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Selection of parenchymal preserving or total pancreatectomy with/without islet cell autotransplantation surgery for patients with chronic pancreatitis

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ABSTRACT

Background: The selection of surgery between parenchymal preserving (PPS) and total pancreatectomy (TP) with/without islet cell autotransplantation (IAT) for chronic pancreatitis (CP) patients varies based on multiple factors with a scarcity in literature addressing both at the same time. The aim of this manuscript is to present an algorithm for the surgery selection based on dominant area of disease, ductal dilatation, and glycemic control and compare outcomes.

Methods: From 2017 to 2021, CP patients offered surgery at a single institution were retrospectively evaluated.

Results: 51 patients underwent surgery (20 [39.2%] TPIAT, 4 [7.8%] TP, and 27 [52.9%] PPS – 9 Whipple procedures, 15 distal pancreatectomies, and 3 duct drainage procedures). No significant difference was observed in baseline characteristics or perioperative outcomes except median length of stay (8 days [IQR 6–10] vs. 13 days [IQR 9–15.5], $p < 0.001$), attributed to insulin requirement and education for TPIAT group. No differences in postoperative complications, such as clinically significant leak and intra-bdominal fluid collection (3 [11.1%] vs 2 [10%], $p = 1.0$), hemorrhage (0 vs. 2 [10.0%], $p = 0.2$), delayed feeding (1 [3.7%] vs. 5 [25.0%], $p = 0.07$), or wound infection (4 [14.8%] vs. 0, $p = 0.1$) between PPS and TPIAT groups, respectively, were observed nor requirement of long-acting insulin at discharge (2 [15.4%] vs. 7 [43.8%], $p = 0.1$) for pre-operatively non-diabetic patients. No significant difference in weaning off narcotics and no mortality observed.

Conclusion: The most appropriate selection of surgery based on the algorithm yields good and comparable outcomes.

1. Introduction

Chronic pancreatitis (CP) is an extremely challenging disorder for both patients and providers [1]. Patients suffer from immense physical and psychological problems, including chronic abdominal pain, which often lead to narcotic dependence, nutritional deficiencies, and poor quality of life [2]. CP is associated with pancreatogenic diabetes mellitus, which in turn is associated with higher rates of hypoglycemia, and in some CP patients there is an increased risk of pancreatic cancer [3]. Medical and endoscopic therapies are the initial approaches for the treatment of CP, and patients are often referred to surgeons when these options fail [4]. Recent reports have emerged that suggest a benefit of early surgical intervention in patients with CP [5]. Multiple patient and institution-related factors result in widely variable practices regarding the timing of surgery and range of surgeries offered.

Pancreatic surgeries have evolved over time for both malignant

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as well as benign disease. The evolution of different procedures for chronic pancreatitis is due to the anatomical variance in disease of the pancreas. Historically, pancreaticoduodenectomy (Whipple procedure) has been widely used because the inflammatory changes disproportionately involve the head of the pancreas [6]. Due to the perioperative complications associated with resection of the duodenum and disruption of the natural drainage of the pancreas, alternatives such as the Beger and Frey procedures were developed [7,8]. This procedure also included coring out the inflamed bulky head of pancreas keeping the posterior wall of head and neck intact, opening the dilated duct longitudinally and creating a longitudinal pancreatojejunostomy, combining a decompressive operation with resection [8]. Before the routine use of endoscopic stents, isolated ductal drainage surgery including the Puestow procedure and the Partington-Rochelle was employed for some patients with CP to release the abnormally high pressure in a dilated ductal system, leaving parenchyma intact and decreasing perioperative morbidity and mortality [9]. For isolated disease of the pancreatic body and tail for example as it occurs after the disconnected duct due to previous severe acute pancreatitis, distal pancreatectomy can be performed with limited morbidity and good postoperative quality of life outcomes [10,11]. All these surgeries are parenchymal preserving pancreatic surgery (PPS) where some parenchyma of pancreas is left behind as opposed to total pancreatectomies.

In some patients, CP is associated with severe symptoms but radiologically there are neither any particular areas of inflammation/calcifications which can be localized to head or tail, nor is there significant duct dilatation. Such cases need to be treated with total pancreatectomy (TP). While TP is the most likely to completely alleviate pain and risk of pancreatic cancer, the resultant severe metabolic consequences of endocrine and exocrine insufficiency must be seriously considered [3,12]. Total pancreatectomy and autologous islet cell transplantation (TPIAT) was first described in 1978 with an aim to address the disabling diabetes [13]. Since this time, science has evolved and more data have been generated regarding TPIAT, showing stability in glycemic control, avoidance of severe hypoglycemic episodes, and tremendous improvement in quality of life in both adult and pediatric patients [14–17]. The extent and magnitude of this procedure have been the subject of criticism; however, its importance in the management of selected patients with severe CP symptoms cannot be overlooked.

As the choice of surgery for CP varies widely, often based on individual surgeon preference or institutional capabilities, decision-making regarding patient selection and type of surgery remains difficult. The choice of surgery often relies on perception of superiority of one procedure over the other based on anecdotal experience. Institutions may have their individual pattern of selection, but there is limited documentation in the literature of an established algorithm for selecting PPS or TP (with/without IAT) or comparison of their immediate outcomes. This manuscript seeks to address this gap by presenting an algorithm for selection of these surgeries based on anatomical distribution of disease and physiological function of the pancreas (endocrine in terms of diabetes), as well as comparing the relevant outcomes between them.

2. Methods

We performed a retrospective analysis of all patients who underwent surgical management of CP from February 2017 to April 2021 at our institution. Each patient who was referred for surgery underwent a detailed clinical assessment, laboratory testing, and radiological and endoscopic evaluation. Patients without medical contraindications for whom surgery was deemed necessary underwent one of the following: PPS, TPIAT, or TP without IAT, based on an algorithm which was developed using guidance from literature and experience (Fig. 1). The algorithm was initiated once it was determined that the patient had exhausted endoscopic and medical management options. The designated surgery was discussed and validated by a multidisciplinary group comprised of an expert interventional gastroenterologist, endocrinologist, and radiologist. All patients who presented with CP of unclear etiology underwent genetic testing for pancreatitis gene panel and if found to have positive findings were selected for TPIAT. The remaining were selected based on dominant area of disease as determined by CT, MRI, or endoscopic ultrasound (EUS) findings. We defined non-dominant disease as absence of calcification on CT scan, or the presence of a dilated duct and retention of contrast on T1 delayed MRI images to suggest severe fibrosis [18]. In other words, to be categorized as dominant disease in a certain part of the pancreas required either calcification, dilated duct or severe retention of contrast on T1 delayed MRI images suggestive of severe fibrosis. The ductal drainage procedure (Frey's procedure) was offered to patients who had more than 1 cm dilatation of the duct associated with pathology in head of pancreas.

For endocrine assessment, each patient underwent preoperative assessment of glycemic function and diabetes stratification with measurement of HbA1c, C-peptide, and by review of previous or current insulin requirements. Every patient with alcohol-related disease underwent evaluation by a psychologist and social worker and required abstinence and counselling in a manner similar to our liver transplant program. For those patients considered for TPIAT, further evaluation included obtaining a stimulated C-peptide and continuous glucose monitoring (CGM) as previously described [19]. In brief, to measure a stimulated C-peptide, a registered nurse (RN) drew a baseline C-peptide, then, following administration of 1-mg IV glucagon, drew sequential serum C-peptide levels at 5-min intervals for a total of 15 min. Continuous glucose monitoring involved placement of a blinded mode Dexcom Pro G5 (DexCom, Inc., San Diego, California, USA) applied to the abdomen or a Freestyle Libre Pro (Abbott Laboratories, Abbott Park, Illinois, USA) applied to the upper arm with calibration in clinic by an RN. The continuous glucose monitors recorded data every 5 min, continuously, over a five-day period.

All surgeries were performed by a single surgeon (CSD), eliminating technical bias. PPS was defined as any surgical procedure on the pancreas that would preserve some parenchyma and not being total pancreatectomy, such as pancreaticoduodenectomy, distal pancreatectomy, and ductal drainage procedures. TPIAT surgery was performed as previously described [20]. The pancreas was digested in the Good Manufacturing Practice (GMP) facility of the university enterprise. At the GMP facility, the pancreas was washed in a solution of antibiotics and cut at the level of the neck to access the pancreatic duct after removing the fat, blood vessels, and connective tissues. Two catheters were placed into the transected duct, one towards the pancreatic head and duodenum and one towards the tail. After enzymatic infusion, the pancreas was distended and then cut into small pieces of approximately 1-2-cm^3. The tissue was then transferred to the Ricordi chamber for digestion. Once the digestion was completed and the pancreatic islet cells isolated, several washes were performed. The final islet cell product was analyzed by gram-stain for sterility, endotoxin, and viability. Cells were infused intraoperatively through splenic vein stump. Post-operative anticoagulation and follow up protocol was performed as previously described [21].

Demographic characteristics and perioperative outcomes were analyzed retrospectively from prospectively collected data. Perioperative variables analyzed were length of surgery (minutes), estimated blood loss (mL), intensive care unit (ICU) admission, ICU length of stay (days), hospital length of stay (days), perioperative

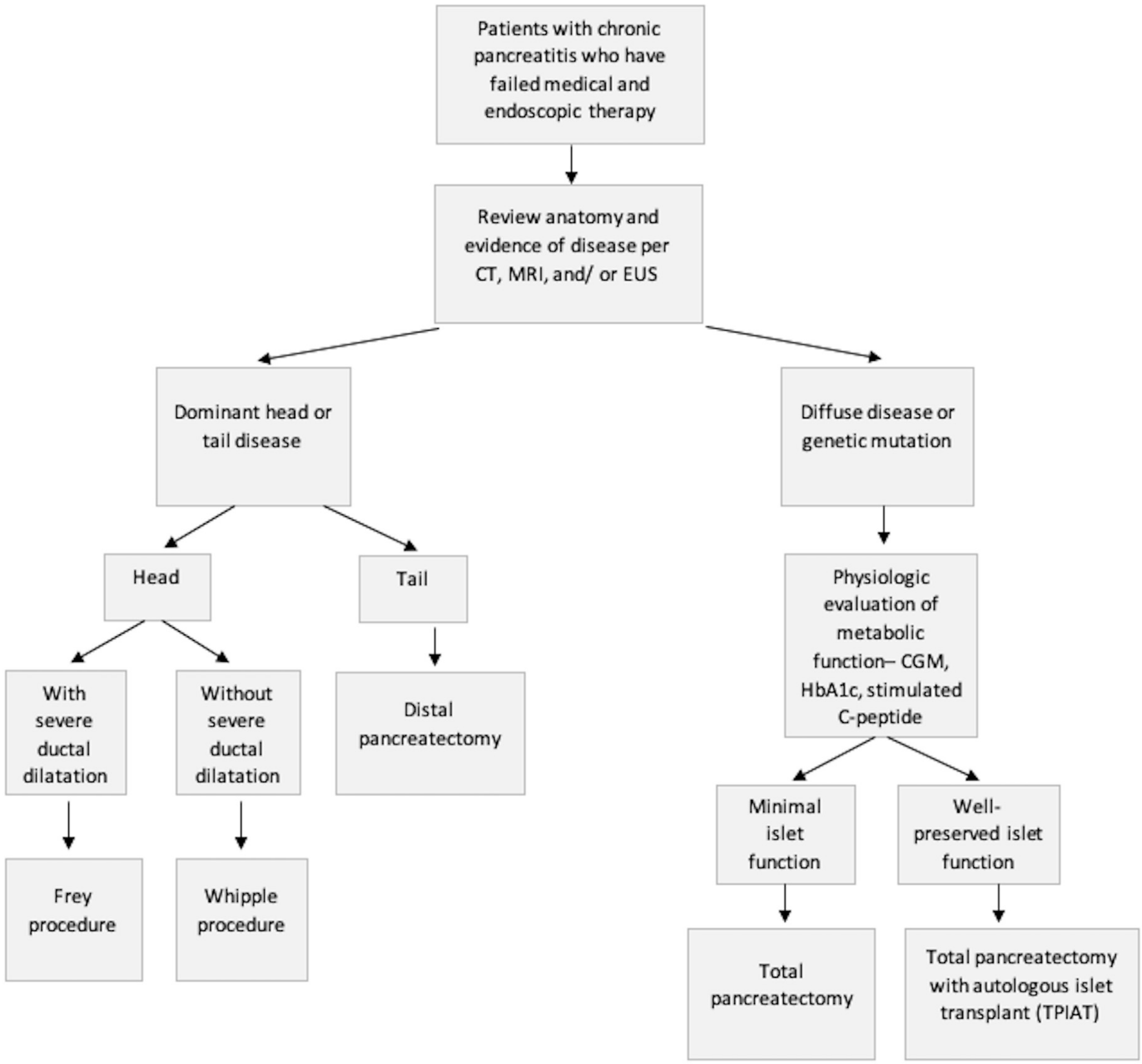

Fig. 1. Surgery selection algorithm for patients considered for the surgical management of chronic pancreatitis.

complications, and 30-day readmission rate. Perioperative complications included post-operative pancreatic fistula, post-pancreatectomy hemorrhage, and delayed gastric emptying as defined by consensus grading systems developed by The International Study Group of Pancreatic Surgery (ISGPS) [21–23].

Intermediate and longer-term outcomes analyzed included glycemic control, assessment of broad Quality of life (QOL) and reduction in narcotic use. In our program, it is a requirement that each patient is engaged with a pain management provider before surgery and thus, upon discharge they follow with them for pain management including narcotic use. As objective QOL measures, such as the Short Form-36, were administered at various time points during data gathering, we analyzed a simple 3 question assessment of overall post-operative quality of life in terms of improved, worsened, and unchanged. Glycemic outcomes were evaluated as previously described [18]. Severe hypoglycemic event was defined as that which required hospitalization and hypoglycemic unawareness was defined as < 54 mg/dL requiring assistance or self -reported unawareness.

Bivariable analyses comparing each perioperative and intermediate/long-term outcome between PPS and TPIAT were conducted. Patients that underwent total pancreatectomy without islet cell transplant were reviewed separately and not included in the bivariable analysis. Continuous variables were compared using student's t-test and Kruskall-wallis rank test for parametric and non-parametric variables, respectively. Categorical variables were compared using chi-squared or fisher's exact tests as indicated. Glycemic outcomes were further stratified by patients those were preoperatively diabetic, defined as an HbA1c level $\geq$6.5% in accordance with the 2018 American Diabetes Association guidelines [24].

All analyses were conducted using STATA v16.0 (StataCorp, College Station, TX). We reported data as confidence intervals set at 95% and statistical significance at $\alpha = 0.05$. The University of North Carolina Institutional Review Board approved this study.

3. Results

3.1. Patient characteristics

Over the study period, 51 patients underwent operative management, of which 27 (52.9%) underwent PPS, 20 (39.2%) underwent TPIAT, and 4 (7.8%) underwent total pancreatectomy. Of those that underwent PPS, 9 (33.3%) were Whipple procedures, 15 (55.6%) were distal pancreatectomies, and 3 (11.1%) were duct drainage procedures. Patients were followed for a median 1.5 years (IQR 1–3).

When comparing PPS to TPIAT, patients that underwent PPS were more often older (mean age 52.1 years (SD 15.4) vs. 39.5 (SD 13.9), p = 0.01) (Table 1). There was no significant difference in proportion of males (n = 16 [59.3%] vs. 8 [40.0%], p = 0.2), median body mass index (BMI) (27.1 [IQR 22.6–31.1] vs. 24.1 [22.5–29.8], = 0.5), or comorbidities, such as diabetes (n = 14 [51.9%] vs. 4 [20.0%], p = 0.03), hypertension (n = 13 [48.2%] vs. 4 [20.0%], p = 0.07), or smoking history (n = 16 [59.3%] vs. 9 [45.0%], p = 0.3).

The etiologies of CP in our patients are described in Table 1. All patients were referred with CP diagnosis. Four patients in TPIAT group had genetic mutations (1 SPINK1, 1 both PRSS and SPINK1, 2 had CFTR). Though final pathology resulted as neoplasm, as listed in etiology table in few of PPS cases, they all were referred as with predominant problem of CP with questionable etiology or mass. The median symptom length prior to surgery was similar between PPS and TPIAT patients (45.5 months [IQR 12–108] vs. 54 months [IQR 24–114], p = 0.1). There were no significant differences in proportion of those with prior abdominal surgeries (n = 12 [44.4%] vs. 11 [55.0%], p = 0.5) or median number of prior endoscopies (1 [IQR 1–2] vs. 1 [IQR 0–4], p = 0.9). In the TPIAT group, only 4 (20%) had prior pancreas-related surgeries (Whipple procedures requiring completion pancreatectomy) while the remainder were largely cholecystectomies. Among the PPS group, 2 underwent open cystgastrostomies and the remaining 10 were cholecystectomies. There was also no significant difference in preoperative work up between groups, magnetic resonance imaging (MRI) (n = 21 [77.8%] vs. 13 [65.0%], p = 0.3), EUS (n = 20 [74.1%] vs. 10 [50.0%], p = 0.09), or endoscopic retrograde cholangiopancreatography (ERCP) (n = 11 [40.7%] vs. 9 [45.0%], p = 0.8). Calcifications were present on imaging studies of 7 (25.9%) PPS patients and 9 (45.0%) TPIAT patients.

The four total pancreatectomies without islet cell auto-transplantation were performed for chronic pancreatitis due to alcohol (1), biliary obstruction (1), pancreatic divisum (1), and neoplasm (1). Due to their severe diabetic status and poor pre-operative c-peptide, islet auto-transplant was not considered for these patients. Their mean age was 40.5 years (SD 12.4) and 2 (50%) were male. Two had prior abdominal surgeries and the median number of endoscopic procedures was 1.5 (IQR 1.0–4.5). Preoperatively, all 4 underwent CT and EUS and 3 underwent MRIs and ERCPs. Calcifications were present in 3 (75%) of the cases.

3.2. Perioperative characteristics and outcomes

Median length of surgery, including time for intubation and line placement, was shorter for PPS than TPIAT (6 h [IQR 5–8] vs. 11 h [IQR 10–12], p < 0.001); however, when we excluded the approximately 5 h of islet isolation and then infusion time, there was no significant difference in length of surgery between the two techniques (6 h [IQR 5–8] vs. 6 h [IQR 5–7], p = 1.0) (Table 2). Estimated blood loss was similar between PPS and TPIAT (250 mL [IQR 150–400] vs. 300 mL [IQR 150–500], p = 0.5) and few intra-operative transfusions were required (n = 3 (11.1%) in PPS vs. 0 TPIAT, p = 0.3). No inadvertent injury occurred in either group. Epidurals were used in 23 (85.2%) PPS patients; however, epidurals were not used in TPIAT due to postoperative intravenous anti-coagulation protocol used to prevent portal vein thrombosis [25].

Postoperatively, ICU admission occurred for 7 (25.9%) PPS patients and all 20 TPIAT patients due to the critical care requirement for continuous insulin infusion (Table 2). For those that required ICU admission, the median ICU length of stay was shorter for PPS (2 days [IQR 1–3] vs. 6 days [IQR 5–7], p = 0.001), also attributable to insulin titration in the TPIAT group. There were no statistically significant differences in postoperative complications following PPS vs. TPIAT. Three post-operative pancreatic fistulas (2 biochemical leaks, 1 class B) occurred in the PPS group. Post-pancreatectomy hemorrhage occurred in two (10%) of the TPIAT group (1 class B, 1 class C). There was no post-pancreatectomy hemorrhage in the PPS group. Delayed feeding occurred in five

Table 1
Patient demographics and clinical characteristics of patients undergoing parenchymal preserving surgery(PPS) and total pancreatectomy with islet cell autotransplnatation(TPIAT).

	PPS (n = 27 [57.5%])	TPIAT (n = 20 [42.6%])	Total (N = 47)	p
Age (y), mean (SD)	52.1 (15.4)	39.5 (13.9)	46.7 (15.9)	0.01
Male, n (%)	16 (59.3)	8 (40.0)	24 (51.1)	0.2
Body mass index (kg/m^2), median (IQR)	27.1 (22.6–31.1)	24.1 (22.5–29.8)	25.4 (22.6–30.5)	0.5
Co-morbidities, n (%)				
Diabetes	14 (51.9)	4 (20.0)	18 (38.3)	0.03
Hypertension	13 (48.2)	4 (20.0)	17 (36.2)	0.07
Renal disease	2 (7.4)	0 (0)	2 (4.3)	0.5
Cardiac disease	4 (14.8)	0 (0)	4 (8.5)	0.1
Cirrhosis	1 (3.7)	0 (0)	1 (2.1)	1.0
Smoker, n (%)	16 (59.3)	9 (45.0)	25 (53.2)	0.3
Pancreatitis etiology, n (%)				<0.001
Idiopathic/unknown	2 (7.4)	4 (20.0)	5 (10.6)	
Alcoholic	9 (33.3)	5 (25.0)	14 (29.8)	
Obstructive	3 (11.1)	3 (15.0)	6 (12.8)	
Pancreatic divisum	0 (0)	4 (20.0)	4 (8.5)	
Genetic mutation (hereditary pancreatitis)	0 (0)	4 (20.0)	5 (10.6)	
Neoplasm	10 (37.0)	0 (0)	10 (21.3)	
Trauma	3 (11.1)	0 (0)	3 (6.4)	
Symptom length (months), median (IQR)	45.5 (12–108)	54 (24–114)	48 (18–108)	0.1
Have had prior abdominal surgeries, n (%)	12 (44.4)	11 (55.0)	23 (48.9)	0.5
Number of prior endoscopic procedures, median (IQR)	1 (1–2)	1 (0–4)	1 (1–3)	0.9
Preoperative studies, n (%)				
CT	25 (92.6)	20 (100)	45 (95.7)	0.2
MRI/MRCP	21 (77.8)	13 (65.0)	34 (72.3)	0.3
EUS	20 (74.1)	10 (50.0)	30 (63.8)	0.09
ERCP	11 (40.7)	9 (45.0)	20 (42.6)	0.8
Calcifications present on preoperative imaging, n (%)	7 (25.9)	9 (45.0)	16 (34.0)	0.2

Table 2
Perioperative characteristics and outcomes.

	PPS (n = 27 [57.5%])	TPIAT (n = 20 [42.6%])	Total (N = 47)	p
Epidural, n (%)	23 (85.2)	0 (0)	12 (48.9)	<0.001
Intra-operative characteristics				
Length of surgery (hours), median (IQR)	6 (5–8)	11 (10–12)	8.4 (5.5–11)	<0.001
Length of surgery excluding isolation time (hours), median (IQR)	6 (5–8)	6 (5–7)	6 (5–8)	1.0
Estimated blood loss (mL), median (IQR)	250 (150–400)	300 (150–500)	300 (150–500)	0.5
Required transfusion, n (%)	3 (11.1)	0 (0)	3 (6.9)	0.3
Inadvertent injury, n (%)	0 (0)	0 (0)	0 (0)	–
Post-operative characteristics				
ICU admission, n (%)	7 (25.9)	20 (100.0)	27 (57.5)	<0.001
Length of ICU stay (days), median (IQR)	2 (1–3)	6 (5–7)	6 (3–6)	0.001
Length of intubation (days), median (IQR)	2 (1–3)	1 (1–2)	1 (1–1)	0.7
Post-operative pancreatic fistula, n (%)	3 (11.1)	0 (0)	3 (6.9)	0.3
Postpancreatectomy hemorrhage, n (%)	0 (0)	2 (10.0)	2 (4.3)	0.2
Delayed gastric emptying, n (%)	1 (3.7)	5 (25.0)	6 (12.8)	0.07
Wound infection, n (%)	4 (14.8)	0 (0)	4 (8.5)	0.1
Length of stay (days), median (IQR)	8 (6–10)	13 (9–15.5)	9 (7–13)	<0.001
Readmitted in 30 days, n (%)	5 (18.5)	2 (10.0)	7 (14.9)	0.7
Mortality, n (%)	0 (0)	0 (0)	0 (0)	–

ICU = Intensive care unit.

(25%) of the TPIAT group (4 class A, 1 class B) and one (3.7%) of the PPS group (class A). There was no statistical difference in rate of wound infection between the PPS and TPIAT groups (n = 4 [14.8%] vs. 0, p = 0.1). In those that underwent total pancreatectomy without islet cell transplant, a chyle leak requiring total parenteral nutrition occurred in 1 (25.0%) patient, causing significantly delayed feeding.

The 30-day readmission rate was similar between PPS and TPIAT (n = 5 [18.5%] vs. 2 [10.0%], p = 0.7), and there were no readmissions among the total pancreatectomies (Table 2). Hospital length of stay was shorter for PPS than TPIAT (8 days [IQR 6–10] vs. 13 days [IQR 9–15.5], p < 0.001). There was no mortality in any group. Preoperatively, 9 (33.3%) PPS and 15 (75.0%) TPIAT patients were narcotic dependent. At 1-month post-operation, there was no significant difference in proportion of narcotic dependence between PPS and TPIAT (13 [48.2%] vs. 13 [65.0%], p = 0.2). All patients reported 'improved' quality of life at median follow up. This was noted from follow-up notes which had 3 objective questions as described in methods. All specimens were analyzed for histopathology. A small amount of tissue was obtained at the time of isolation from TPIAT patients as well. The pathology findings described either severe parenchymal atrophy and fibrosis, severe calcific disease, and/or neoplastic disease.

For the four total pancreatectomies, the median length of surgery was 9.1 h (IQR 9.0–10.6) including anesthesia induction and lining time. The median estimated blood loss was 200 mL (IQR 150–250) and none required blood transfusion or had an inadvertent injury. All required the ICU postoperatively with a median length of stay in the ICU 3 days (IQR 3–4). Postoperative complications occurred in only 1 (25%) total pancreatectomy, a chyle leak with resultant delayed feeding. The median length of stay following total pancreatectomy was 10 days (IQR 8–15.5). There were no readmissions or mortality.

3.3. Glycemic outcomes

Preoperatively, 14 (51.9%) PPS patients and 4 (20.0%) TPIAT patients were diabetic (Table 1). There was no difference in median HbA1c between all PPS vs. TPIAT patients (5.7 [IQR 5.3–7.7] vs. 5.6 [IQR 5.2–5.9], p = 0.3) (Table 3) or when stratified by those that were preoperatively diabetic (8.0 [7.7–8.3] vs. 8.0 [6.8–9.2], p = 1.0). Prior to surgery, 4 (14.8%) PPS patients and 2 (10.0%) TPIAT required long-acting insulin. In pre-operative glycemic function assessment of those patients who underwent TPIAT, patients without diabetes pre-operatively had a median HbA1c of 5.5% (5.1–5.8%), a median baseline C-peptide of 3.1 ng/mL (1.1–9.0 ng/mL), a median delta C-peptide of 2.6 ng/mL (0–4.4 ng/mL), and median percent time spent in a euglycemic state of 91.5% (28–99%). Of those patients who underwent TPIAT, patients with diabetes pre-operatively had a median HbA1c of 8.0% (6.8–9.2%), a median baseline C-peptide of 2.4 ng/mL (1.8–7.4 ng/mL), a median delta C-peptide of 0.6 ng/mL (0–1.9 ng/mL), and a median percent time spent in a euglycemic state of 64% (16–80%). Patients who underwent total pancreatectomy without islet transplant had a median pre-operative HbA1c of 7.6% (5.6–17.2%) and a median C-peptide of 1.0 ng/mL (0.1–13.0 ng/mL). The median long-acting basal insulin requirement for these patients was 17.5 units pre-operatively (8–85 units), with median of 0.27 units of basal insulin per kg of body weight (0.13 units/kg – 0.88 units/kg).

At discharge, long-acting insulin was required in a higher proportion of TPIAT patients overall (6 [22.2%] PPS vs. 11 [55.0%] TPIAT, p = 0.03). However, of those that were not diabetic preoperatively, there was no difference in long-acting insulin requirement at discharge between PPS vs. TPIAT (2 [15.4%] vs. 7 [43.8%], p = 0.1). Among all patients, 13 out of 20 (65%) TPIAT patients still required long-acting insulin at 12 months post-operatively compared to 9 of 27 (33.3%) PPS patients (p = 0.07). No patient in either group suffered a severe symptomatic hypoglycemic event (Table 3).

4. Discussion

The decision about the choice of surgery for CP is often influenced by the bias of surgeon and medical institution. Apart from the cases of disconnected duct leading to isolated CP in the portion of gland upstream to the disruption, CP is diffuse glandular disease, though often predominance of disease is observed in one part of the gland. This may prompt performance of PPS. But the proponent of TPIAT will argue that no gland is "normal," and, hence, TP should be performed. At the same time, proponents of PPS will deem TPIAT as a very aggressive procedure. With increasing awareness and availability of islet cell autotransplantation, more and more surgeons will have the option, and also challenge, of choosing the correct surgery. Currently, the North American centers that publish large series on TPIAT have few to no comparative PPS data. There is a scarcity in literature in which both the procedures are addressed at the same time. The development of various surgical approaches

Table 3
Glycemic outcomes of all PPS vs. TPIAT.

	PPS (n = 27 [57.5%])	TPIAT (n = 20 [42.6%])	Total (N = 47)	p
Hemoglobin A1c (%) preoperatively, median (IQR)	5.7 (5.3–7.7)	5.6 (5.2–5.9)	5.7 (5.2–6.6)	0.3
Preoperatively require long-acting insulin, n (%)	4 (14.8)	2 (10.0)	5 (12.8)	1.0
Insulin requirement at discharge, n (%)				0.03
Require insulin	6 (22.2)	11 (55.0)	17 (36.2)	
Insulin independent	21 (77.8)	9 (45.0)	30 (63.8)	
Insulin requirement at 3 months, n (%)				0.1
Require insulin	8 (29.6)	12 (60.0)	20 (42.6)	
Insulin independent	15 (55.7)	7 (35.0)	22 (46.8)	
Missing	4 (14.8)	1 (5.0)	5 (10.6)	
Insulin requirement at 6 months, n (%)				0.1
Require insulin	8 (29.6)	12 (60.0)	20 (42.6)	
Insulin independent	14 (51.9)	7 (35.0)	21 (44.7)	
Missing	5 (18.5)	1 (5.0)	6 (12.8)	
Insulin requirement at 9 months, n (%)				0.1
Require insulin	8 (29.6)	12 (60.0)	20 (42.6)	
Insulin independent	14 (51.9)	7 (35.0)	21 (44.7)	
Missing	5 (18.5)	1 (5.0)	6 (12.8)	
Insulin requirement at 1 year, n (%)				0.07
Require insulin	9 (33.3)	13 (65.0)	22 (46.8)	
Insulin independent	12 (44.4)	6 (30.0)	18 (38.3)	
Missing	6 (22.2)	1 (5.0)	7 (14.9)	
Severe hypoglycemic event, n (%)	0 (0)	0 (0)	0 (0)	–
Hypoglycemic unawareness, n (%)	0 (0)	3 (15.0)	3 (6.4)	1.0

and the debate over choice of surgery clearly suggest that the surgical approach chosen should be tailored to the individual patient. At our institution we have availability and expertise in both PPS and TPIAT, which led us to evaluate broad comparative outcomes and evaluate an algorithm which would help in surgical decision making. Our aim was not to identify superiority of one operation over another but whether there were any advantages or disadvantages of selecting one over another to our patients. Our results suggest usefulness of the algorithm to select type of surgery.

In this series of patients, both PPS and TPIAT provided safe and desirable outcomes. We noted a significant difference in age between patients undergoing PPS and TPIAT. This can be related to etiology and resultant anatomical and physiological differences that would influence their placement in the algorithm. The ICU and hospital length of stays were higher in the TPIAT group. This was due to the need for insulin infusion in the immediate postoperative period to allow for islet cell rest. Our institutional policy mandated that an insulin drip can only be administered in the ICU. Patients who were not on insulin preoperatively needed education before discharge, which also delayed discharge by several days. This is an important finding for potential process improvement. All patients could have been given pre-operative diabetic education to decrease post-operative length of stay. Overall, patients with TPIAT required higher doses of insulin, and this alone is often the main factor in selecting PPS for patients with more localized disease. At the same time, absence of hypoglycemic episodes and unawareness supports the safety of TPIAT therapy. According to the Collaborative Islet Transplant Registry (CITR), a total of 819 auto-islet recipients have been reported between 1999 and 2015 within North America (11 of 23 sites), Europe (4 sites), and Australia contributing 754, 63, and 2 patients, respectively. Of these cases there have been no hypoglycemia-related mortality [26].

Interestingly, a few patients in our series had completion pancreatectomy after previous Whipple procedure, which provides some support for the use of TPIAT as the first-line approach in select patients. Two patients had severe complications following Whipple procedure done at outside institution with ductal issues leading to pancreatic fibrosis in the remainder of the gland, amongst other issues. The other two had unknown etiology of pancreatitis and hence possible progression of disease. Nevertheless, these patients also had symptomatic relief for several years before TPIAT, including some of younger age. It would be helpful to have larger data sets including prospective studies to further assess the advantages and disadvantages to PPS followed by TPIAT.

Out of our entire- cohort, 4 diabetic patients who had acceptable stimulated cpeptide response were offered TPIAT. However, other 4 patients underwent total pancreatectomy without autoislet transplantation. For patients with benign disease this may be perceived as a radical approach; however, all of these patients were severely disabled, narcotic dependent, and unable to perform activities of daily living or maintain gainful employment. They had complete endocrine and exocrine deficiency suggestive of end stage pancreatic disease. One of them had liver dysfunction in the form of primary sclerosing cholangitis. We believed there were no other non-surgical options for improving their quality of life, and all patients improved following surgery. There is evidence that AIT can be performed in diabetic patients, and we offer this approach as long as their beta cell function is adequate with stimulated c-peptide levels more than 2 ng/mL [27]. There is a high level of concern for metabolic dysfunction without AIT, though many patients still have an improved QOL. Patients who develop brittle DM-related complications can be treated with pancreas transplantation [28].

The strength of this study is that our data allowed the development of an algorithm to assist in determining the surgical approach for CP patients. In absence of widespread documentation of comparative data, our center was uniquely poised to provide comparative outcome data. There are some limitations to this study. The small sample size could have introduced type II error; however, the limited numbers of surgical CP patients precludes the ability to significantly increase a single-center's sample size. Patients were not randomized, though such a study will be difficult to randomize from ethical and practical perspective especially in a single center. This study offers preliminary data for planning prospective studies. Some definitions used in this study may appear as not well-defined, such as dominant disease. We did not use EUS to appreciate subtle changes of CP. Etiologies in some patients who underwent TPIAT may infer that some patients had recurrent acute pancreatitis rather than "CP", but we determined pathologically and clinically that all had severe parenchymal changes. We could not obtain objective QOL measures, such as the Short Form-36 survey, from all the patients on consistent basis, and thus we relied on subjective report from most patients. Additionally, narcotic use was described dichotomously, reported in terms of opioid use or not. Future studies will provide a more standardized approach using morphine milligram equivalents to increase comparability. Since our program is relatively young, we did not measure long term outcomes; however, our aim was to evaluate this comparative data from peri-operative, short and intermediate point of view.

In conclusion, pancreatic surgery for chronic pancreatitis is technically difficult, and decisions regarding the optimal surgical approach for individual patients in CP are equally difficult. When all surgical options are available to the surgeon, the appropriate selection of surgery based on this algorithm, resulted in good and comparable outcomes. In the future, multi-center, protocolized, randomized trials will help to validate the generalized applicability and compare PPS and TPIAT.

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Declaration of competing interest

None.

References

[1] Mihaljevic AL, Kleeff J, Friess H, Büchler MW, Beger HG. Surgical approaches to chronic pancreatitis. Best Pract Res Clin Gastroenterol 2008;22:167–81. https://doi.org/10.1016/j.bpg.2007.10.015.
[2] Braganza JM, Lee SH, McCloy RF, McMahon MJ. Chronic pancreatitis. Lancet 2011;377:1184–97. https://doi.org/10.1016/S0140-6736(10)61852-1.
[3] Gardner TB, Adler DG, Forsmark CE, Sauer BG, Taylor JR, Whitcomb DC. ACG clinical guideline: chronic pancreatitis. Am J Gastroenterol 2020;115:322–39. https://doi.org/10.14309/ajg.0000000000000535.
[4] Dominguez-Munoz JE, Drewes AM, Lindkvist B, Ewald N, Czako L, Rosendahl J, et al. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis. Pancreatology 2018;18:847–54. https://doi.org/10.1016/j.pan.2018.09.016.
[5] Issa Y, Kempeneers MA, Bruno MJ, Fockens P, Poley JW, Ahmed Ali U, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. JAMA 2020;323: 237–47. https://doi.org/10.1001/jama.2019.20967.
[6] Andersen DK, Frey CF. The evolution of the surgical treatment of chronic pancreatitis. Ann Surg 2010;251:18–32. https://doi.org/10.1097/SLA.0b013e3181ae3471.
[7] Buchler MW, Friess H, Miiller MW, Wheatley AM, Beger HG. Randomized trial of duodenum-preserving pancreatic head resection versus pylorus-preserving Whipple in chronic pancreatitis. Am J Surg 1995;169:65–70.
[8] Frey CF, Smith GJ. Description and rationale of a new operation for chronic pancreatitis. Pancreas 1987;2:701–7. https://doi.org/10.1097/00006676-198711000-00014.
[9] Partington PF, Rochelle RE. Modified Puestow procedure for retrograde drainage of the pancreatic duct. Ann Surg 1960;152:1037–43. https://doi.org/10.1097/00000658-196012000-00015.
[10] Kleeff J, Stöß C, Mayerle J, Stecher L, Maak M, Simon P, et al. Evidence-based surgical treatments for chronic pancreatitis. Dtsch Arztebl Int 2016;113: 489–96. https://doi.org/10.3238/arztebl.2016.0489.
[11] Hutchins RR, Hart RS, Pacifico M, Bradley NJ, Williamson RCN. Long-term results of distal pancreatectomy for chronic pancreatitis in 90 patients. Ann Surg 2002;236:612–8. https://doi.org/10.1097/00000658-200211000-00011.
[12] Parsaik AK, Murad MH, Sathananthan A, Moorthy V, Erwin PJ, Chari S, et al. Metabolic and target organ outcomes after total pancreatectomy: mayo Clinic experience and meta-analysis of the literature. Clin Endocrinol 2010;73: 723–31. https://doi.org/10.1111/j.1365-2265.2010.03860.x.
[13] Sutherland DER, Matas AJ, Najarian JS. Pancreatic islet cell transplantation. Surg Clin 1978;58:365–82. https://doi.org/10.1016/S0039-6109(16)41489-1.
[14] Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. Pancreatology 2014;14:27–35. https://doi.org/10.1016/j.pan.2013.10.009.
[15] Chinnakotla S, Radosevich DM, Dunn TB, Bellin MD, Freeman ML, Schwarzenberg SJ, et al. Long-term outcomes of total pancreatectomy and islet auto transplantation for hereditary/genetic pancreatitis. J Am Coll Surg 2014;218:530–43. https://doi.org/10.1016/j.jamcollsurg.2013.12.037.
[16] Bellin MD, Abu-El-Haija M, Morgan K, Adams D, Beilman GJ, Chinnakotla S, et al. A multicenter study of total pancreatectomy with islet autotransplantation (TPIAT): POST (Prospective Observational Study of TPIAT). Pancreatology 2018;18:286–90. https://doi.org/10.1016/j.pan.2018.02.001.
[17] Baldwin XL, Williams BM, Schrope B, Desai CS. Review: what is new with total pancreatectomy and autologous islet cell transplantation? Review of current progress in the field. J Clin Med 2021;10:2123. https://doi.org/10.3390/jcm10102123.
[18] Khan KM, Desai CS, Kalb B, Patel C, Grigsby BM, Jie T, et al. MRI prediction of islet yield for autologous transplantation after total pancreatectomy for chronic pancreatitis. Dig Dis Sci 2013;58:1116–24. https://doi.org/10.1007/s10620-012-2448-1.
[19] Vonderau JS, Williams BM, DeCherney S, Jones MS, McKnight L, Hanson M, et al. Use of continuous glucose monitoring for evaluation of hypoglycemia pre- and post-operatively for patients undergoing total pancreatectomy with autologous islet cell transplant. Clin Transplant 2021:e14450. https://doi.org/10.1111/ctr.14450.
[20] Desai CS, Stephenson DA, Khan KM, Jie T, Gruessner AC, Rilo HL, et al. Novel technique of total pancreatectomy before autologous islet transplants in chronic pancreatitis patients. J Am Coll Surg 2011;213:e29–34. https://doi.org/10.1016/j.jamcollsurg.2011.09.008.
[21] Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Position statement Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761–8. https://doi.org/10.1016/j.surg.2007.05.005.
[22] Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. Pancreas the 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years after. Surgery 2017;161:584–91. https://doi.org/10.1016/j.surg.2016.11.014.
[23] Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH)-An international study group of pancreatic surgery (ISGPS) definition. Surgery 2007;142:20–5. https://doi.org/10.1016/j.surg.2007.02.001.
[24] American Diabetes Association. Classification and diagnosis of diabetes: standards of medical care in diabetes - 2018. Diabetes Care 2018;41:S13–27. https://doi.org/10.2337/dc18-S002.
[25] Williams BM, Baldwin X, Vonderau JS, Hyslop WB, Desai CS. Portal flow dynamics after total pancreatectomy and autologous islet cell transplantation. Clin Transplant 2020;34:e14112. https://doi.org/10.1111/ctr.14112.
[26] CITR Coordinating Center. Collaborative islet transplant Registry: tenth annual report. https://www.citregistry.org/content/reports-publications-presentations. [Accessed 15 April 2021].
[27] Bachul PJ, Grybowski DJ, Anteby R, Basto L, Perea L, Golab K, et al. Total pancreatectomy with islet autotransplantation in diabetic and pre-diabetic patients with intractable chronic pancreatitis. J Pancreatol 2020;3:86–92. https://doi.org/10.1097/jp9.0000000000000048.
[28] Gruessner RWG, Sutherland DER, Dunn DL, Najarian JS, Jie T, Hering BJ, et al. Transplant options for patients undergoing total pancreatectomy for chronic pancreatitis. J Am Coll Surg 2004;198:559–69. https://doi.org/10.1016/j.jamcollsurg.2003.11.024.