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Earlier surgery improves outcomes from painful chronic pancreatitis

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Abstract

The timing of surgery for painful chronic pancreatitis (CP) may affect outcomes.

Clinical course, Izbicki pain scores, and pancreatic function were retrospectively compared and analyzed between patients undergoing either early or late surgery (< 3 or ≥ 3 years from diagnosis) for painful CP in a single center from 2007 to 2012.

The early surgery group (n = 98) more frequently than the late group (n = 199) had abdominal pain with jaundice (22.4% vs 9.5%, $P = .002$) and pancreatic mass +/− ductal dilatation (47% vs 27%, $P < .001$), but less frequently abdominal pain alone (73.5% vs 85.9%, $P = .009$), ductal dilatation alone (31% vs 71%, $P < .001$), parenchymal calcification (91.8% vs 100%, $P < .001$) or exocrine insufficiency (60% vs 72%, $P = .034$); there were no other significant differences. The early group had longer hospital stay (14.4 vs 12.2 days, $P = .009$), but no difference in complications. Significantly greater pain relief followed early surgery (complete 69% vs 47%, partial 22% vs 37%, none 8% vs 16%, $P = .01$) with lower rates of exocrine (60% vs 80%, $P = .005$) and endocrine insufficiency (36% vs 53%, $P = .033$).

Our data indicate that early surgery results in higher rates of pain relief and pancreatic sufficiency than late surgery for chronic pancreatitis patients. Frey and Berne procedures showed better results than other surgical procedures.

Abbreviations: CP = chronic pancreatitis, ISGPF = International Study Group on Pancreatic Fistulae, PD = pancreaticoduodenectomy, POPF = postoperative pancreatic fistula, PPPD = pylorus-preserving, SD = standard deviation.

Keywords: chronic pancreatitis, endocrine pancreatic insufficiency, exocrine pancreatic insufficiency, pain relief, surgery

1. Introduction

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas with an increasing annual incidence characterized by intractable pain and poor quality of life.[1] As the disease progresses there is continuous destruction of the pancreatic parenchyma, chronic pain, local complications (including duodenal, biliary and pancreatic duct obstruction, and pancreatic pseudocysts), compromised pancreatic exocrine and endocrine function, as well as an increased risk for pancreatic cancer.[1,2] The associated co-morbidities, recurrent symptomatic episodes, and socioeconomic impact make CP one of the most resource intensive diseases to manage.[3]

One key goal of the management of CP is to mitigate pain,[1,4–6] as it is the predominant symptom and its severity significantly correlates with poor quality of life.[7] Unfortunately, the mechanisms of pain secondary to CP have not been fully elucidated, resulting in suboptimal clinical efficacy of targeted treatments.[4] Traditionally, a conservative step-up approach has been advocated to treat painful CP, with surgery regarded as an option when other treatments have failed.[1,5,6] The initial choices of analgesic medications are nonsteroidal anti-inflammatory drugs.[4] But, a large proportion of patients prove refractory to medical therapy.[8] Endoscopic therapy is often performed in such patients in an effort to relieve pancreatic and/or bile duct obstruction and symptomatic pseudocysts.[1,5,6] Randomized controlled studies,[9–11] however, have shown that surgery (either resection or drainage) results in significantly greater and more durable pain relief than endotherapy.[10,11]

There is some evidence to suggest that early surgery is more effective than later surgery in preserving exocrine function in experimental CP.[12] A recent meta-analysis has shown that early surgery is associated with an increased likelihood of complete pain relief together with reduced rates of pancreatic insufficiency and re-intervention.[13] A multicentre retrospective study of 266 patients with CP demonstrated that early surgery within 3 years was more beneficial for pain relief, pancreatic function, and quality of life.[14] Nevertheless other studies suggest or advocate a step-up approach using antioxidants,[15–18] adjuvant analgesics,[19] pancreatic enzyme supplements,[20,21] and endoscopy

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NK and DJ contributed equally to this work.

XL and RS designed the research, corrected, and approved the final manuscript; NK and DJ collected clinical data, interpreted data, carried out the statistical analysis and wrote the paper; WH had important intelligence input and wrote the paper; QMN and JAW had important intelligence input and critically revised the manuscript;

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therapy,[6,21] resorting to surgery at a later stage for those who fail the conservative management.

To determine the relative merits of early and late surgery we analyzed 297 patients who had surgery for CP retrospectively to determine[1] whether early surgery offered better pain control and preservation of pancreatic function than late surgery, and[2] which surgical procedure (resection only or resection +/− drainage or drainage only) was more effective when performed early.

2. Methods

2.1. Patients and data collection

Consecutive CP patients diagnosed by disease history and radiological findings who underwent surgery at West China Hospital between February 2007 and February 2012 were considered for inclusion in this retrospective study. Demographics, symptoms at admission, pancreatic functional status, surgical procedures undertaken, intra- and postoperative outcomes were determined. Risk factors for CP were classified according to the TIGAR-O classification system.[22] Patients were excluded from the study if the diagnosis of CP was not confirmed histologically, if pancreatic cancer was detected on histology, if there was inadequate information or patients were lost to follow-up during 3 years after surgery. Patients were also excluded if they had any surgical procedures on the pancreas prior to the index operation for CP. All the identified patients were followed-up in outpatient clinic and/or by telephone for at least 3 years postoperatively. The research protocol was approved by the institutional review board of West China Hospital and informed consent from patients was waived due to retrospective use of anonymized data. The study followed the STROBE guidelines.

2.2. Patient management and surgical procedures

Patients in West China Hospital with a disease history of CP confirmed radiologically (CT and/or MRI) and with intractable pain are candidates for surgery; we have used narcotic analgesia and endotherapy with surgery as an alternative or subsequently, depending on clinical and radiological features. Pancreaticoduodenectomy (PD) and pylorus-preserving pancreaticoduodenectomy (PPPD) were offered for inflammatory enlargement of the pancreatic head, especially when calcifications were predominantly in the head. Beger's procedure was offered for calcifications located in the head of the pancreas with or without associated enlargement of the pancreatic head; the Berne procedure was an alternative determined intraoperatively. Frey's procedure was offered when calcifications were located throughout the pancreas with or without pancreatic head enlargement, and with or without a dilated main pancreatic duct. The Partington–Rochelle procedure was undertaken as an alternative for a dilated main pancreatic duct in patients with no pancreatic head enlargement.

2.3. Outcome measures

The primary endpoint was pain relief, assessed at the end of follow-up using the Izbicki pain score as described by Cahen et al,[10] with minor modifications and as reported by the patients. It was defined as complete pain relief (Izbicki pain score, ≤ 10 or pain level decrease of 100%), partial (Izbicki pain score > 10 and pain level decrease $> 50\%$) or no relief (Izbicki pain score > 10 and pain level decrease of $< 50\%$).

Secondary end points were intra- and postoperative outcomes including pancreatic function. Postoperative pancreatic fistula (POPF) was defined by the International Study Group on Pancreatic Fistulae (ISGPF A, B, and C) definition.[23] Exocrine insufficiency was defined as faecal elastase levels $<200\,\mu g/g$, or the presence of steatorrhoea, or the need for pancreatic enzyme replacement therapy (>1 year history; overt steatorrhoea without treatment). Endocrine insufficiency was defined by the presence of prediabetes (fasting serum glucose levels >6.0 mmol/L in capillary blood or >6.9 mmol/L in venous plasma on 2 different days) or overt diabetes mellitus. Both exocrine insufficiency and endocrine insufficiency were defined as described by Cahen et al[10]; those who had pancreatic insufficiency at both baseline and follow-up (insufficiency persisted); those who did not have insufficiency at baseline but in whom insufficiency developed during follow-up (insufficiency developed); those who had insufficiency at baseline but not at follow-up (insufficiency resolved), and those who did not have insufficiency at baseline or follow-up (sufficiency persisted). Quality of life was measured by the European Organisation for Research and Treatment of Cancer's quality-of-life questionnaire.[24]

2.4. Statistical analysis

Based on data from previous studies,[14,25] early surgery was defined as surgery performed ≤ 3 years following diagnosis, while late surgery was >3 years. Continuous data are presented as mean ± standard deviation (SD) or median with range depending on normal or skewed distributions, respectively. Categorical variables are described as numbers and in percentages. Mann–Whitney U and Chi-square (or Fisher's exact test) tests were used for continuous and categorical data comparisons, respectively. Intension-to-treat analysis was performed before removal of died patients before follow-up. A P value $<.05$ was considered to be statistically significant. The analyses were performed using IBM SPSS 22.0 statistical software (IBM, Armonk, NY).

3. Results

3.1. Characteristics of included patients

The patient selection process is shown in Figure 1. The initial screen included 417 CP patients. Eighty patients were excluded because they were lost to follow-up or there was insufficient information to determine long-term outcome. A further 31 patients were excluded either because of pancreatic/periampullary cancer, or they had undergone previous surgery, or histopathology was not obtained. A total of 306 patients with CP were included. Four patients died postoperatively in the early surgery group before follow-up: 2 abdominal cavity bleeding after PD, 1 gastrointestinal bleeding after PPPD, 1 gastrointestinal leakage (abdominal cavity infection and respiratory failure) after Beger's procedure; 4 died in the late surgery group: 2 gastroduodenal artery rupture after PD, 1 lung infection after PD, 1 liver and renal failure after Beger's procedure. Thus complete data were available for analysis from 297 patients. The year in which surgery was performed had no significant impact on the allocation of early or late surgery group (each year $P > .05$). The preoperative patient characteristics are outlined in Table 1. There were no statistically significant differences in age, gender, TIGAR-O classification, pain pattern and endocrine insufficiency, and the presence of both pancreatic head mass and ductal

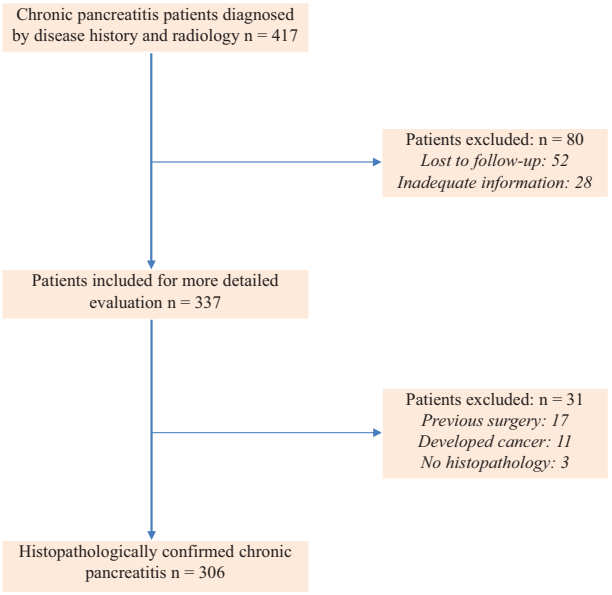

Figure 1. Patient selection flow chart.

dilatation between the early and late surgery groups. There was a higher proportion of patients in the early surgery group who had abdominal pain with jaundice (22.4% vs 9.5%, $P=.002$), pancreatic head mass (26.5% vs 11.1%) or pancreatic duct stone without ductal dilatation or mass (20.4% vs 15.6%), but lower proportion with abdominal pain alone (73.5 vs 85.9%), pancreatic duct dilatation alone (30.6% vs 70.9%) and parenchymal calcification (91.8% vs 100%) when compared to the late surgery group (all $P<.05$). The proportion of patients with exocrine insufficiency was significantly lower in the early surgery group as compared to the late surgery group (60.2% vs 72.4%, $P=.034$), while there was no difference in endocrine sufficiency (25.5% vs 31.2%, $P>0.05$).

3.2. Intra- and postoperative complications

Patients underwent surgery at a median 25 months (range 11–36) from initial CP diagnosis in the early surgery group compared with 81 months (range 45–122) in the late surgery group. There was no difference in follow-up time between the 2 surgery groups (65 months [36–96] vs 73 months [36–89], $P>.05$). Details of the intra- and postoperative complications and length of hospital stay are provided in Table 2. There were no significant differences in the mean operation time, intraoperative blood transfusion, volume of transfused packed red blood cells and the overall

Table 1

Characteristics of CP patients prior to surgery.

Patient characteristics	Total n = 297	Early n = 98	Later n = 199	*P* value*
Gender, n (%)				.450
Male	216 (72.7)	74 (75.5)	142 (71.4)	
Female	81 (27.3)	24 (24.5)	57 (28.6)	
Age in years, mean ± SD	47 ± 12.4	47.2 ± 11.3	48 ± 9.2	.521
Symptoms				
Abdominal pain alone	243 (81.8)	72 (73.5)	171 (85.9)	**.009**
Abdominal pain + jaundice	41 (13.8)	22 (22.4)	19 (9.5)	**.002**
Abdominal pain + diarrhoea	8 (2.7)	2 (2)	6 (3)	1.000
Abdominal pain + black pool	5 (1.7)	2 (2)	3 (1.5)	.666
Key radiological appearance				
Mass alone	48 (16.2)	26 (26.5)	22 (11.1)	**.001**
Ductal dilatation	171 (57.6)	30 (30.6)	141 (70.9)	< **.001**
Mass + ductal dilatation	51 (17.2)	20 (20.4)	31 (15.6)	.299
Ductal stone without dilatation or mass	27 (9.1)	22 (22.4)	5 (2.5)	< **.001**
Parenchymal calcification	289 (97.3)	90 (91.8)	199 (100)	< .001
TIGAR-O classification, n (%)				.870
Toxic-metabolic (alcohol and smoking)	118 (39.7)	37 (37.8)	81 (40.7)	
Idiopathic	142 (47.8)	49 (50)	93 (46.7)	
Hereditary	1 (0.3)	0 (0)	1 (0.5)	
Autoimmune	1 (0.3)	1 (1)	0 (0)	
Recurrent or severe acute pancreatitis	23 (7.7)	7 (7.1)	16 (8)	
Obstructive	7 (2.4)	2 (2)	5 (2.5)	
Others	5 (1.7)	2 (2)	3 (1.5)	
Pain pattern, n (%)				.517
Continuous	174 (58.6)	60 (61.2)	114 (57.3)	
Intermittent	123 (41.4)	38 (38.8)	85 (42.7)	
Exocrine function, n (%)				**0.034**
Insufficiency	203 (68.4)	59 (60.2)	144 (72.4)	
Normal	94 (31.7)	39 (39.8)	55 (27.6)	
Endocrine function, n (%)				0.315
Insufficiency	87 (29.3)	25 (25.5)	62 (31.2)	
Normal	210 (70.7)	73 (74.5)	137 (68.8)	

* Early vs late.

SD = standard deviations.

P value in bold indicates early vs late was significant different at level of 0.05.

Table 2

Comparisons of intra- and postoperative outcomes.

Parameters	Early n = 98	Later n = 199	*P* value
Intraoperative blood transfusion, n (%)	22 (22.5)	41 (20.6)	.714
Volume of packed red cells in ml, mean ± SD	380 ± 104	402 ± 128	.141
Intensive care unit stay in days, mean ± SD	1.8 ± 3.1	1.4 ± 2.5	.233
Complications, n (%)	21 (21.4)	33 (16.6)	.309
Haemorrhage	4 (4.1)	7 (3.5)	.809
Re-laparotomy	4 (4.1)	6 (3)	.632
POPF (ISGPF A)	13 (13.2)	14 (7)	.079
POPF (ISGPF B/C)	5 (5.1)	6 (3.0)	.514
Infection	5 (5.1)	9 (4.5)	.825
Hospital stay in days, mean ± SD	14.4 ± 8	12.2 ± 6.1	.009
Izbicki pain score*	24 ± 14	31 ± 16	.031
Pain relief*, n (%)			.010
No relief	8 (8.2)	32 (16.1)	
Partial relief	22 (22.4)	74 (37.2)	
Complete relief	68 (69.4)	93 (46.7)	
Exocrine function*, n (%)			.005
Insufficiency persisted	46 (46.9)	133 (66.8)	
Insufficiency developed	13 (13.3)	23 (11.6)	
Insufficiency resolved	13 (13.3)	11 (5.5)	
Sufficiency persisted	26 (26.5)	32 (16.1)	
Endocrine function*, n (%)			.033
Insufficiency persisted	20 (20.4)	58 (29.1)	
Insufficiency developed	15 (15.3)	47 (23.6)	
Insufficiency resolved	5 (5.1)	4 (2)	
Sufficiency persisted	58 (59.2)	90 (45.2)	
Global quality of life	73.14 (0–100)	62.76 (0–89)	.004

ISGPF = International Study Group of Pancreatic Fistula, POPF = postoperative pancreatic fistulae, SD = standard deviations.
* Assessed at follow-up as indicated in the Methods section.

complication rate between the 2 groups. The early surgery group had a higher incidence of grade A POPF (13.2% vs 7%, $P = .079$) and was associated with a longer hospital stay (mean 14.4 vs 12.2 days, $P = .009$) compared to the late surgery group.

3.3. Endpoints

Izbicki pain scores at follow-up were significantly lower in the early surgery group compared to the late surgery group (24 ± 14 vs 31 ± 16, $P = .031$; Table 2). Complete or partial pain relief was achieved in 91.8% of patients in the early surgery group, significantly higher than 83.9% in the late surgery group ($P = .01$). A much higher proportion of patients in the early surgery group had complete pain relief (69.4% vs 46.7%, $P < .001$), and the proportion of patients with no pain relief in the early surgery group was smaller (8.2% vs 16.1%, $P = .06$).

Early surgery was followed by a reduced incidence of exocrine insufficiency (60.2% vs 80.39%, $P = .005$) and endocrine insufficiency (35.7% vs 52.7%, $P = .033$), with a trend of a higher rate of resolution of both exocrine and endocrine insufficiency in the early surgery group (Table 2). Early surgery group also showed a better quality of life than later surgery group (Table 2).

3.4. Comparison of the impact of individual surgical procedures on pain relief

The influence of different surgical procedures on postoperative pain relief in the early and late surgery groups was analyzed and is summarized in Table 3. There were no significant differences in pain relief between the early and late surgery groups when only resections (PD, PPPD and Beger's procedure) or drainage procedures (Partington–Rochelle) were compared. In contrast, patients undergoing a combination of resection with drainage (Frey and Berne procedures) experienced significantly greater pain relief in the early surgery group compared to the late surgery group (Frey $P = .031$, Berne $P = .028$). There were no statistically significant differences in pain relief between different early surgical interventions likely due to small patient numbers. There was however a trend toward complete pain relief following Frey (82.6%), Berne (75.9%), and Partington–Rochelle (70%) procedures when compared with other procedures (50%–61.5%).

3.5. Comparison of individual surgical procedures on pancreatic function

The impact of different surgical procedures on postoperative pancreatic exocrine and endocrine function is summarized in Table 4. Similar to the findings obtained for pain relief, patients undergoing Frey and Berne procedures in the early surgery group had consistently high rates of exocrine (Frey $P = .001$, Berne $P = .02$) and endocrine (Frey $P = .037$, Berne $P = .049$) function preservation when compared with patients undergoing the same procedures in the late surgery group. This was not the case for the other surgical procedures, with the exception of patients undergoing Beger's procedure in the early surgery group who had significantly better preservation of endocrine function ($P = .038$). Intention-to-treat analyses including patients who died did not change any findings on endpoints.

4. Discussion

Our study clearly demonstrates that early surgery results in more effective pain relief and better preservation of pancreatic exocrine

Table 3

Comparison of individual surgical procedures performed early or late on pain relief.

Procedures	No relief	Partial relief	Complete relief	*P* value
Resection, n (%)				
PD				1.000
Early (n = 9)	1 (11.1)	3 (33.3)	5 (55.6)	
Late (n = 19)	4 (21.1)	5 (26.3)	10 (52.6)	
PPPD				.704
Early (n = 13)	2 (15.4)	3 (23.1)	8 (61.5)	
Late (n = 18)	3 (16.7)	7 (38.9)	8 (44.4)	
Beger				.436
Early (n = 14)	1 (7.1)	6 (42.9)	7 (50)	
Late (n = 35)	8 (22.9)	12 (34.3)	15 (42.9)	
Resection + drainage, n (%)				
Frey				**.031**
Early (n = 23)	0 (0)	4 (17.4)	19 (82.6)	
Late (n = 30)	5 (16.7)	10 (33.3)	15 (50)	
Berne				**.028**
Early (n = 29)	3 (10.3)	4 (13.8)	22 (75.9)	
Late (n = 69)	9 (13)	27 (39.1)	33 (47.8)	
Drainage, n (%)				.328
Partington–Rochelle				
Early (n = 10)	1 (10)	2 (20)	7 (70)	
Late (n = 28)	3 (10.7)	13 (46.4)	12 (42.9)	

PD = pancreaticoduodenectomy, PPPD = pylorus-preserving pancreaticoduodenectomy.

P value in bold indicates early vs late for Frey and Berne was significant different at level of 0.05, respectively.

and endocrine function. The study, the largest comparing early versus late surgery for painful CP to date, also demonstrates that drainage and resection (e.g., Frey and Berne procedures) had better outcomes than resection or drainage alone.

The early surgery group was comparable to the late surgery group with respect to the operation time, intraoperative blood transfusion, transfused red volume of packed blood cells, duration of intensive care unit stay, and the overall complication rate, which indicate that it was safe. The incidence of POPF B/C was similar in both groups, but early surgery was associated with a higher incidence of POPF A, and thus with a longer hospital stay. This may be because in CP at an earlier stage the pancreas tends to have more functional units, less fibrosis (soft pancreas) and the exocrine pancreas is able to produce more fluid. It has been demonstrated that the soft pancreas has a higher POPF rate after surgery than the hard pancreas.[26]

Table 4

Comparison of individual surgical procedures performed early or late on exocrine and endocrine function.

	Exocrine function					Endocrine function				
Procedures	Insufficiency persisted	Insufficiency developed	Insufficiency resolved	Sufficiency persisted	*P* value	Insufficiency persisted	Insufficiency developed	Insufficiency resolved	Sufficiency persisted	*P* value
Resection, n (%)										
PD					.630					.874
Early (n = 9)	5 (62.5)	3 (25.0)	0 (0)	0 (0)		3 (37.5)	3 (37.5)	0 (0)	2 (25.0)	
Late (n = 19)	12 (63.2)	4 (21.1)	0 (0)	3 (15.8)		6 (31.6)	6 (31.6)	0 (0)	7 (36.8)	
PPPD					.524					1.000
Early (n = 13)	8 (57.1)	3 (21.4)	2 (14.3)	1 (7.1)		5 (35.7)	4 (28.6)	0 (0)	5 (35.7)	
Late (n = 18)	12 (63.2)	2 (10.5)	1 (5.3)	4 (21.1)		6 (31.6)	5 (26.3)	0 (0)	8 (42.1)	
Beger					.582					.038
Early (n = 14)	7 (50)	2 (14.3)	3 (21.43)	2 (14.3)		2 (14.3)	0 (0)	2 (14.3)	10 (71.4)	
Late (n = 35)	22 (62.9)	5 (14.3)	3 (8.6)	5 (14.3)		12 (34.3)	7 (20)	1 (2.9)	15 (42.9)	
Resection + drainage, n (%)										
Frey					.011					.037
Early (n = 23)	10 (43.5)	0 (0)	3 (13)	10 (43.5)		4 (17.4)	1 (4.3)	3 (13)	15 (65.2)	
Late (n = 30)	22 (73.3)	3 (10)	1 (3.3)	4 (13.3)		9 (30)	8 (26.7)	1 (3.3)	12 (40)	
Berne					.020					.049
Early (n = 29)	11 (37.9)	3 (10.3)	4 (13.8)	11 (37.9)		3 (10.3)	4 (13.8)	0 (0)	22 (75.9)	
Late (n = 69)	47 (68.1)	7 (10.1)	4 (5.8)	11 (15.9)		21 (30.4)	14 (20.3)	1 (1.4)	33 (47.8)	
Drainage, n (%)										
Partington–Rochelle					.644					.626
Early (n = 10)	5 (50)	2 (20)	1 (10)	2 (20)		3 (30)	3 (30)	0 (0)	4 (40)	
Late (n = 28)	18 (66.7)	2 (7.4)	2 (7.4)	5 (18.5)		4 (14.8)	7 (25.9)	1 (3.7)	15 (55.6)	

PD = pancreaticoduodenectomy, PPPD = pylorus-preserving pancreaticoduodenectomy.

A major challenge in the management of CP patients is the treatment of pain.[4] The pain in CP is multifactorial with a number of proposed mechanisms, although by the time patients present there is often a significant neuropathic component.[27] Neural plasticity, neural inflammation, and an altered distribution of sympathetic and sensory fibres are seen in CP and these changes correlate with the severity of neuropathic pain.[28] Patients with CP exhibit central hyperalgesia and alterations in brain resting activity, which decrease their pain threshold.[28] Traditionally it was considered that pain in CP would ultimately resolve spontaneously or "burn out," owing to progressive destruction of the pancreatic parenchyma.[29] More recent data indicate that repeated episodes of pancreatic inflammation lead to peripheral and central nociceptive nerve sensitisation, which leads to a chronic pain state that might be avoided by earlier intervention.[30] Narcotic analgesics commonly used to treat unresolved pain are associated with addiction and unfavourable side effects, including opioid hyperalgesia. Recent meta-analyses indicate that the antineuropathic pain medications pregablin,[31] antioxidants,[16,32,33] and pancreatic enzyme replacement therapy[34] have little effect on pain relief. An improved understanding of the patterns of pain in CP is needed and the Dutch CARE trial,[35] presently underway, seeks to address this.

CP patients in whom pain is refractory to medications and endotherapy eventually undergo surgery, often as a last resort.[1,5,6] Recently, surgery has been shown to be superior to endotherapy for both short- and long-term pain control in randomized trials,[9–11] confirmed in a meta-analysis based on these trials.[36] Intermediate and long-term follow-up studies[37–42] have shown that patients undergoing resection with or without drainage procedures have sustained pain relief with substantially improved quality of life. Our CP patients who had intractable pain following medical management and endotherapy were advised to have surgery; in our study, the complete and partial pain relief rates were similar to or higher than in previous studies. We used a cut-off of 3 years to define early and late surgery, in keeping with previous studies;[14,25] many of our patients had little response to medical management and had undergone one or more endoscopic interventions by this time. Other studies have suggested that surgical intervention prior to the start of opioid dependence might be beneficial,[38,43] but this could be considered too early to justify a major operation; nevertheless, a higher number of preceding endoscopic interventions is associated with a worse outcome.[14,38]

A further challenge in the management of CP patients is the preservation of pancreatic function, dependent in some patients on life style modification. Nealon and Thompson[44] have shown in a small randomized trial that surgical drainage (modified Puestow procedure) was better than conservative management in preserving pancreatic function. In our study the overall rate of exocrine and endocrine insufficiency was 72.4% and 47.1%, respectively, lower than previous published work, possibly due to a shorter follow-up time. There was a significantly lower incidence of exocrine insufficiency in the early surgery group prior to surgery, and early surgery was associated with more frequent preservation of pancreatic function, in keeping with previous studies.[14,25,36] This finding may simply be attributed to CP that is not as advanced, but drainage and/or resection can remove obstruction and restore pancreatic secretion, preventing further pancreatic damage. Exocrine insufficiency commonly develops 5 to 10 years after the onset of CP, accompanying progressive destruction of the gland, but tends to be underdiagnosed and is under-treated in CP patients;[5] early surgery may help to correct this. CP may also lead to type 3c diabetes mellitus and patients with long-standing diabetes mellitus may develop CP.[5] CP is a known risk factor for pancreatic cancer and diabetes mellitus may increase that risk;[45] surgery in CP may reduce this risk. In a study by Ueda et al[46] of 87 patients who underwent surgical drainage of the pancreas, only 1 patient developed pancreatic cancer, with no cancers developing in 125 patients who underwent pancreatic resection. Of 352 patients who did not undergo surgery, however, 18 developed pancreatic cancer.

The choice of surgical procedure is important and there are a significant number of randomized controlled trials comparing the different options. In this study, the choice of procedure was based on radiological morphology and surgeon preference. A recent meta-analysis[47] suggested that duodenum-preserving pancreatic resection (Beger's or Frey procedures) had similar outcomes to PD with respect to mortality, adverse events and quality of life, but may be associated with a shorter hospital stay and less blood loss. A further meta-analysis[48] showed that the Frey procedure is safe and effective, which when compared to PD is followed by fewer overall complications and better short and long term pain relief, pancreatic function preservation and quality of life. Compared with Beger's procedure, the Frey procedure had a reduced operation time and was associated with lower morbidity.[48] Our study corroborates these findings and suggests that resection plus drainage procedures (both Frey and Berne procedures) had better outcomes when performed early.

This study has several limitations. It was performed retrospectively and the sample sizes in the individual surgical groups were small, which may have resulted in some bias. The early and late surgical groups did have differences prior to surgery, especially in pancreatic morphology, but this has been shown not to relate to pain severity or the response to intervention. We did not obtain precise data for symptom onset, narcotic medicine and endotherapy prior to operation for comparisons. Data on quality of life, one of the better parameters to assess treatment effects in CP, were not available. The validated PANQOLI tool is now available and should be used in future studies. The results of the prospective, multicenter randomized controlled trial comparing early surgery and an optimised step-up approach are eagerly awaited.[49] Unfortunately this trial has used the Izbicki pain score, as in the present study, which assesses only 4 aspects of pain.[10] A more comprehensive pain assessment tool is required to capture all important aspects of pain, since pain is the primary indication for intervention and the reduction of pain is the primary endpoint of intervention studies.[50] While our data indicate the benefits of early surgery and the surgical procedures that are most effective, these findings need to be confirmed in prospective randomized controlled trials.

Author contributions

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