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ORIGINAL ARTICLE

Surgical treatment for chronic pancreatitis: A single-center retrospective study in Japan

Ippei Matsumoto | **Keiko Kamei** | **Takaaki Murase** | **Yuta Yoshida** | **Kohei Kawaguchi** | **Masataka Matsumoto** | **Shumpei Satoi** | **Atsushi Takebe** | **Takuya Nakai** | **Yoshifumi Takeyama**

Department of Surgery, Kindai University Faculty of Medicine, Osaka-sayama, Japan

Correspondence
Ippei Matsumoto, Department of Surgery, Kindai University Faculty of Medicine, 377-2 Ohno-higashi, Osakasayama 589-8511, Osaka, Japan.
Email: ippeimm@gmail.com

Abstract

Background/Purpose: To determine the short- and long-term results of surgical treatments for chronic pancreatitis (CP) at a high-volume center in Japan.

Methods: The records of 151 consecutive patients undergoing surgery for CP were retrospectively reviewed. Selection of surgical procedures used had been according to the Japanese Clinical Practice Guidelines for CP 2015. Long-term (≥1 year) follow-up was performed in 100 patients (median of 37 months).

Results: Surgical drainage procedures were performed in 107 patients (Frey operation in 81, longitudinal pancreaticojejunostomy in 26), pancreatic resection in 37 (subtotal stomach-preserving pancreaticoduodenectomy in 11, distal pancreatectomy in 26), and other procedures in six. The rates of postoperative mortality and morbidity were 1% and 26%, respectively. The rates of complete and partial pain relief were 62% and 37%. The frequency of occurrence of severe morbidity was significantly higher after pancreatic resection than in patients receiving drainage procedures (13% vs 2%, $P = .019$). The rate of new-onset diabetes was also significantly higher after resection than drainage (60% vs 25%, $P = .017$).

Conclusions: Surgical treatment for painful chronic pancreatitis can be safe and effective. An optimal procedure should guarantee pain relief and preserve a maximum of pancreatic function.

KEYWORDS

chronic pancreatitis, Frey operation, longitudinal pancreaticojejunostomy, pancreaticoduodenectomy, surgical treatment

1 | INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory disease characterized by irreversible destruction of the pancreas. This leads to loss of functional parenchyma ultimately resulting in endocrine and exocrine insufficiency. Surgical treatment is often required in CP patients for the intractable pain caused by excessive pancreatic inflammation. In the 2000s, two prospective randomized controlled trials (RCTs) showed that surgery was more effective than endoscopic intervention in terms of pain relief, preserving physical health, and reducing the number of future procedures required, over both the short and the long term.[1-3] However, given recent advances in endoscopic intervention and its lesser invasiveness relative to surgery, this

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procedure is currently regarded as the treatment choice for CP following failure of conservative treatment. Surgical treatment has been reserved for later in the disease course after endoscopic intervention itself has failed. On the other hand, several observational studies showed that early surgery leads to better pain relief and less postoperative opioid use compared to late surgery.[4-8] However, whether to use a step-up approach or immediate early surgery is still under debate and evidence-based treatment protocols have not been established.

Several surgical procedures are available for the treatment of pain in CP and can be categorized into three types: drainage (focusing on ductal hypertension), resection (focusing on inflammatory masses in the pancreatic head), and mixed procedures with elements of both. However, although the selection of which surgical procedures to apply is constrained by the degree and extent of the main duct dilation and gland morphology, there may be inconsistencies in standardizing treatment due to the present variety of surgical procedures available, as well as institutional policy, and surgeon preference and experience. In our center, choice of treatment and selection of surgical procedures is decided at weekly multidisciplinary meetings of gastroenterologists, endoscopists and surgeons. In all cases, selection of surgical procedures is consistent with the Japanese Clinical Practice Guidelines for CP 2015.[9]

There are several reports in the literature on the short- and long-term outcomes of surgical treatments for CP in large series of patients in other countries, but there are very few large Japanese studies.[10,11] Moreover, it is important to demonstrate the safety and efficacy of surgical treatment for CP not only to surgeons but also gastroenterologists and endoscopists at the present time. To this end, the purpose of the current study was to evaluate patient characteristics, indications, and results of surgical treatments for CP at a specialized center in Japan.

2 | METHODS

2.1 | Study design

Case records of 151 consecutive CP patients who underwent surgical treatment at the Hospital of the Kindai University Faculty of Medicine between January 2005 and November 2016 were reviewed retrospectively. All patients were diagnosed with chronic pancreatitis by clinical history, ultrasonography, computed tomography, endoscopic ultrasonography, and/or endoscopic retrograde cholangiopancreatography. Their clinical characteristics and short- and long-term results after surgery were evaluated. Patients with a follow-up period of 12 months or longer (n = 100) were included in the analysis of long-term results. The patients provided written informed consent for surgical treatment according to the rules and regulations of our institution. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of Kindai University Faculty of Medicine (approval number: 29-006).

2.2 | Indications for surgery and selection of surgical procedure

Indications for surgery and selection of the surgical procedure based on the Japanese Clinical Practice Guidelines for CP 2015[9] were determined after a multidisciplinary meeting review. The indication for surgery was mostly abdominal pain in symptomatic patients after failure of conservative treatment and/or endoscopic interventions. Dilation of the main pancreatic duct (MPD) was taken as the indicator for selection of drainage as the surgical procedure. In this study, longitudinal pancreaticojejunostomy (LPJ) and the Frey operation were both categorized as surgical drainage procedures in the sub-analysis that compared these patients with those receiving surgical resection. The indicator for LPJ was dilation of the MPD without lesions in the head of the pancreas whereas an inflammatory mass or pancreatic stone in the head of the pancreas, together with dilation of the MPD, was the indicator for the Frey operation. If there was no dilation of the MPD, pancreatic resection was performed. Pancreatic head resection was indicated in inflammatory pseudotumor/suspected pancreatic cancer in the pancreas head and/or duodenal and distal common bile duct obstruction. The standard procedure for pancreatic head resection in our center is subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) in which the distal stomach is divided 3–4 cm proximal to the pylorus ring. Indications for distal pancreatectomy were localized severe complications involving the pancreatic tail, such as pseudocysts and/or pseudoaneurysms. Definition of worsening imaging findings included at least following one over the preoperative period; increased diameter of the main pancreatic duct, increased number and/or size of pancreatic stone and/or calcification of the pancreas, development in stenosis or obstruction of the portal vein system, or formation of collateral veins.

2.3 | Definition of postoperative complications

Postoperative complications were evaluated by means of a modified Clavien-Dindo grading system.[12] Postoperative pancreatic fistula (POPF) was assessed and categorized into three grades (biochemical leak, grade B POPF, or grade C POPF) using the revised International Study Group on Pancreatic Fistula (ISGPF) clinical criteria 2016.[13] Clinically

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relevant POPF was defined as grade B or C POPF. The amount of amylase in the drainage fluid on postoperative day (POD) 1, 3 and 5 was measured in all patients with drainage tubes over that period. Postpancreatectomy hemorrhage was classified into grade A, B, or C according to criteria of the International Study Group of Pancreatic Surgery.[14]

2.4 | Evaluation of long-term post-surgery results

Information on pain relief, readmission, and reoperation was extracted from the existing medical records. Endocrine insufficiently was estimated based on the diabetic status of the patients as defined either by the World Health Organization criteria of fasting plasma glucose level ≥126 mg/dL detected on two or more separate days, or fasting plasma glucose level ≥126 mg/dL detected once and ≥200 mg/dL two hours after a 75-g glucose challenge. Additionally, assessment may have been based on records of treatment with oral anti-diabetic agents or insulin injections. Exocrine insufficiently was defined as the presence of steatorrhea, persistent weight-loss or the need for enzymatic supplementation. Fecal elastase measurements were not available. Body weight, serum albumin, and serum total cholesterol levels before and after surgery were evaluated as markers of nutritional status.

2.5 | Statistical analysis

Data are expressed as median (range) in the text. Categorical data are expressed numerically as percentages. The paired Student's *t*-test was used to compare body weight, serum albumin, and serum total cholesterol levels before and after surgery. Student's *t*-test or Mann–Whitney test were used for continuous variables and the chi-square test for categorical variables. $P < .05$ was considered statistically significant. All analyses were performed using JMP 13.0 for Macintosh (SAS Institute, Inc).

TABLE 1 Patients' clinical characteristics

Sex	
Male	126 (83)
Female	25 (17)
Age	53 (20-84)
Body mass index (kg/m^2)	24.9 (15.9-28.7)
Time from diagnosis of CP to surgery (mo)	27 (1-360)
Previous endoscopic intervention	83 (57)
Etiology	
Alcohol	104 (69)
Idiopathic	27 (18)
Pancreatic divisum	6 (4)
Pancreaticobiliary maljunction	3 (2)
Autoimmune	2 (1)
Hereditary	1 (1)
Others	8 (5)
Pancreatic stone or calcification	123 (81)
Diabetes mellitus	57 (38)
Insulin dependent	32 (21)
Oral antidiabetics	10 (7)
Diet or no treatment	15 (10)

Note: Values represent median (range), or number (%).

Abbreviation: CP, chronic pancreatitis.

TABLE 2 Indications for surgery and preoperative complications

Acute exacerbation	127 (85)
Recurrent episodes	126 (83)
Chronic pain	115 (76)
Intractable pain	110 (73)
Worsening imaging findings	110 (86)
Long period of pancreatic stenting	26 (17)
Bile duct stenosis or obstruction	25 (17)
Duodenal stenosis or obstruction	6 (4)

Note: Values represent number (%).

3 | RESULTS

3.1 | Patients' characteristics and indications for surgery

The clinical characteristics of patients who underwent surgery are shown in Table 1. The patient cohort consisted of 126 (83%) males and 25 (17%) females with a median age of 53 years (range, 20–84) and a median period from the diagnosis of chronic pancreatitis to surgery of 27 months (rang, 1–360 months). Eighty-three patients (57%) had had endoscopic interventions before surgery. The etiology of CP was alcohol abuse in 104 patients (69%), idiopathic in 27 (18%), and pancreatic divisum in six (4%). Diabetes mellitus was evident in 57 patients (37%). Table 2 shows the indications for surgery and preoperative complications, which included a history of acute exacerbation in 127 (85%), recurrent episodes of pain in 126 (83%), chronic pain in 115 (76%), and intractable pain in 110 (73%). One hundred ten (86%) of 128 cases exhibited worsening imaging findings over the preoperative period. Other factors included a long period of residence of pancreatic stents in 26 (17%), bile duct stenosis or obstruction in 25 (17%), and duodenal stenosis or obstruction in six (4%). Surgical drainage procedures were performed in

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107 patients (71%). Of these, 81 (54%) underwent the Frey operation and 26 (17%) underwent LPJ. Seventeen patients required biliary drainage (choledocoduodenostomy in 11 patients, and choledocojejunostomy in six) during the drainage procedure. Pancreatic resection was performed in 38 (25%). Of these, 11 patients (7%) underwent SSPPD and 27 patients (18%) distal pancreatectomy (Table 3).

3.2 | Intraoperative and short-term results of surgery

Operative data and postoperative complications are shown in Table 4. Median duration of surgery was 255 minutes (range, 105–575 minutes) and median intraoperative blood loss was 530 mL (range, 5–12 798 mL). Forty-six patients (30%) required intraoperative blood transfusions. One patient with concomitant splenic abscess associated with an infected pseudocyst of the pancreatic tail died from sepsis after distal pancreatectomy. The mortality rate was 1%. Overall morbidity (Clavien-Dindo classification grade II or more) was present in 40 patients (26%). Fourteen patients (9%) developed biochemical leakage according to the ISGPF classification. However, only three (3%) developed clinically relevant POPF grade B and none suffered grade C. Five patients (4%) developed postpancreatectomy hemorrhage. Three patients (2%) required relaparotomy on POD1, 1, and 26, due to bleeding from the splenic artery, gastric perforation, and infected hematoma, respectively. The first patient required distal pancreatectomy. The second patient required suturing closure of the perforated gastric wall. The last patient underwent open drainage. All patients recovered from the complications. Median duration of postoperative hospital stay was 11 days (range, 5–91 days).

3.3 | Long-term results of surgery

Patients with a follow-up period of 12 months or longer were included in the analyses of long-term results. Of 151 patients, one patient died from surgical complication and the

TABLE 3 Surgical procedures

Drainage procedure	107 (71)
Frey operation	81 (54)
Longitudinal pancreaticojejunostomy	26 (17)
Pancreatic resection	38 (25)
Subtotal stomach-preserving pancreaticoduodenectomy	11 (7)
Distal pancreatectomy	27 (18)
Others	6 (4)

Note: Values represent number (%).

TABLE 4 Short-term results of surgery (n = 151)

Operation time (min)	255 (105-575)
Operative blood loss (mL)	530 (5-12 798)
Intraoperative blood transfusion	46 (30)
Mortality	1 (1)
Morbidity (Clavien-Dindo classification)	
Grade II	25 (17)
Grade III	12 (8)
Grade IV	2 (1)
Postoperative pancreatic fistula (ISGPF)	
Biochemical leak	14 (9)
Grade B	4 (3)
Grade C	0 (0)
Postpancreatectomy hemorrhage (ISGPS)	
Grade A	1 (1)
Grade B	3 (2)
Grade C	1 (1)
Relaparotomy	3 (2)
Postoperative hospital stay (d)	11 (5-91)

Note: Values represent median (range), or number (%).

Abbreviations: ISGPF, International Study Group of Pancreatic Fistula; ISGPS, International Study Group of Pancreatic Surgery.

TABLE 5 Long-term results of surgery (n = 100)

Pain relief (n = 93)	
Complete relief	58 (62)
Partial relief	34 (37)
No relief	1 (1)
Readmission	47 (47)
Deterioration of glucose tolerance	17 (17)
Acute exacerbation or abdominal pain	12 (12)
Acute cholangitis and/or biliary stenosis	10 (10)
Ileus	4 (4)
Others	6 (6)
Reoperation	11 (11)
Choledocoduodenostomy	3 (3)
Frey operation	3 (3)
Longitudinal pancreaticojejunostomy	2 (2)
Distal pancreatectomy	2 (2)
Total pancreatectomy	1 (1)
Diabetes mellitus, yes	62 (62)
Insulin dependent	44 (44)
Oral antidiabetics	4 (4)
Diet or no treatment	14 (14)
New-onset diabetes after surgery	21 (36)
Pancreatic exocrine insufficiency	45 (45)

Note: Values represent median (range), or number (%).

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follow-up period did not reach 12 months in 19 patients after surgery. An additional 31 patients were followed at referral hospitals or lost to follow-up. Consequentially, 100 patients were eligible for the present evaluation of long-term results. The median follow-up period of the patients was 37 months (range, 12–129 months).

Long-term results are shown in Table 5. Before surgery, 93 patients suffered from abdominal pain. Of these, complete pain relief was achieved in 58 (62%). Partial relief was noted in 34 patients (37%), but there was no pain relief in the one remaining patient (1%). Fifty-eight patients had no diabetes mellitus before surgery. Of these, 21 patients (36%) developed new-onset diabetes after surgery. As a result, the proportion of diabetic patients increased to 62% over the follow-up period. Pancreatic exocrine insufficiency was seen in 45 patients (45%). During the follow-up period, 47 patients (47%) required readmission. The main reasons for readmission included deterioration of glucose tolerance in 17 patients (17%), acute exacerbation or abdominal pain in 12 (12%), and acute cholangitis and/or biliary stenosis in 10 (10%). Reoperation was required in 11 patients (11%). Surgical procedures included choledocoduodenostomy in three patients (3%), Frey operation in three (3%), LPJ in two (2%), and total pancreatectomy in one (1%).

3.4 | Changes of body weight, serum albumin levels, and serum total cholesterol levels before and after surgery

Median body weight before and after surgery was 53.6 kg (range, 34.3–82.0 kg) and 57.0 kg (range, 30.0–83.0 kg), respectively (Figure 1A). This difference was not statistically significant ($P = .067$). Median serum albumin levels before and after surgery were 4.2 g/dL (range, 1.4–5.3 g/dL) and 4.3 g/dL (range, 2.3–5.2 g/dL), respectively (Figure 1B), also not significant ($P = .169$). Median serum total cholesterol levels before and after surgery were 169 mg/dL (range, 59-314 g/dL) and 174 mg/dL (range, 99–313 mg/dL), respectively (Figure 1C), again not statistically significant ($P = .567$).

3.5 | Comparison of short- and long-term results in patients with drainage procedures-vs-pancreatic resection

Table 6 shows short- and long-term outcomes in patients receiving drainage procedures or pancreatic resection. For short-term results, operative blood loss was significantly higher in the pancreatic resection group than in the drainage group (median 408 vs 1094 mL, $P < .001$). The morbidity rate (Clavien-Dindo classification grade III or more) was significantly higher in patients receiving pancreatic resection than drainage (13% vs 2%, $P = .019$). Postoperative hospital stays were significantly longer after pancreatic resection (median, 10 vs 13 days, $P = .004$). With respect to long-term results, the rate of complete pain relief was 62% and 60% for the drainage procedure and pancreatic resection groups, respectively. The rate of new-onset diabetes was significantly higher after pancreatic resection (25% vs 60%, $P = .017$). Moreover, four patients (6%) improved diabetes after the drainage procedure.

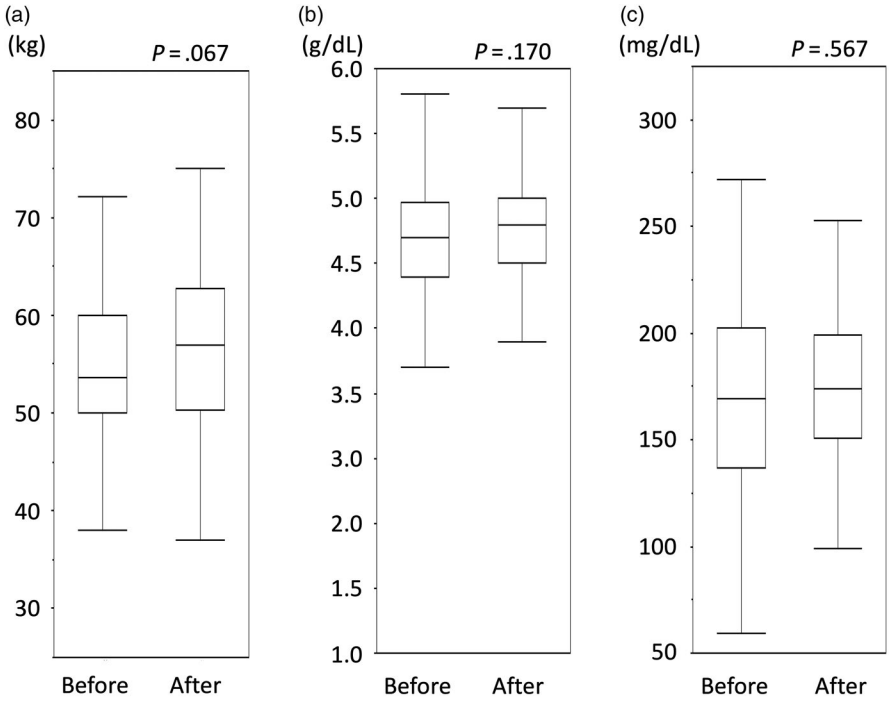

FIGURE 1 Changes of body weight (A), serum albumin levels (B), and serum total-cholesterol levels (C) before and after surgery

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TABLE 6 Short- and long-term results of drainage procedure and pancreatic resection

	Drainage procedure	Pancreatic resection	*P* value
Short-term results			
Operation time (min)	256 (105-575)	232 (135-530)	.232
Operative blood loss (mL)	408 (5-4680)	1094 (80-11 990)	<.001
Morbidity (Clavien-Dindo classification grade III or more)	2/107 (2)	5/38 (13)	.019
Postoperative hospital stay (d)	10 (5-52)	13 (7-91)	.004
Long-term results			
Complete pain relief	43/69 (62)	12/20 (60)	.748
Diabetes mellitus	43/69 (62)	16/20 (80)	.063
New onset diabetes after surgery	10/40 (25)	9/15 (60)	.017
Pancreatic exocrine insufficiency	37/69 (54)	6/20 (30)	.106

Note: Values represent median (range), or number (%).

4 | DISCUSSION

The primary goal of surgical treatment for CP is long-term pain relief that influences the quality of life. Although the efficacy of surgical treatment for CP had already been documented in previous studies, there may be hesitation before recourse to surgery due to the potential risks of complications in what is essentially a benign disease. Moreover, endoscopic intervention is available as the current treatment of choice. However, when endoscopic results are unsatisfactory, surgery may still be required. The present study clearly demonstrated that surgical treatment for CP results in effective pain relief with acceptable rates of mortality and morbidity. Most patients prior to surgery (about 80%) suffered from pain including acute exacerbation, recurrent episodes, chronic pain, and intractable pain. Notably, worsening imaging findings over time were seen in 110 (86%) patients. These findings suggest that disease progression with deterioration of both exocrine and endocrine function might be occurring, requiring surgical intervention. The median period from diagnosis of CP to surgery was 27 months. Previous studies had reported that the median period from diagnosis of CP to surgery was 40–64 months.[11,15] This difference may be due to the fact that in surgical intervention at our facility is likely to be undertaken earlier than in previous studies. Before surgery, 83 (57%) patients had undergone endoscopic intervention. Previous studies showed that early surgical intervention resulted in superior pain relief, less de novo exocrine insufficiency, and less need for reintervention.[5-8] Yang et al. reported that the optimal cutoff time for the duration of preoperative CP was 26.5 months.[7] More recently, a multicenter RCT comparing early surgery and an optimized step-up approach has been reported.[16] According to the results of that trial, over 18 months of follow-up, the early surgery group had a lower Izbicki pain score than patients in the group randomized to receive the endoscopy-first approach (37 vs 49; between-group difference, −12 points [95% confidence interval, −22 to −2]; $P = .02$).

Although several different surgical procedures have been established, our own selection of approaches is simple and consistent. The presence of dilation of the MPD is taken as an indication for the drainage procedure, whereas dilation of the MPD without lesions in the head of the pancreas is an indication for LPJ. On the other hand, dilation of the MPD and an inflammatory mass or pancreatic stone in the head of the pancreas is an indication for the Frey operation. Extended drainage operations, such as the Beger,[17] and Berne techniques,[18] were established to treat CP patients with enlarged pancreatic masses due to inflammation. These procedures represent a combination of limited pancreatic head resection together with drainage. However, Japanese patients with CP rarely present with such large pancreatic head masses.[10,19] Previous RCTs and systematic reviews showed that the Frey operation was associated with less morbidity than the Beger procedure and delivered similar levels of pain relief, increase in quality of life, and pancreatic function.[20-22] Thus, Frey operation is our standard operation in patients with pancreatic head lesions and MPD dilation. If there is no dilation of the MPD, pancreatic resection is performed according to the location of the pancreatic lesion. This simple strategy is adopted in the Japanese Clinical Practice Guidelines for CP 2015.[9]

Differences in short- and long-term outcomes between drainage procedures and pancreatic resection for CP are incompletely understood. In the comparison of drainage procedure and pancreatic resection reported here, the occurrence of severe morbidity was significantly lower in patients receiving a drainage procedure than pancreatic resection (2% vs 13%, $P = .019$), even though achievement of complete pain relief was equivalent for both procedures (62% vs 60%, $P = .748$). Our results are in accordance with the study by Izbicki et al.[23] who performed an RCT comparing the Frey operation with pylorus-preserving

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pancreatoduodenectomy. The Frey operation resulted in significantly lower rates of morbidity (19% vs 53%, $P < .05$) and a better quality of life with equal pain relief (90% vs 87%). The present study showed that new-onset of diabetes was significantly less frequent in patients with the drainage procedure than the pancreatic resection (25% vs 60%, $P = .017$). A recent systematic review showed that the type of pancreatic resection, a smaller remnant pancreatic volume and a higher preoperative hemoglobin A1c were risk factors for new-onset diabetes after pancreatectomy.[24] Moreover, CP was associated with a significantly higher risk of new-onset diabetes in patients undergoing pancreatectomy.[25,26] Therefore, attempts should be made to utilize a drainage procedure, not pancreatic resection, to preserve parenchymal integrity where possible.

In the present study, complete pain relief and partial pain relief was achieved in 58 (62%) and 34 (62%) patients, respectively, over a median follow-up period of 37 months. However, it should be noted that the readmission rate was quite high, at 47%. The main reasons for readmission were deterioration of glucose tolerance, acute exacerbation or abdominal pain, and acute cholangitis and/or biliary stenosis. Moreover, reoperation was required in 11 patients (11%). These findings were probably due to underlying disease with pancreatic dysfunction, and the unchanged drinking habits of some patients. Fisher et al[27] reported a high 90-day readmission rate of 42.3% in patients undergoing duodenum-preserving pancreas head resection or pancreatoduodenectomy for CP.Their results showed that the most common reasons for readmission were pain control, infectious complications, and recurrent pancreatitis.

Postoperative nutritional status is important, as well as assessing pain relief, because it also affects the quality of life in CP patients. We looked at body weight, serum albumin levels, and serum total cholesterol levels before and surgery as markers of nutritional status. None of these three factors was improved significantly after surgery, but rather well-maintained. Nutritional status is multifactorial, including the influence of preoperative status, exocrine and endocrine insufficiency, alcohol abuse, pain relief, and patient education. Further research will be needed to devise means to improve nutritional status after surgery.

The present study has some limitations. It was a single-center retrospective study with a relatively small number of patients. Although patient selection and indications for surgery were decided in multidisciplinary meetings, selection bias may still have been present. For the evaluation of long-term results, 31 patients were lost to follow-up and pain relief was not evaluated using measures such as visual analogue scales or Izbicki pain score. However, this is the first report from Japan to evaluate the results of surgical treatment with consistent selection of the procedure. Because the Japanese Clinical Practice Guidelines propose indications and selection approach for surgical procedure,[9] a prospective, multicenter study will be required to show the safety and efficacy of surgical treatment for CP in Japan. It was difficult to evaluate exocrine dysfunction because only the BT-PABA test is available in Japan, and not often used in clinical practice. Insurance coverage of fecal elastase measurement, which is a more convenient, effective, and reliable test, is greatly anticipated.[28]

In conclusion, surgical treatment for painful chronic pancreatitis can be safe and effective. Understanding the underlying pathology is important for selecting the most appropriate surgical procedure, which should guarantee pain relief and preserve a maximum of pancreatic function.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

ETHICAL APPROVAL

The study was approved by Ethics Review Committee of Kindai University Faculty of Medicine (approval number, 29-006).

ORCID

Ippei Matsumoto https://orcid.org/0000-0003-3965-3693

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