcotics experienced improved health-related quality of life. Nearly 50% of our patients had either full or partial islet graft function at 10 years, with a significant proportion (13% of our cohort) maintaining insulin independence at 10 years. Clearly, durable islet graft function after TPIAT is achievable, particularly in patients younger than 18 years old with a higher islet mass transplanted (ie > 4,000 IEQs/kg).

Author Contributions

Study conception and design: Bellin, Chinnakotla
Acquisition of data: Bellin, Ali, Petersen, Chinnakotla
Analysis and interpretation of data: Bellin, Mongin, Chinnakotla
Drafting of manuscript: Bellin, Chinnakotla

Critical revision: Bellin, Beilman, Sutherland, Ali, Petersen, Mongin, Kirchner, Schwarzenberg, Trikudanathan, Freeman, Pruett, Chinnakotla

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Discussion

DR KATHERINE MORGAN (Charleston, SC): The experience at University of Minnesota with total pancreatectomy and intraportal islet cell autotransplant (TPIAT) over 4 decades is unparalleled, and I am grateful for their willingness to lead the charge with evaluating outcomes, both in this study and as the lead center in the NIH/National Institute of Diabetes and Digestive and Kidney Diseases-funded multicenter POST study.

Islet transplant is a radical and irreversible intervention. Patients are trading one disease, chronic pancreatitis, for two others—diabetes and pancreatic exocrine insufficiency. As the collective experience with TPIAT has matured, the group of patients that has emerged as most clearly benefiting from this procedure are the patients with hereditary pancreatitis, which obviously entails a very young patient population, including children. The mean age of all patients in this study was only 36 years. Defining long-term outcomes after TPIAT is truly essential for best clinical decision-making and patient counseling. This study represents the longest-term comprehensive outcomes data available.

I recently completed a peer-to-peer review with an MD at an insurance company to get approval for an upcoming islet transplant on an adolescent. Interestingly, the insurance doctor told me he had been a surgery resident briefly at the Mayo Clinic under Dr Jon Van Heerden, and he was very excited to talk to me at length. He had great angst, however, in approving the procedure because the patient was so young and he did not know what her outcome would be later in life. I cannot wait to send him this published manuscript. In the manuscript, nearly half the patients in the study were identified as having idiopathic pancreatitis and only 14% were identified as having hereditary pancreatitis. Do you perform routine genetic testing on all patients? Does the presence of a genetic mutation alter your algorithm for the management of these patients? Seven percent of patients had insulin-requiring diabetes before operation. How do you determine which diabetic patients are candidates for surgery?

Sixty percent of the long-term patients complained of abdominal pain of any kind after transplant. Can you detail this further? Are these the patients with persistent opioid use? Do you think there is a component of narcotic bowel? Did etiology predict persistent postoperative abdominal pain? Younger patients and those with a larger islet mass transplanted were most likely to be insulin independent. This suggests earlier total pancreatectomy with islet auto transplant is better. How have these data affected your algorithm for management of chronic pancreatitis patients? What are the considerations for the best timing for this procedure in children?

DR MARLON F LEVY (Richmond, VA): What do we know about glycemic control in these patients? Do you have any data on hypoglycemic unawareness? It has been a minor frustration for me that in the islet field, we have defined graft failure as loss of function, but really focusing only on insulin and the glucagon story gets forgotten. In fact, we know that even with return to complete insulin dependence, hypoglycemic unawareness becomes a very important side effect of having islets, even a very small dose.

Next, I focused on your 72% 10-year survival. Is that low or is it really what we would expect? Are there any data on survival of that length of time for major noncancer pancreatic surgery? I do note that 28 of your 50 patients who died by year 10 died with functioning grafts.

Is all your data adult or is any of it pediatric? I know that University of Minnesota has substantial experience in pediatric patients. Are you able to parse out survival statistics between adults and pediatrics? I think to Dr Morgan's comment, this would be a helpful data point to have.

Finally, I wonder if you would consider including the Kaplan-Meier curve for all of the patients who had this procedure. I note that the curve that you showed is for roughly 200 or so patients with 10-year survival or more, but I think it would be instructive for all of us to be able to look at survival across the entire spectrum.

DR SELWYN VICKERS (Birmingham, AL): All of us who have done the procedure have had that patient for whom you have completed a successful operation and have seen no significant pain relief. On whom do you not operate? When I was at Minnesota, we talked about having criteria that would increase the opportunities for successful outcomes in both reduction of narcotics as well as pain relief. What are your criteria for a patient who would not undergo an operation at the University of Minnesota? I know there are a number of procedures that are done, such as Puestow's, that really decrease islet yield and may also indicate who does not get a total pancreatectomy.

The 15-year and 10-year periods really speak to islet senescence. Have you looked at potentially new homes for islet placement? The liver has traditionally been the place. We have talked about the pouch of the stomach, the omentum, that may have more trophic