Surgery for Chronic Pancreatitis

The Role of Early Surgery in Pain Management

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Objectives: To examine if surgery performed for pain of chronic pancreatitis (CP) within 3 years diagnosis has greater odds of achieving complete pain relief than later surgery and to find optimal surgical timing for attaining pain relief in CP.

Methods: Retrospective review of records at a tertiary institution 2003 to 2011 for CP where the operative indication was pain. Outcomes were pain-free status, opioid use, and pancreatic insufficiency at 3-year follow-up. Univariate analysis by Fisher exact tests. Receiver operating curve to calculate cutoff threshold time for surgery.

Results: Outcomes for 66 patients were included. Median preoperative CP duration was 28 months (interquartile range, 12, 67). Twenty-six patients (39.4%) were free of pain at the 3-year follow-up. Thirty-four patients (51.5%) were opioid users at follow-up. Postoperatively, 34 patients (51.5%) demonstrated endocrine, and 32 patients (48.5%) demonstrated exocrine insufficiency. The optimal cutoff point for preoperative CP duration was 26.5 months (area under the curve, 0.66). Shorter duration of CP before surgery was a predictor of pain-free status and reduced postoperative opioid use at follow-up.

Conclusions: Results from a single institution analysis suggest early surgical intervention of 26.5 months or less of diagnosis is associated with improved pain control, and optimal timing for surgery may be earlier than previously thought.

Key Words: chronic pancreatitis, pain, opioid, surgery, puestow, early surgery

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Chronic pancreatitis (CP) is an inflammatory disease characterized by debilitating episodes of pain, which can progress to be constant and incapacitating.[1] The annual incidence of CP in the United States is around 4 to 12/100,000 persons.[2,3] With the main etiologies of CP in developed countries being alcohol abuse, idiopathic, and biliary.[4] Chronic pancreatitis can lead to pancreatic endocrine and exocrine dysfunction, pancreatic cancer, opioid use, and mortality, and thus contributes much burden to society.[4]

Adequate management of pain in CP has proven challenging.[4] Pain of CP was historically thought to be self-limiting, but this has been overtaken by newer theories. Ductal hypertension and hypersensitization of peripancreatic nerves have both been attributed to the indefinite pain experienced by a proportion of patients.[1] Based on this theory, some centers have suggested that surgery should occur early in the disease process. Traditionally, surgery has been reserved for later in the disease process after conservative therapy and endoscopic interventions have failed. Animal studies have demonstrated reversal of histological changes of CP, as well as restoration of pancreatic function after early surgical drainage.[5,6] Two studies comparing initial intervention with endoscopy against surgery suggested early surgery may lead to more pain relief and thus minimize the risk of lifelong opioid use.[7,8] A Dutch study demonstrated that surgery within 3 years of symptom onset was associated with more pain relief and less pancreatic dysfunction after a median of 62 months of follow-up.[9]

The objectives of this study were to use a cohort of patients undergoing operations at a single center to examine if surgery performed for pain of CP within 3 years of diagnosis has greater odds of achieving significant pain relief than surgery after 3 years of diagnosis, and to attempt to determine an optimal timing cutoff for surgery to help patients with CP attain pain relief.

MATERIALS AND METHODS

Inclusion Criteria

This was a retrospective review of medical records at a tertiary institution from January 1, 2003, and March 1, 2011. Both administrative data, including insurance provider and zip codes, and clinical data, including intraoperative anesthesia notes, discharge letters, clinic letters, laboratory values and history of medications dispensed, were reviewed. All patients aged 16 years or older who presented to the hospital with a diagnosis of recurrent acute or CP, and who received a definitive surgical procedure in this same period, were eligible to be included in this study. We only included patients whose operative indication was pain. The diagnosis of CP was confirmed on chart review: either by pathology, imaging, or both. Patients were identified using hospital Decision Support data by International Classification of Diseases-9 coding. Definitive surgical procedures were defined as lateral pancreaticojejunostomy (Puestow procedure); Frey procedure; pancreaticoduodenectomy, including the Whipple procedure; total pancreatectomy; distal pancreatectomy; and duodenum-preserving pancreatic head resection (Beger procedure).

Exclusion Criteria

To establish a dedicated CP cohort with sufficient follow-up, patients were excluded if pathology demonstrated neoplasm including pancreatic adenocarcinoma and cholangiocarcinoma, if patients died before 3-year follow-up postoperatively, if there was inadequate information at 3 years follow-up, or if patients were lost to follow-up before 3 years postoperatively. Patients were also excluded if the index surgery was nonelective or if they had any surgical procedures performed on the pancreas before the index surgery. Patients who had pancreas divisum were excluded because for these patients, there is a clear anatomical indication for surgery. This paper sought to answer the question of surgery for patients in whom there was no clear indications.

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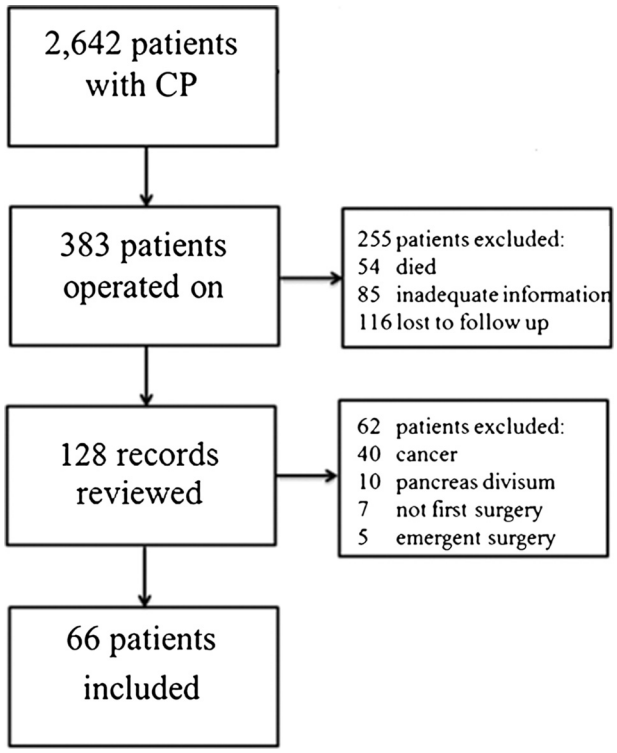

FIGURE 1. Patient selection process.

Outcomes

Primary outcome was pain-free status at 3 years follow-up. Secondary outcomes were need for opioid pain relief, exocrine pancreatic function, and endocrine pancreatic function. Pain levels were measured subjectively using the patient's own reports, their functional ability, and their requirements for analgesia. Patients were assigned to the "pain free" group if (1) patients did not take regular analgesia; (2) pain did not impair their ability to perform activities of daily living, including work or study; or (3) patients were not hospitalized in the past 12 months for exacerbations of pain. Exocrine pancreatic dysfunction was defined as a positive fecal elastase test or need for pancreatic enzymes. Endocrine pancreatic dysfunction was defined as impaired glucose tolerance as documented by clinical notes or laboratory values (glucose tolerance test, fasting glucose over 100 mg/dL, or HbA1c over 6.5%) or diagnosed diabetes mellitus.

Statistical Analysis

Duration of CP before surgery was categorized into quartiles. Normality was tested formally using Shapiro-Wilk tests. All *P* values were 2-sided, and *P* values less than 0.05 were considered significant. Categorical variables were analyzed by Fisher exact tests. Receiver operating curve (ROC) was conducted to calculate the cutoff threshold for time under which surgery has benefit for pain relief. The R-based web program developed by Budczies et al[10] was used to calculate area under the curve (AUC) and optimal cutoffs by Manhattan distance. The ROC curve was unadjusted. Unadjusted AUC greater than 0.8 was considered "excellent," 0.7 to 0.8 was considered "very good," 0.6 to 0.7 was considered to be "good," 0.5 to 0.6 was considered to be "adequate," and less than 0.5 was considered "poor." Unadjusted odds ratios (ORs) were calculated using Firth Penalized Likelihood[11] and presented with their 95% confidence intervals (95% CI). The CIs which did not cross one were considered to be significant. Statistical analysis was conducted using SAS v9.3 (SAS Institute, Cary, NC).

RESULTS

During the study period, 2,642 patients were admitted with the diagnosis of CP. 383 of these patients (14.5%) received a definitive surgical procedure. Of these, 66 patients were eligible per stringent criteria for inclusion in the study. Figure 1 shows a flow diagram of patient selection process. Of these patients, 42 patients (63.6%) were free of pain at any time postoperatively and 26 patients (39.4%) were free of pain at follow-up.

Pain Relief

Table 1 compares patient demographic information and preoperative parameters of patients who were free of pain at follow-up against those who were not. Patients who were free of pain at follow-up were more likely to be older, have fewer comorbidities,

TABLE 1. Patient Demographics and Preoperative Patient Parameters by Pain Relief Status at 3 Year Follow-Up

	Pain (%)	Pain-Free (%)	Total (%)	*P*
Age, y				<0.0001
< 45	13 (32.5)	3 (11.5)	16 (24.2)	
45–54	18 (45.0)	4 (15.4)	22 (33.3)	
55–64	6 (15.0)	12 (46.2)	18 (27.3)	
≥ 65	3 (7.5)	7 (26.9)	10 (15.2)	
Sex				0.62
Female	22 (55.0)	12 (46.2)	34 (51.5)	
Male	18 (45.0)	14 (53.9)	32 (48.5)	
Payer type				0.80
Private insurance	25 (37.5)	15 (42.3)	40 (60.6)	
Nonprivate insurance	15 (62.5)	11 (57.7)	26 (39.4)	
Ethnicity				0.99
White	33 (82.5)	21 (80.8)	54 (81.8)	
Non-white	7 (17.5)	5 (19.2)	12 (18.2)	
Etiology				0.52
Alcoholic	20 (50.0)	12 (46.2)	32 (48.5)	
Biliary	3 (7.5)	5 (19.2)	8 (12.1)	
Idiopathic	13 (32.5)	6 (23.1)	19 (28.8)	
Other	4 (10.0)	3 (11.5)	7 (10.6)	
Comorbidity				<0.01
0	3 (7.5)	0 (0.0)	3 (4.5)	
1	1 (2.5)	7 (26.9)	8 (12.1)	
2	13 (32.5)	10 (38.5)	23 (34.8)	
3 or greater	23 (57.5)	9 (34.6)	32 (48.5)	
Time from diagnosis				0.02
< 15 months	11 (27.5)	11 (42.3)	22 (33.3)	
15–49 mo	11 (27.5)	12 (46.2)	23 (34.9)	
> 49 mo	18 (45.0)	3 (11.5)	21 (31.8)	
Preoperative opioid use	23 (57.5)	9 (34.6)	32 (48.5)	0.08
Endocrine insufficiency	11 (27.5)	5 (19.2)	16 (24.2)	0.56
Exocrine insufficiency	13 (32.5)	8 (30.8)	21 (31.8)	0.99

and have less CP duration. Table 2 lists operative characteristics. Sensitivity and specificity analysis was conducted on unadjusted data using yearly cutoffs. An ROC curve was drawn to analyze the best time cutoff from diagnosis to surgery. Figure 2 shows the ROC curve. The best cutoff point for unadjusted preoperative CP duration was 26.5 months with an AUC of 0.66.

Opioid Use

Interestingly, 35 patients (53.0%) were opioid users at time of operation and 34 patients (51.4%) were opioid users at follow up. Nine patients who were initially not opioid users were opioid users at time of follow-up, and 10 patients who were initially opioid users were not opioid users at the time of follow-up. These patients had median CP duration of 24 months, and 7 of 9 patients had CP durations of 26.5 months or less. Patients who used opioid postoperatively were younger (unadjusted ORs compared with over 65 years: <45 years 12.0; 95% CI, 1.76–81.7; 45–54 years 7.0; 95% CI, 1.2–41.4) and more likely to have CP durations of greater than 3 years (OR, 3.4; 95% CI, 1.2–9.6) (Table 3).

Pancreatic Insufficiency

Preoperatively, 21 patients (31.8%) demonstrated exocrine pancreatic insufficiency. In comparison, 34 patients (51.5%) demonstrated postoperative exocrine pancreatic insufficiency. Patients who demonstrated postoperative exocrine pancreatic insufficiency were younger (unadjusted ORs compared with over 65 years, <45 years 10.2; 95% CI, 1.7–112.7; 45–54 years, 7.5, 95% CI: 1.3–78.9; 54–65 years, 9.7; 95% CI, 1.7–104.9).

Sixteen patients (24.2%) were diabetic at time of operation, and 32 patients (48.5%) were diabetic by follow-up. There were no significant predictors of postoperative diabetes other than preoperative pancreatic insufficiency, both endocrine and exocrine. Type of procedure performed was not a significant predictor of developing de novo postoperative endocrine or exocrine pancreatic insufficiency.

TABLE 2. Operative Characteristics for Pain Relief Status at 3 Year Follow-Up

	Pain (%)	Pain-Free (%)	Total n	*P*
Type of operation				0.99
Puestow	13 (32.5)	8 (30.8)	21	
Whipple + PPPD	10 (25.0)	7 (26.9)	17	
Distal and subtotal pancreatectomy	14 (35.0)	9 (34.6)	23	
Frey and all drainage procedures	3 (7.5)	2 (7.7)	5	
Outcomes at 3 y				
Endocrine insufficiency	21 (52.5)	11 (42.3)	32	0.46
Exocrine insufficiency	23 (57.5)	11 (42.3)	34	0.31
Complications				0.12
None	20 (50.0)	19 (73.1)	39	
Readmission	12 (30.0)	2 (7.7)	14	
Surgical site infection	4 (10.0)	4 (15.4)	8	
Anastomotic leak	2 (5.0)	0 (0.0)	2	
Obstruction	1 (2.5)	0 (0.0)	1	
Medical	1 (2.5)	1 (3.9)	2	

PPPD indicates pylorus-preserving pancreaticoduodenectomy.

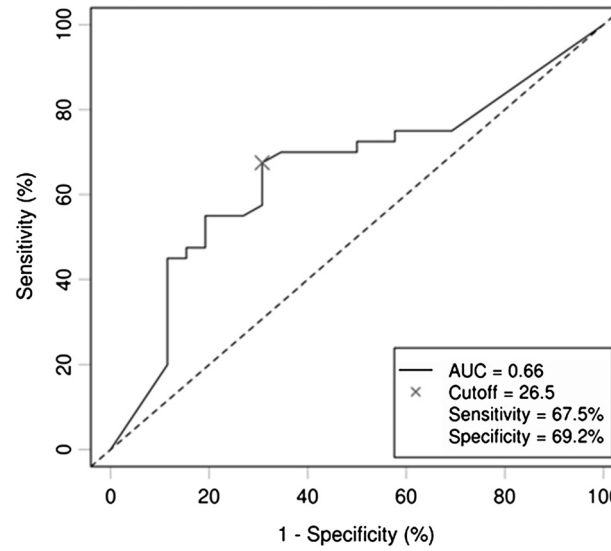

FIGURE 2. ROC to determine best cutoff from diagnosis to surgery.

Predictors of Early Surgery

Nearly half of patients (47.0%) received surgery at or before 26.5 months from diagnosis of CP. Comparisons of characteristics of patients receiving surgery at or before 26.5 months from diagnosis against those who received later surgery did not show statistically significant differences in the distributions of age, sex, ethnicity, payer type, etiology, or comorbidity scores in these patients. Interestingly, more patients who received early surgery had private health insurance (51.6% vs 28.6%), but this was not statistically significant, likely due to small sample size.

DISCUSSION

This retrospective study from a single institution has demonstrated that early surgery for CP is associated with increased odds of being pain-free, not using opioids, and not having exocrine

TABLE 3. Outcomes for Patients Who Underwent Surgery at 26.5 Months or Less from Diagnosis to those who Underwent Later Surgery

Outcome	Surgery ≤26.5 mo (%)	Surgery after 26.5 mo (%)	*P*
Postoperative opioid use			0.05
Opioid use	11 (35.5)	20 (57.1)	
No opioid use	20 (64.5)	15 (42.9)	
Pain status at 3 y follow-up			<0.01
Pain-free	18 (58.1)	8 (22.9)	
Not pain-free	13 (41.9)	27 (77.1)	
Postoperative enzyme use			0.22
Enzyme use	13 (41.9)	21 (60.0)	
No enzyme use	18 (58.1)	14 (40.0)	
Postoperative diabetes mellitus			0.99
Diabetes	15 (48.4)	17 (48.6)	
No diabetes	16 (51.6)	18 (51.4)	

insufficiency at 3-year follow-up. It also suggests that the cutoff for early surgery may be earlier than previously stated in the literature, as early as 26.5 months.

Literature is limited comparing early to late surgery in CP. A prospective study from the Dutch Pancreatitis group reported surgery at 3 years or less from symptom onset had increased relative risk of pain relief (relative risk, 1.32; 95% CI, 1.06–1.66) and lower odds of developing pancreatic endocrine insufficiency by follow-up (adjusted OR, 0.57; 95% CI, 0.33–0.96).[9] Another prospective observational study reported that surgery more than 3 years after diagnosis was associated with increased odds of de novo exocrine pancreatic insufficiency (OR, 2.47; $P = 0.002$).[12] This study also observed higher rates of pain in those whose symptom duration was more than 3 years preoperatively (43% vs 37%), but this was not statistically significant. A recent completed meta-analysis by our group suggested early surgery produce superior pain relief and less need for reinterventions.[13]

Surgery for CP is well documented, with favorable perioperative morbidity and mortality when compared to equivalent procedures for neoplasm.[14–16] Several procedures for CP have been described.[1,17] There are a number of studies comparing the efficacy of these procedures.[18] One of the strengths of this study is demonstrating the universality of the benefit of early surgery across different procedures. In this series, procedure selection was based on the anatomy of active disease and operative feasibility given the peripancreatic inflammation and adhesions. Being a retrospective study, procedure selection was also based on evidenced-based practice of the time. Hence, it is worth noting that there was a high proportion of Puestow procedures performed, especially in the early part of this series. Several randomized controlled trials since have suggested that the Puestow procedure is inferior to other surgical procedures for CP in managing pain in the long term.[19] This may partly explain why the proportion of pain free patients was lower in this series than that reported in other more recent series.

This is the first study of its kind using data from the United States and confirms the benefit of early surgery reported in previous studies. Furthermore, it extends the data by comparing the demographics of patients receiving early surgery with those receiving late surgery. To our knowledge, this is the first study to report calculations for optimal cutoff times for surgery. There are inconsistencies in the literature in defining early surgery. Some report symptom duration, whereas others report time from diagnosis. We attempted to use strict definitions of duration of CP from diagnosis, as reported in referral letters or from records of the admission in which the diagnosis was made. A consensus of definitions in this field will become even more important in moving forward with further prospective studies.

This study has several limitations. This was a retrospective review, and although we worked through hospital Decision Support to capture all possible patients with CP, a proportion of miscoding is likely. Because of our strategy of broad identification then strict inclusion/exclusion criteria to evaluate the possible effect surgical intervention, our final operative cohort with adequate follow-up is modest in size.

The relatively small sample size also reflects the rarity of surgery in this setting. One hundred sixteen patients were lost to follow-up. These patients were assumed to be followed by gastroenterologists in the community, and only referred to us for the surgical aspect of their care. Upon analysis of demographic factors, we did not find statistically significant differences between patients who were lost to follow up and patients who were included in this study. We also did not independently correlate duration of CP with the extent of pancreatitis on imaging. The decision to operative is often times based on the degree of pain, and quality of life (QOL) metrics, and not all patients will have the same rate of disease progression. The sample size also lead to lower AUC, and the calculations for optimal cutoff will need to be repeated in a prospective study. However, we believe our calculations suggesting an earlier cutoff time than previously stated in the literature will guide clinician decision making.

Because of the retrospective nature of this study, we did not have objective measurements of pain, such as on the McGill Pain Survey or the Visual Analogue Scale. We were also unable to gather information which was not routinely recorded on variables now known to be important, such as smoking, abstinence from alcohol, or body weight.[20] Furthermore, QOL data were missing for many patients. In CP, QOL closely correlates with pain scores.[21] Opioid use has been correlated with inability to work and perform activities of daily living independently, and in the absence of systematic measures of QOL, this was used as a conservative proxy for determining patients' QOL.[22]

Our data from a single institution support the consideration of appropriate surgical intervention within 26.5 months of diagnosis of CP. This study suggests optimal time cutoff for surgery is much earlier than previously reported. Although this cutoff remains to be validated with larger and prospective studies, it sheds new light on previous studies with inconclusive findings of the benefits of early surgery using historical cutoffs. The findings from this retrospective review warrant the development of longitudinal studies, pancreatitis management algorithms, and potentially, prospective clinical trials to determine predictors of, and promote, improved outcomes in CP.

The management of CP is complex and should be multidisciplinary in its nature. Early consultation with dedicated pancreatologists, including surgical specialists, is warranted.

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