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Clinical Outcome in Relation to Timing of Surgery in Chronic Pancreatitis

A Nomogram to Predict Pain Relief

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Objective: To evaluate the effect of timing of surgery on the long-term clinical outcome of surgery in chronic pancreatitis (CP).

Design: Cohort study with long-term follow-up.

Setting: Five specialized academic centers.

Patients: Patients with CP treated surgically for pain.

Interventions: Pancreatic resection and drainage procedures for pain relief.

Main Outcome Measures: Pain relief (pain visual analogue score ≤4), pancreatic function, and quality of life.

Results: We included 266 patients with median follow-up of 62 months (interquartile range, 31-112). Results were presented as odds ratios (ORs)with 95% confidence intervals after correction for bias using bootstrap-corrected analysis. Pain relief was achieved in 149 patients (58%). Surgery within 3 years of symptoms was independently associated with more pain relief (OR, 1.8; 95% CI, 1.0-3.4; *P*=.03) and less endocrine pancreatic insufficiency (OR, 0.57; 95% CI, 0.33-0.96; *P*=.04). More pain relief was also observed in patients not taking opioids preoperatively (OR, 2.1; 95% CI, 1.2-4.0; *P*=.006) and who had 5 or fewer endoscopic treatments prior to surgery (OR, 2.5; 95% CI, 1.1-6.3; *P*=.04). The probability of achieving pain relief varied between 23% and 75%, depending on these risk factors.

Conclusions: The timing of surgery is an important risk factor for clinical outcome in CP. Surgery may need to be considered at an earlier phase than it is now, preferably within 3 years of symptomatic CP. Likelihood of postoperative pain relief can be calculated on an individual basis using the presented nomogram.

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CHRONIC PANCREATITIS (CP) is a severe disease with negative impact on the social functioning of patients, with repeated hospitalization and inability to work.[1,2] Pain is the most severe symptom in CP. Endocrine and exocrine pancreatic insufficiencies, occurring in 50% and 80% of patients, respectively, within 5 years of disease onset and a variety of local complications such as pancreatic pseudocysts, bile duct and gastric outlet obstruction, and portal hypertension also contribute to morbidity.[3-5] Therefore, CP has a significant deleterious effect on health status and quality of life.[6,7]

Surgical intervention plays an important role in the management of pain but is generally kept as a last resort when other more conservative treatments have failed and the disease has progressed.[8,9] The choice to continue conservative treatment for prolonged periods is mainly based on the paradigm that CP is a self-limiting disease in which pain will ultimately resolve spontaneously owing to progressive parenchymal destruction of the gland (burnout hypothesis).[3] The observations that 50% to 60% of patients are still in pain 10 years after onset of the disease and that 40% to 75% of patients will undergo a surgical intervention for pain in the course of their disease have led to doubts about this paradigm.[3,10-13]

Scarce experimental and clinical data suggest that the timing of surgery plays a more important role than generally

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thought and could be an important determinant of the success of surgery.[14-16] However, these studies lack evidence regarding the effect of timing of surgery in terms of clinical outcomes. Therefore, existing guidelines are contradicting and lack a clear recommendation regarding this issue.[8,17-19] We initiated a multicenter cohort study to evaluate the effect of timing of surgery on long-term clinical outcome of surgery in CP, with the hypothesis that early surgical intervention is beneficial in terms of pain relief, pancreatic function, and quality of life.

METHODS

STUDY POPULATION

In 5 Dutch university centers specialized in the treatment of CP, consecutive patients with CP undergoing pancreatic surgery for pain were identified from registries for surgical procedures. Periods of inclusion varied from 8 to 15 years between centers, depending on availability of electronic registration. The study population overlaps partially with patients from 2 previously published studies that present general outcomes of surgery in CP in 3 participating centers.[20,21] Inclusion criteria were age 18 years or older, confirmed diagnosis of CP, and pain as the primary indication for surgery. Eligible surgical procedures were drainage procedures (pancreaticojejunostomy), duodenum-preserving pancreatic head resections (Beger and Frey procedures), pancreaticoduodenectomy, and left-sided pancreatic resection (tail resection).[17,22,23] Exclusion criteria were other indications for surgery, previous pancreatic surgery, and known malignancy at the time of operation. This study was conducted according to the guidelines of the Central Committee on Research Involving Human Subjects in the Netherlands and the principles outlined in the Declaration of Helsinki.[24] Written informed consent was obtained from all participants.

STUDY OUTCOMES

The primary outcome was pain relief. Pain was assessed using a visual analogue scale (VAS) and scored from 0 to 10, with 0 being no pain and 10 being the worst imaginable pain.[25] Success of surgery with respect to pain relief was defined as a VAS score of 4 or less, a value commonly used in clinical practice as a threshold for acceptable pain relief. Secondary outcomes included endocrine and exocrine pancreatic insufficiency and quality of life. Endocrine insufficiency was defined as manifest diabetes mellitus treated medically or a serum fasting glucose level of more than 6.7 mmol/L (to convert to milligrams per deciliter, divide by 0.055). Exocrine function was defined as a fecal elastase-1 of less than 200 μg/gram. Quality of life was evaluated using the Short Form-36 quality of life questionnaire.[26]

TIMING OF SURGERY AND OTHER RISK FACTORS

We defined timing of surgery in relation to the following: (1) reported duration of pain symptoms before surgery, representing the relation between surgery and disease onset; (2) use of preoperative opioid analgesics, representing the relation between surgery and medical management; and (3) number of endoscopic interventions prior to surgery, representing the relation between surgery and endoscopic treatment. Other previously reported factors that potentially influence the outcome of surgery were also included. These were age, sex, type of surgical procedure, preoperative body mass index (calculated as weight in kilograms divided by height in meters squared), postoperative complications necessitating a reoperation, continued alcohol or tobacco use, and duration of follow-up.[15,27,28]

DATA RETRIEVAL

Patient characteristics, medical history, and performed interventions were collected retrospectively from medical records. Patients known to be alive were invited to participate and requested to prospectively fill out study questionnaires regarding medical history and current outcome. Onset of pain symptoms was defined as the first episode of pain identified by the patient as the typical pain associated with CP for which the patient was initially referred to a specialist. The questionnaires were sent to patients to avoid observer bias. Patients were offered an outpatient clinic visit by their treating physicians, if no such visit was recently conducted. During the outpatient clinic visit, serum and feces samples were collected to measure fasting glucose and fecal elastase-1 levels, respectively. The questionnaires were checked for completeness and compared with data of medical records for accuracy. Discrepancies between the questionnaire and medical records were resolved by discussing with the patient and a further scrutinizing of medical records. Patients not able to come to the outpatient clinic were asked to send the questionnaire and fecal sample by mail. Information regarding endocrine pancreatic function was obtained from the family physician or other treating physicians after patient's permission.

DATA AND STATISTICAL ANALYSIS

Baseline characteristics and primary and secondary outcomes were presented. For quality of life, the mean scores for the age-matched Dutch general population were also provided for comparison. Factors potentially associated with study outcome in univariable analysis ($P < .20$) were included in a multivariable model. A 2-tailed $P < .05$ was considered statistically significant. Results were presented as odds ratios (ORs) with 95% confidence intervals after correction for bias by means of accelerated nonparametric bootstrap-corrected analysis based on 5000 samples, as well as the corresponding P value. To aid clinical decision making, independent risk factors were included in a nomogram to indicate the probability of postoperative pain relief for individual patients, as outlined by Iasonos et al.[29] For endocrine pancreatic insufficiency, a predefined subgroup analysis for patients not having a left-sided pancreatic resection was performed.

RESULTS

Of 423 patients potentially eligible for this study, 90 (21%) were deceased at the time of the study (**Table 1**). Cause of death was related to index surgery in 8 patients (1.9%), pancreatic cancer in 8 (1.9%), other malignancies in 19 (4.5%), causes related to CP in 10 (2.4%), causes not related to CP in 29 (6.9%), and unknown causes in 16 (3.8%). Of 333 living patients, 266 (80%) could be contacted and agreed to participate. Table 1 shows the most important characteristics of participating patients as well as all screened patients (no significant difference regarding basic characteristics). Alcohol was the etiology of CP in 139 patients (52%). The median reported duration of pain in the study cohort was 36 months (interquartile range, 13-81 months), and the median duration of postoperative follow-up was 62 months (interquartile range, 31-112 months).

Table 1. Preoperative Characteristics of Study Population

Characteristic	No. (%)	
	Study Cohort (n = 266)[a]	Screened Patients (n = 423)[b]
Male	174 (65)	271 (64)
Age, mean (range), y	49 (19-76)	49 (19-79)
Deceased	0 (0)	90 (21)
Preoperative BMI, mean (SD)	21.5 (4.0)	
Etiology		
Alcohol	139 (52)	
Idiopathic	51 (19)	
Biliary	15 (6)	
Other	34 (13)	
Unknown	27 (10)	
Reported duration of pain, median (IQR), mo	36 (13-81)	
Preoperative opioid use	143 (54)	
Postoperative follow-up, median (IQR), mo	62 (31-112)	70 (34-117)
Type of surgical intervention		
PJ	113 (43)	182 (43)
Frey procedure	38 (14)	49 (12)
Beger procedure	33 (12)	60 (14)
P-PPD	34 (13)	50 (12)
Left-sided resection	48 (18)	82 (19)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; PJ, pancreaticojejunostomy; P-PPD, pylorus-preserving pancreaticoduodenectomy.
[a] Study cohort includes all eligible patients that were available for long-term follow-up.
[b] All screened patients included patients operated on for chronic pancreatitis during the same period.

Table 2. Overview of Primary and Secondary Study Outcomes

Outcome	Patients, No.	Outcome, No. (%)
Pain		
Pain relief (VAS ≤ 4)	259	149 (58)
VAS score, median (IQR)	259	3.2 (5-6.3)
Endocrine pancreatic insufficiency		
Fasting serum glucose, median (IQR), mg/dL	248	108 (92-143)
Glycosylated hemoglobin, median (IQR), %	239	6.7 (5.9-7.5)
Endocrine insufficiency (overall)	258	152 (59)
New-onset endocrine insufficiency[a]	258	102 (40)
Exocrine pancreatic insufficiency		
Fecal elastase 1 level, median (IQR), μg/g	230	21 (15-140)
Postoperative exocrine insufficiency	230	179 (78)
Quality of life (Short Form-36)		
Physical composed score, mean (SD)[b]	264	41 (11)
Mental composed score, mean (SD)[b]	264	52 (12)

Abbreviations: IQR, interquartile range; VAS, visual analogue scale.
[a] Newly developed endocrine insufficiency not present at time of surgery.
[b] Mean (SD) age-matched Dutch general population norms for physical composed score is 50 (10) points, and for the mental composed scores is 50 (11) points.

PRIMARY AND SECONDARY OUTCOMES

Study outcomes are presented in **Table 2**. The overall median VAS score was 3.2 (interquartile range, 0.5-6.3). A pain VAS of 4 or less was present in 149 patients (58%). After median disease duration of 8 years, endocrine insufficiency and exocrine insufficiency developed in 60% and 79% of patients, respectively. For quality of life, the mean (SD) physical composed score was 41 (11) (9 points lower than the matched general population), whereas the mean (SD) mental composed score was 52 (12) (similar to the matched population).

PAIN RELIEF AND TIMING OF SURGERY

Univariable analysis identified 6 factors that were potentially associated with pain relief (**Table 3**). These were duration of pain symptoms, opioid use, endoscopic interventions and postoperative reoperation, left-sided resection, and length of follow-up. Multivariable analysis identified

Table 3. Univariable Analysis of Risk Factors Associated With Pain Relief

Risk Factors, Subgroups	Patients, No.	Pain Relief (VAS≤4)		
		No. (%)	Odds Ratio	*P* Value
Timing of Surgery				
Reported duration of pain				.004
≤3 y	121	80 (66)	2.2	
>3 y	124	59 (47)		
Preoperative opioid use			2.4	.001
No	138	93 (67)		
Yes	121	56 (46)		
Endoscopic treatments, No.				
≤3	181	111 (61)	1.8	.03
>3	69	32 (46)		
≤5	218	131 (60)	2.5	.02
>5	32	12 (38)		
Other Factors				
Age at surgery, y			1.01	.30
Sex			1.03	.92
Female	88	51 (58)		
Male	171	98 (57)		
Postoperative relaparotomy			0.45	.04
Yes	30	12 (40)		
No	229	137 (60)		
Type of procedure				
Drainage	108	60 (55)	0.87	.59
Head resection	103	55 (53)	0.76	.28
Left-sided resection	48	34 (71)	2.03	.04
Continued alcohol consumption			1.11	.69
Yes	102	59 (58)		
No	134	74 (55)		
Continued smoking				
Yes	172	97 (56)	0.78	.40
No	64	40 (63)		
Length of follow-up, mo			1.01	.08

Abbreviation: VAS, visual analogue scale.

Table 4. Multivariable Analysis of Risk Factors Associated With Pain Relief

Timing of Surgery	Odds Ratio (95% CI)[a]	*P* Value
Reported duration of pain ≤3 y	1.81 (1.02-3.37)	.03
No preoperative opioid use	2.14 (1.23-3.96)	.006
Endoscopic treatments, No. (≤5 procedures)	2.46 (1.10-6.27)	.04

[a] 95% confidence intervals were calculated using bootstrap-corrected analysis.

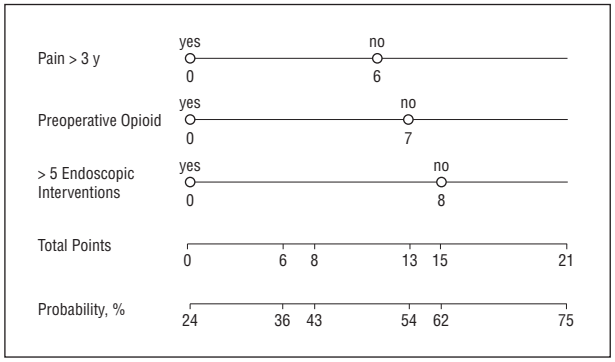

Figure. Nomogram indicating the probability of long-term pain relief in patients operated on for chronic pancreatitis. Points are assigned to patients according to the 3 risk factors (upper part of the nomogram). The probability for achieving pain relief corresponds with the sum of points for that patient (bottom 2 lines).

the 3 factors related to timing of surgery as independent risk factors for pain relief (**Table 4**). Pain duration of 3 years or less (OR, 1.81; 95% CI, 1.02-3.37; *P*=.03), no preoperative use of opioids (OR, 2.14; 95% CI, 1.23-3.96; *P*=.006), and 5 or less endoscopic procedures prior to surgery (OR, 2.46; 95% CI, 1.10-6.27; *P*=.04) were all independently and significantly associated with higher rates of pain relief. A nomogram indicating the probability of pain relief based on these risk factors is depicted in the **Figure**. Patients with unfavorable scores for all 3 risk factors (ie, operated on after 3 years of onset of symptoms, treated with preoperative opioids, and underwent more than 5 endoscopic interventions prior to surgery) have a probability of 23% for achieving postoperative pain relief. This probability increases to 75% without unfavorable scores on any of the 3 risk factors.

ENDOCRINE AND EXOCRINE PANCREATIC INSUFFICIENCY

Potential risk factors for postoperative endocrine insufficiency were included in a multivariable model

Table 5. Multivariable Analysis of Risk Factors for Pancreatic Insufficiency and Quality of Life

Characteristic	Odds Ratio (95% CI)[a]	*P* Value
Overall endocrine pancreatic insufficiency		
Reported duration of pain <3 y	0.58 (0.34-0.95)	.04
Drainage procedure	0.48 (0.28-0.78)	.008
Follow-up duration/mo	1.01 (1.00-1.01)	.01
New-onset endocrine pancreatic insufficiency		
Reported duration of pain < 3 y	0.57 (0.33-0.96)	.04
Drainage procedure	0.45 (0.26-0.73)	.006
Follow-up duration/mo	1.01 (1.01-1.02)	<.001
Exocrine pancreatic insufficiency[b]		
Pancreatic head resection	3.31 (1.33-12.61)	.006
Left-sided pancreatic resection	0.23 (0.10-0.49)	<.001
	Coefficient (95% CI)[a]	
Physical composed score[c]		
Preoperative opioid use	−4.81 (−7.36 to −2.28)	<.001
Postoperative relaparotomy	−4.82 (−8.83 to −0.79)	.02
Mental composed score[d]		
Preoperative opioid use	−5.34 (−8.01 to −2.70)	<.001
Pancreatic head resection	−3.75 (−6.61 to −0.90)	.01

[a] 95% confidence intervals were calculated using bootstrap-corrected analysis.
[b] Other factors entered in the model included preoperative opioid use, low preoperative body mass index (<20), and postoperative complications requiring reoperation.
[c] Other factors entered in the model included type of surgical procedure.
[d] Other factors entered in the model included age and continued smoking.

(**Table 5**). Short duration of pain before surgery (less than 3 years) and drainage procedures were associated with less endocrine pancreatic insufficiency. Longer follow-up was associated with an increase in the risk for endocrine insufficiency. A subgroup analysis without patients with left-sided pancreatic resection showed identical results. For exocrine pancreatic insufficiency, pancreatic head resection was associated with increased risk for insufficiency (OR, 3.31; 95% CI, 1.33-12.61; $P=.006$), whereas left-sided pancreatic resection was associated with less exocrine pancreatic insufficiency compared with a drainage procedure (OR, 0.23; 95% CI, 0.10-0.49; $P<.001$).

QUALITY OF LIFE

Multivariable analysis identified preoperative opioid use and postoperative complications requiring reoperation as independent risk factors for a lower physical composed score (Table 5). For mental composed score, preoperative opioid use and pancreatic head resection were independently associated with diminished quality of life. Other perioperative risk factors, including continued smoking and alcohol use, were not associated with quality of life.

COMMENT

The main finding of this study is the identification of timing of surgery as an important determinant of long-term clinical outcome in CP. Surgery within 3 years of onset of symptoms was associated with higher rates of pain relief and lower rates of endocrine pancreatic insufficiency. Surgery before use of opioids and before repetitive endoscopic interventions was associated with higher rates of pain relief. All these findings favor a treatment strategy that allows for surgery at an earlier stage in CP over the current practice of delayed surgery.

The recommendation from current guidelines vary substantially regarding the timing of surgery in CP.[8,18,30,31] A recent Italian guideline recommended that "pancreatic surgery should be performed after failure of medical treatment and to avoid opioid addiction."[31] In their argumentation, the authors provided data to support the burnout hypothesis, in which CP is thought to resolve spontaneously over time. They do note that more recent studies have shown that "remission is unpredictable and a percentage of patients will suffer of pain indefinitely" and that "a delay in treatment may affect quality of life, increase medical and social costs and cause narcotic addiction."[31] Therefore, these comments contradict their main recommendation. A South African guideline also fails in providing a clear recommendation and states that "interventions should be considered if there is an escalated need and/or continuous usage of opioids."[30] No attempt was made to define what constitutes an acceptable use of opioids. The guideline does not discuss potential benefits of early surgery, but it warns of the compromise of pancreatic function that may be associated with surgery. The American Gastroenterological Association in 1998 recommended a trial of endoscopic intervention early in CP.[8] In case of failure of endoscopic therapy or if not performed, the guideline instructs physicians to "discuss with patient watchful-waiting vs narcotic analgesics and risk of addiction vs benefit and risks of surgery," leaving the issue to timing of surgery unresolved. Finally, German guidelines do not provide any recommendation regarding this issue.[18]

It is clear that current guidelines have trouble weighing the benefits and risks associated with surgery compared with alternative treatments. Guidelines that rec-

ommend opioid treatment in CP often insufficiently address its severe drawbacks. First, there is a risk for narcotic dependency, which substantially impacts social functioning and quality of life.[7,9] Second, prolonged opioid use is associated with progression into a state of central sensitization and hyperalgesia.[32-34] This phenomenon was found to play a role in the outcome of pancreatic surgery and other types of treatments in CP such as splanchnicectomy.[20,21,35] Finally, opioid treatment under current practice does not constitute adequate pain relief because as much as 75% of patients will eventually require surgery during their disease.[3,11-13]

Endoscopic intervention constitutes another alternative strategy to surgery in current guidelines.[8] Endoscopic treatment in patients with severe pain who are not responding to opioid treatment was shown to be inferior to surgery in 2 randomized trials and a recent meta-analysis.[36-38] Surgery achieved higher rates of pain relief, less exocrine pancreatic insufficiency, and higher quality of life, with comparable morbidity and mortality. However, to our knowledge, no study to date has compared endoscopy and surgery for patients in an early stage of CP. Our study showed that repetitive endoscopic interventions owing to lack of successful pain relief are associated with a less favorable outcome when surgery is eventually performed. Additionally, each endoscopic intervention is associated with a relatively small risk for morbidity but the cumulative risk may be substantial.[36,37] Although endoscopy is less invasive than surgery, present data emphasize that endoscopic interventions in CP should be limited to a short trial, as suggested by the American Gastroenterological Association's guidelines.

Although no previous studies have addressed the timing of surgery directly to our knowledge, the results in our study are supported by findings from other experimental and clinical studies. Pathophysiological studies of pain in CP show that allowing pancreatic pain to exist for a prolonged period of time is associated with peripheral and central nerve sensitization. This can lead to a self-perpetuating pain state, which is very difficult to reverse and manage.[39] Another study, based on an experimental model of early vs late surgical drainage for CP in piglets, demonstrated that the histology of the pancreas and the exocrine pancreatic function were significantly better in early compared with delayed surgery.[14] These studies suggest that the deleterious effect of pancreatic duct obstruction on histology and function is related to the duration of disease. This is further supported by 2 observational studies showing that surgical interventions, especially drainage procedures, have the potential to delay the progressive loss of pancreatic function in patients with CP.[15,16,40] A small randomized, controlled trial showed that surgical drainage of patients with CP with a dilated pancreatic duct in an early stage of the disease (ie, presence of only mild pain symptoms) resulted in more patients with adequate pain relief and pancreatic function compared with nonsurgical treatment.[16] However, the study had a small sample size and some concerns regarding its methods.

Based on the findings of our study, we suggest the following strategy for the treatment of CP. When patients present with continuous severe pain and they are not good candidates for endoscopy, treatment with opioids can be tried for a limited period, with frequent assessment of the analgesic and possible adverse effects. Prescribed opioids should have long durations of action (eg, slow-release preparations) and have slow access to the central nervous system (to decrease the likelihood of addiction).[9] In case of limited effect, one should not hesitate to try a different opioid or discontinue an otherwise insufficient therapy. If after several months, pain does not subside and continuous opioid treatment is still needed, surgery may be considered. If patients are suitable candidates for endoscopy, a limited trial of endoscopic interventions can be started. The success of endoscopy should preferably be determined in 5 or less endoscopic interventions to optimize outcome of future surgery. If endoscopy does not provide persistent pain relief, then surgery should be considered. In patients with prolonged disease who have become suitable candidates for surgery at a later stage in the disease, evidence shows that surgery is the preferred treatment.[36,37]

It is clear that this strategy still needs further specification regarding the exact optimal timing of surgery. Before such conclusions can be drawn, we have to await the results of the Early Surgery vs Optimal Current Step-up Practice for Chronic Pancreatitis trial within the Dutch Pancreatitis Study Group (isrctn.org Identifier: ISRCTN45877994). This randomized controlled trial compares a strategy of early surgery as soon as patients develop the need for opioid analgesics vs a step-up approach of opioid analgesics, if needed, followed by a limited period of endoscopic interventions and surgery, if previous steps are insufficient to relieve pain. The step-up approach is the control arm and has been formulated by national experts in consensus meetings to represent the best current practice in the treatment of CP based on literature and the findings of this study. The early surgery approach is the innovative arm of the study, with its hypothesis based on the results of this study as well.

The main strengths of our study are the large number of patients included, the long follow-up, and the specific design, primarily addressing the effect of timing of surgery. Other studies had smaller numbers and evaluated a wide range of risk factors for outcome of surgery, and consequently lack strict definition and verification of important variables.[27,28] The presentation of study results in a nomogram facilitates understanding of the potential effect of present findings on individual patients and aids in decision making. The nomogram is internally validated by means of bootstrapping. Prospective external validation in an independent control cohort needs to follow to test its applicability in different populations in clinical practice. A limitation to the study is the predominantly retrospective data collection. To improve reliability, we spent time and effort to verify important variables and risk factors. Nonetheless, retrospective collection of certain variables such as etiology remains a challenge.

Our study shows that timing of surgery is an important determinant of long-term outcome and CP and provides evidence in favor of earlier surgical intervention. It also provides a nomogram to predict success of surgi-

cal intervention with respect to pain relief. Randomized trials, such as the ongoing Early Surgery vs Optimal Current Step-up Practice for Chronic Pancreatitis trial, are necessary to further advance our knowledge.

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