

## Observational Study

# Surgery for chronic pancreatitis in Finland is rare but seems to produce good long-term results

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## Abstract

### BACKGROUND

Abdominal pain in chronic pancreatitis (CP) may require invasive interventions. Surgical procedures are rare, and little is known about the long-term results.

### AIM

To study the nationwide frequency of pancreatic surgery for CP in Finland, and postoperative symptoms and quality of life (QoL).

### METHODS

All patients in Finland with a diagnosis of CP who had undergone pancreatic surgery during 2000-2008 were selected from a national register. Only patients with CP as an indication for pancreatic surgery were included. Medical records were studied and questionnaires QLQ-C30, PAN26 and AUDIT, and symptom questionnaires were sent out.

### RESULTS

During the 9-year period, pancreatic surgery for CP was performed on 30 patients [77% men, median age 45 (21-62) years]. Eighty-three percent underwent endoscopic procedures before surgery. Surgery was performed a median 2 (0-10) years after the original CP diagnosis, and 17% developed postoperative complications. Primary pain relief after surgery was reported in 70% of cases. Need for strong pain medication was lower after surgery. Eight of 21 (38%) returned the questionnaires and 88% reported that surgery had reduced their pain and 63% were almost or entirely pain-free at a median 14 (10-18) years after surgery. QoL results did not differ from those in our control Finnish CP group.

### CONCLUSION

**Data sharing statement:** We are not give permission to share data because the data is being used to future studies and patient data is not allowed to be shared because of the EU Regulation on the protection of personal data.

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Surgery for CP is rare in Finland and most patients had prior endoscopic procedures. Patients who returned the questionnaires reported less pain and good QoL during the 14-year follow-up.

**Key Words:** Surgery; Pain; Chronic pancreatitis; Quality of life; Complication

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**Core Tip:** Our study provides valuable insight on the current state of chronic pancreatitis (CP) surgery for chronic pain in Finland. We included all the CP patients who underwent surgery for CP symptoms during 2000-2008 in Finland. We found that surgery is rare. We estimate that 0.6%-0.8% of CP patients undergo surgery for CP pain, which produces good long-term effects. Opiate usage was reduced after surgery. Most of the patients had undergone endoscopic procedures before surgery. Complications after CP surgery were rare.

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## INTRODUCTION

Chronic pancreatitis (CP) leads to permanent morphological changes in the pancreatic tissue such as ductal lesions and calcifications. Persistent inflammation may cause abdominal pain and also lead to pancreatic insufficiency, seen as secondary diabetes and malnutrition as well as various complications[1-4].

There are several mechanisms behind CP pain. High pressure in the pancreatic ducts due to pseudocysts or strictures may cause pain. High alcohol consumption and smoking may lead to oxidative stress, increasing pain. Exocrine insufficiency may result in low vitamin and antioxidant levels, causing pain. Even pancreatic ischemia may be behind the development and pain of CP[5-9].

Conservative pain treatment is often not enough and invasive treatments such as endoscopic stenting and surgery are needed. Endoscopic treatments, such as pancreatic stenting and celiac plexus interventions, are less invasive than surgery, but the long-term results may be of limited benefit[10-13].

Surgery for CP is planned individually depending on the pancreatic findings. Surgical methods can be classified as pancreatic drainage, pancreatic resection or a combination of these. The earliest surgery for CP was pancreaticoduodenectomy (PD) [14-17]. Duodenum-preserving surgery for CP includes the Frey, Puestow, Berger and Berne modifications, where pancreatic tissue is resected and/or drained and a pancreatojejunostomy is performed using a Roux-Y jejunal loop[18-23].

Surgery for CP is rare and no universal recommendations exist. Some evidence suggests that earlier surgery for CP may improve results. To the best of our knowledge, there are no nationwide data in Finland on the frequency of the various surgical procedures, or on the effect on pain and quality of life (QoL) during long-term follow-up after surgery.

The aim of this study was to investigate the variety of surgical procedures used and their impact during a long-term follow-up on symptoms and QoL in patients operated on for CP nationwide in Finland in 2000-2008.

## MATERIALS AND METHODS

### Study design and patients

All the pancreatic resections [Nordic Classification of Surgical Procedures codes JLC\* (resection of the pancreas) or JLW96 (other operations on pancreas)] performed in Finland during 2000-2008 for a diagnosis of CP (ICD-10 code: K86.01, K86.1, K86.08,

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k86.8 and K86.9) were selected from the Finnish National Institute for Health and Welfare HILMO register. There were 97 patients. After reviewing their medical records, only 30 patients with CP as an indication for pancreatic surgery were included in the final database (Figure 1).

From the patient archives, information was gathered about medical history, time of CP diagnosis, etiology of CP, previous CP treatments, type of current surgical therapy, postoperative complications, possible reoperations, and exocrine and endocrine pancreatic insufficiency. The date of death was recorded on September 22, 2017.

QLQ-C30, PAN-26[24] and AUDIT questionnaires and a nonstandardized questionnaire about pain before and after surgery were sent to the patients.

A previously reported Finnish general CP cohort from 2014-2015 was used as a control for the AUDIT, QLQ-C30 and PAN26 questionnaires[25]. In the control cohort, the median age was 58 (26-95) years, 67% were male and median time after diagnosis was 4 (1-42) years. Around 68% and 58% of patients had alcohol and smoking, respectively, as a risk factor for CP. Calcifications were found in 66% of the patients and ductal lesions were present in half of the patients. Endoscopic procedures were performed on 27% of patients and 9% underwent surgery.

### Ethical aspects

The study was approved by the Ethics Committee of Tampere University Hospital, Finland (ETL code R16153). The data from the HILMO register was provided by the Finnish National Institute for Health and Welfare with a license/permission (THL/1854/5.05.00/2012)

### Statistical analysis

Data are presented as median (range). The statistical analyses were performed using Pearson's  $\chi^2$  or Fisher's exact test. For analysis of the QLQ-C30 and PAN26 questionnaires, the Mann-Whitney *U* test was used. The EORTEC scoring manual was used for the QLQ-C30 and PAN26 questionnaires, and the responses were scored as 0-100. A higher score on QoL/functioning indicated better QoL and a lower score on symptoms (*e.g.*, pain or insomnia) represented better QoL.  $P < 0.05$  was considered statistically significant.

## RESULTS

Thirty patients underwent pancreatic surgery for CP in Finland during the period 2000-2008 and formed the final study cohort.

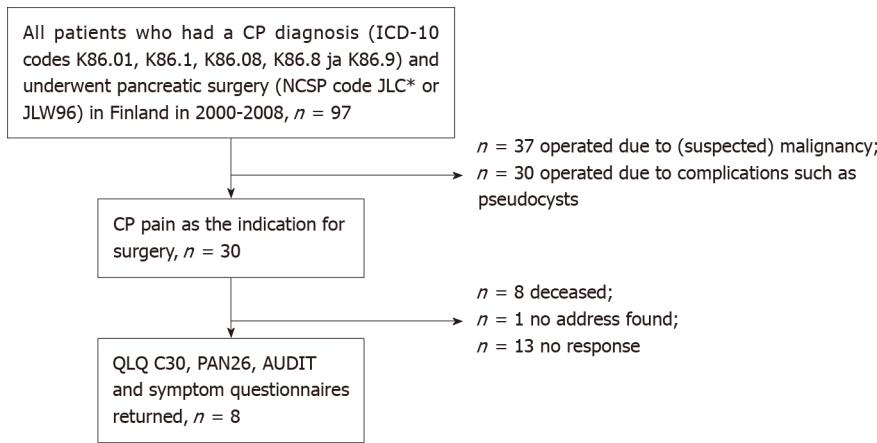
Surgery was performed in 13 different hospitals; median two (range 1-7) per hospital. Of the patients 77% were men and the median age was 45 (21-62) years. Surgery was performed a median 2 (0-10) years after diagnosis of CP. During the 16 (10-26) years of follow-up, eight patients died, a median 4.5 (0-16) years after surgery. The etiology of CP was alcohol in 60%, while 47% had idiopathic disease. Eighty-seven percent had recurrent episodes of acute pancreatitis (AP).

Half of the patients smoked. All of the smoking patients were on opioids before surgery, compared to 42% in the non-smoking group ( $P = 0.0004$ ).

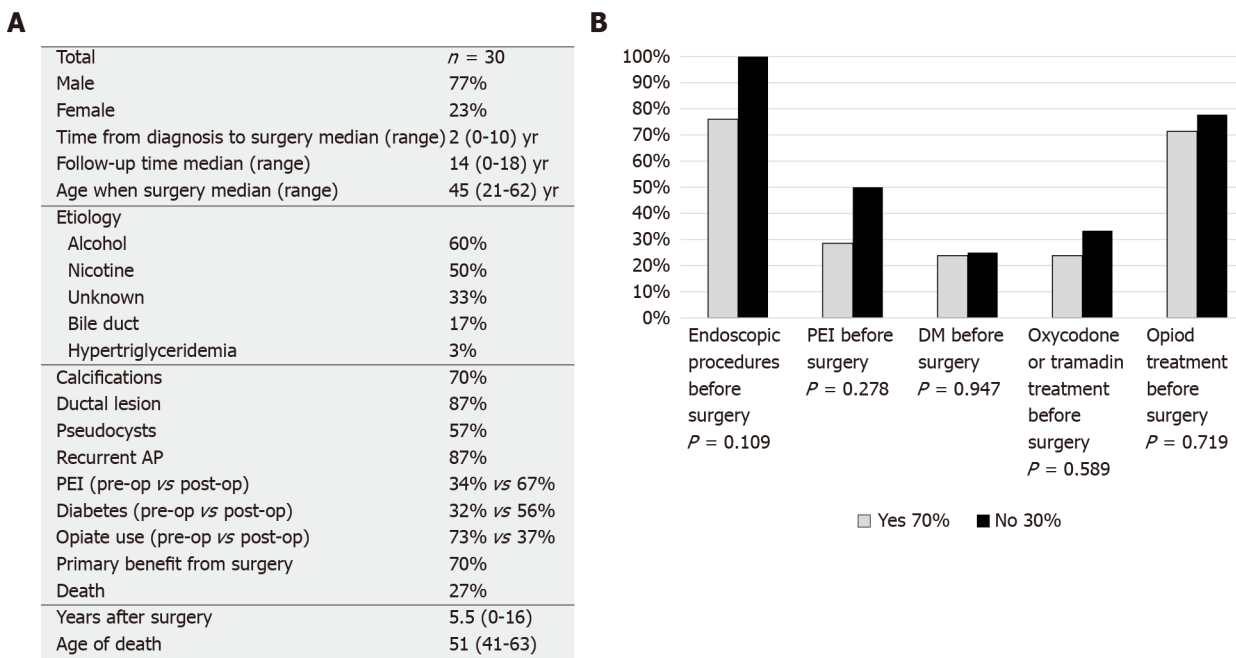
Out of the 30 operations performed in the course of 9 years, one was a drainage procedure (Puestow), nine combined resection and drainage, and there were 20 pancreatic resections (16 distal and 4 pylorus-preserving PD/PDs). Fifteen included splenectomies (Figure 2). Out of the combined pancreatic resection and drainages, four were Frey's procedure, two were Beger's procedure and three were Puestow's drainage combined with caudal resection (Figure 3).

Eighty-three percent ( $n = 25$ ) of the patients had no postoperative complications, 17% ( $n = 5$ ) developed complications: two had Clavien-Dindo (CD) grade 1 complications; two had CD grade 2 complications and one had CD grade 3b complications. One patient died within 3 wk of surgery; this patient had undergone four prior laparotomies and had intraoperative hemorrhage during surgery for CP.

Seventy percent of the patients had reported primary pain relief after the surgery and 64% of those who had undergone previous endoscopic procedures had experienced primary pain relief and all those with no previous endoscopic procedures had experienced primary pain relief, but the nonendoscopic group was so small that the difference was not significant ( $P = 0.10$ ). No correlation was seen in time after diagnosis and primary pain relief ( $P = 0.43$ ) (Figure 2).



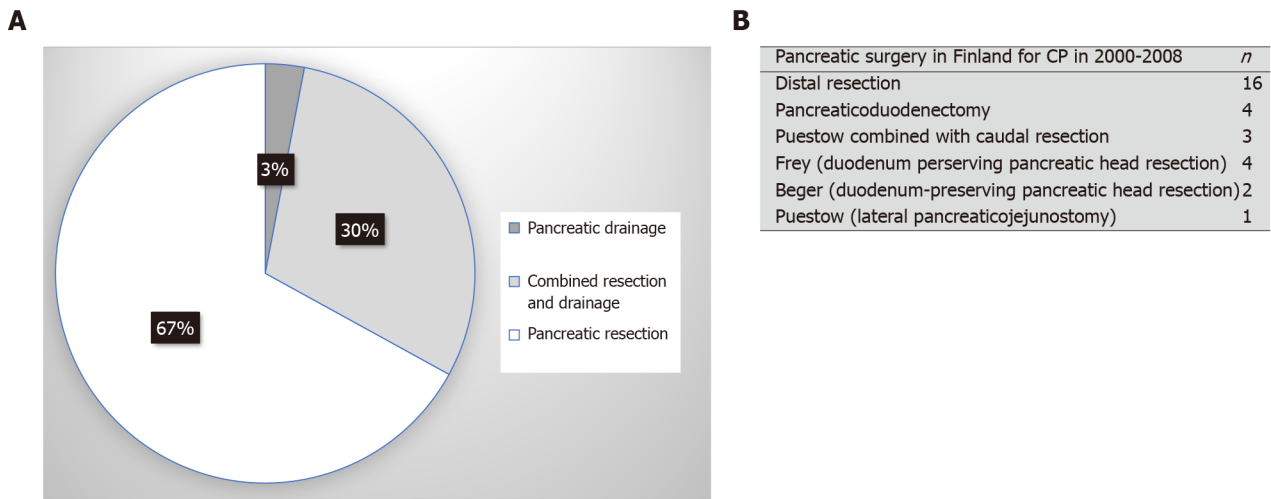
**Figure 1 Flowchart of patients.** The study included all patients who underwent pancreatic surgery for chronic pancreatitis in the whole of Finland in 2000-2008. CP: Chronic pancreatitis.



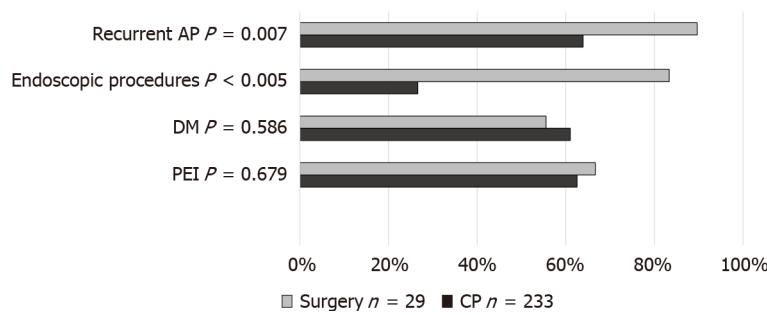
**Figure 2 Demographics and outcome of chronic pancreatitis surgery.** A: Demographics of the surgical chronic pancreatitis patients; B: Surgical chronic pancreatitis patients grouped based on pain relief approximately one year after surgery. AP: Acute pancreatitis; PEI: Pancreatic exocrine insufficiency; DM: Diabetes mellitus.

Pancreatic exocrine insufficiency (PEI) was present in 34% of the patients preoperatively and in 67% postoperatively. Diabetes was seen in 32% of the patients preoperatively and in 56% postoperatively. When comparing CP patients who had surgery (*n* = 25) to the Finnish general CP cohort who did not have pancreatic surgery (*n* = 195) and had a median time after diagnosis of 5-43 years, the frequency of PEI was similar (surgery group 67% vs nonsurgical group 63%, *P* = 0.679). Also, the frequency of diabetes was the same in CP patients not undergoing pancreatic surgery (61%) as in patients undergoing surgery (56%; *P* = 0.586). Seventy-three percent of the patients were on opioids before surgery and 37% after surgery (*P* = 0.004). Opioid use for the control group was not recorded (Figure 4).

Endoscopic retrograde cholangiopancreatography was performed on 83% of the patients prior to surgery. Twenty percent had already undergone prior pancreatic surgery for pancreatic pseudocyst complications. When comparing these parameters to the Finnish general CP cohort, significantly more endoscopic procedures (83% vs 27%, *P* < 0.0001) and recurrent AP (87% vs 67%, *P* = 0.007) were seen in these surgically treated CP patients than in the overall CP patients in the control group (Figure 4).



**Figure 3 Distribution of chronic pancreatitis surgery in Finland.** A: Type of surgery for chronic pancreatitis. Most operations involved a pancreatic resection (pancreaticoduodenectomy or a distal resection); B: Type of surgical operations in detail. CP: Chronic pancreatitis.



**Figure 4 Surgical chronic pancreatitis patients compared to control population, which included nonsurgical chronic pancreatitis patients from the Finnish chronic pancreatitis cohort from 2014 to 2015 (*n* = 233).** There was more recurrent acute pancreatitis and prior endoscopic procedures in the chronic pancreatitis patients who underwent surgery. Pancreatic insufficiency and diabetes were similar between the groups. CP: Chronic pancreatitis; AP: Acute pancreatitis; PEI: Pancreatic exocrine insufficiency; DM: Diabetes mellitus.

Out of the 21 patients asked to complete the questionnaires, eight (38%) returned the QoL questionnaires (QLQ-C30 and Pan-26) and the AUDIT questionnaire. There was no significant difference between the responders and nonresponders in gender, pancreatic calcifications, PEI, recurrent AP or alcohol-related etiology. All the patients who responded had a history of smoking and 63% continued smoking compared to 35% among the nonrespondent patients (*P* = 0.003).

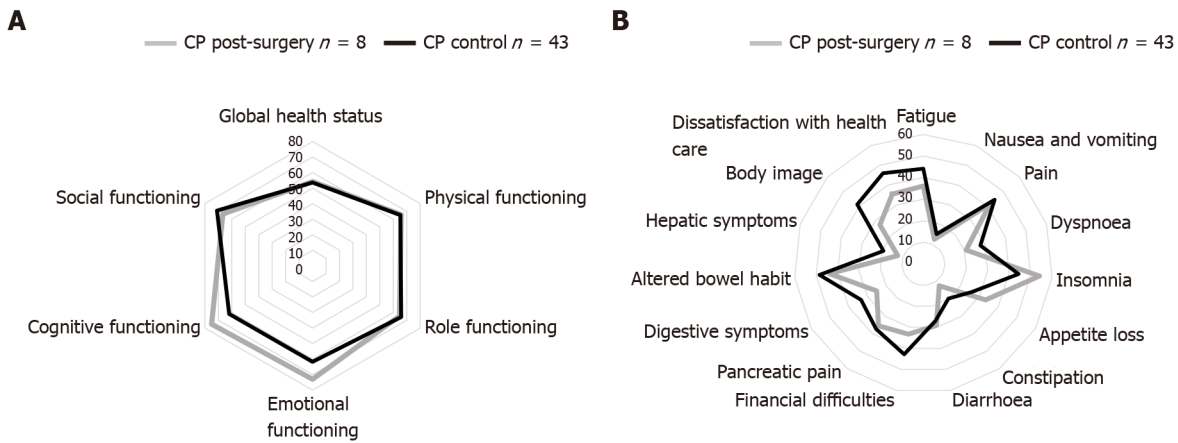
Of the CP patients who responded, 88% reported that the surgery helped their pain and 63% were almost or entirely pain-free 14 (10-18) years after surgery. The AUDIT questionnaire median was 4 (0-28) points, and in the control CP population, the AUDIT score median was 3 (0-39) points (*P* = 0.764).

When comparing the QLQ-C30 and PAN26 responses to the Finnish general CP cohort (Figure 5) the nonsurgery group had more pain, pancreatic pain and hepatic symptoms but this was not significant (*P* = 0.869, *P* = 0.970 and *P* = 0.379). Since all the responding CP patients undergoing surgery were smokers, we compared them to those in the Finnish general CP cohort who had been smoking.

## DISCUSSION

Surgery for CP is rare and no nationwide data with long-term follow-up after surgery are available. Our aim was to find out how common CP surgery is and what the long-term effects on CP patients are. We found that surgery for CP is rare but seems to give long-term pain relief in CP and reduces opiate use.

Approximately three operations for CP pain were performed per year in the whole of Finland. We estimate that 0.6%-0.8% of CP patients undergo surgery for CP pain.



**Figure 5** Quality of life in the chronic pancreatitis patients who underwent surgery, compared to control chronic pancreatitis patients. All patients who answered the quality of life (QoL) questionnaire in the surgical group were smokers. The control group consisted of Finnish chronic pancreatitis patients who did not have surgery and smoking contributing to their disease. A and B: QoL functioning (A) and symptom scores (B) had a tendency to be better in most parameters in the surgical group, but without significance. A higher score was better in the functioning scores (A), and a lower score was better in the symptoms scores (B). CP: Chronic pancreatitis.

Most of the surgical interventions in CP are for treatment of complications (such as pseudocyst infections, hemorrhage and bowel obstruction), or due to suspicion of malignancy. Overall, pancreatic surgery for CP is rare in Northern Europe: < 10%, compared to studies from North America and Hungary, reporting 20% pancreatic surgery in the CP population[26-28]. Most patients had already undergone endoscopic procedures; some of them multiple times. In our study, patients with no previous endoscopic procedures had better pain relief (64% vs 100%) even though the difference was not significant due to the number patients with no previous endoscopies. It seems that in Finland surgical procedures are only considered after endoscopic means have been already tried. Thirty-four percent already had preoperative PEI, indicating advanced CP. Retrospective studies have shown that pancreatic surgery for pancreatic duct decompression is more cost-effective than endoscopy[29,30].

During the time of the study, CP pancreatic surgery was spread over many hospitals in Finland, 13 in total – compared to five centers at present. Most of the patients underwent endoscopic procedures before the operation. The procedures performed were also heterogeneous. In our study there was no correlation in the timing of the surgery and primary pain relief but most of the operations were performed within 3 years of diagnosis (74%). A few retrospective studies have reported that earlier CP surgery (< 3 years after diagnosis) improves the outcome and is also safe. In a prospective, multicenter randomized controlled trial (ESCAPE trial), surgery was reported to produce better outcomes when performed early enough before endoscopic procedures. In CP, the pancreas tends to be harder due to fibrosis, which can lead to fewer postoperative pancreatic fistulas than in a soft normal pancreas. Compared to reports in Europe and North America, the low percentage of CP surgery in Finland suggests that CP patients are operated on too seldom in Finland, which could be due to advances in endoscopic procedures or to a high threshold for performing pancreatic surgery on a benign disease[31-35].

Most of the patients in our study used opioids before surgery, and surgery reduced the need for opioids. Perhaps when opioids are needed surgery should be considered. Thirty-six percent of the patients had opioids after surgery and this could be due to opioid tolerance and addiction. Preoperative opioid use, persistent pain (3 mo) and previous surgery have been shown to be risk factors for postoperative pain in abdominal surgery. Chronic use of opioids in abdominal pain such as in CP can cause hyperalgesia in which abdominal pain paradoxically may become more severe[36-39].

Half of the CP patients undergoing surgery were smokers and they took significantly more opioids before surgery. Smoking has been reported to impair the outcome of pancreatic surgery and QoL[40]. Cessation of smoking and opioid use should be considered before pancreatic surgery for CP.

There was no significant difference in PEI, diabetes or QLQ responses between CP patients undergoing surgery and a Finnish control CP group, even though it seems that the CP patients who underwent pancreatic surgery were a selected patient group with more severe pancreatitis, since they had significantly more endoscopic procedures (83% vs 27%,  $P < 0.0001$ ) and recurrent AP (87% vs 67%,  $P = 0.023$ ) than the

control CP group. Nonoperated and operated CP patients had approximately the same amount of PEI. Surprisingly, diabetes is more common in CP patients without pancreatic surgery. This could be due the decompressing surgery influencing the progression of pancreatitis and slowing pancreatic insufficiency[41,42].

The rate of idiopathic pancreatitis is high in patients who have surgery. In some cases, it could be due to the difficulty in differentiating benign pancreatic masses and malignant tumors, which could affect the decision for surgery[43-45].

The strength of our study is that it involved all the CP patients in Finland. We made a broad selection and only included patients with CP diagnosis and surgery performed for CP pain. To the best of our knowledge, no national study on CP surgery had been published earlier. In spite of the small population, our study provides a valuable description of CP patients who undergo surgery for CP.

The limitations of this study were the small patient number and low response rate of 38%, which is approximately the same as in an earlier study[25]. We gathered the medical histories retrospectively, and one was lost because the patient was deceased, and the record had been deleted. Smoking and alcohol consumption were not always recorded accurately, so presumably these may have been more common.

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## CONCLUSION

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Surgery for CP is rare in Finland, but seems to produce good long-term results. Opiate usage was reduced after surgery. Most of the patients had undergone endoscopic procedures before surgery. Complications after CP surgery were rare. More studies are needed on the timing of CP surgery to ensure maximum benefit for patients.

## ARTICLE HIGHLIGHTS

### **Research background**

Chronic pancreatitis (CP) may need invasive surgical interventions. There is no current knowledge of long-term outcomes and prevalence of surgery for CP.

### **Research motivation**

We wanted to investigate the current state of pancreatic surgery in Finland for CP.

### **Research objectives**

Our objective was to find long-term outcomes of patients who have pancreatic surgery for CP pain in Finland.

### **Research methods**

We gathered all CP patients who had pancreatic surgery in Finland in 2000-2008 *via* the Finnish National Institute for Health and Welfare registry. We gathered information about the time of CP diagnosis, etiology of CP, previous CP treatments, type of current surgical therapy, postoperative complications, possible reoperations, and exocrine and endocrine pancreatic insufficiency.

### **Research results**

We found that surgery for CP is rare in Finland but most patients (70%) are pain free after surgery. Opiate usage was less after surgery.

### **Research conclusions**

CP surgery is rare and produces good long-term results in CP patients.

### **Research perspectives**

Our study was limited because of the small number of patients but we provide a long 16-year follow-up and our study contains all of CP patients in Finland who had pancreatic surgery.

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