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Surgical management of chronic pancreatitis: A narrative review

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Abstract

Chronic pancreatitis is a severe disabling disease with persistent pain as the most prominent symptom often leading to significant quality of life (QoL) reduction. Current international guidelines propagate a step-up approach in which surgery should only be considered as a last resort in patients with failure of both medical and endoscopic interventions. Accumulating evidence, however, suggests that surgery is superior to endoscopic therapy and that early surgical intervention is beneficial in terms of pain relief, pancreatic function and QoL. Several surgical procedures are available with low morbidity and mortality rates, providing excellent long-term results. The purpose of this review was to present an overview of the surgical treatment options for chronic pancreatitis with a focus on the timing of surgery.

KEYWORDS
complications, duodenum-preserving pancreatic head resection, endoscopic interventions, endoscopic therapy, pain, pancreatic function, pancreatoduodenectomy, quality of life, surgical treatment, timing of surgery

INTRODUCTION

Chronic pancreatitis (CP) is a disease characterized by long-standing and progressive inflammation of the pancreas, eventually resulting in replacement of normal parenchyma with fibrotic scarring. This destruction of the normal pancreatic architecture will ultimately lead to an impairment of the glandular function and cause exocrine and endocrine insufficiency resulting in diabetes and maldigestion.[1] Common complications associated with CP are pancreatic and/or biliary duct strictures, pancreaticolithiasis, pancreatic fistulas and pseudocysts, which ultimately lead to recurrent or persistent pain.[2]

The annual incidence of CP is increasing and has been reported to be between 4/100,000 and 13/100,000. Consequently, the prevalence of CP ranges between 120 and 140 cases per 100,000, assuming a survival of 15–20 years.[3] Heavy alcohol consumption is the most common risk factor in western countries, contributing to 70%–80% of all cases.[4] Additional risk factors can be summarized in the TIGAR-O classification system, which comprises six aetiologic groups: toxic-metabolic, idiopathic, genetic, autoimmune, recurrent acute pancreatitis and obstructive groups.[5] Patients with CP have a 15-fold increased risk of developing pancreatic cancer during their lifetime.[6]

Abdominal pain is the most debilitating symptom of CP. Development of pain is experienced in at least 85% of all patients at some point during the course of the disease.[7] The origin of the abdominal pain is traditionally suggested to be due to the structural anatomical changes encompassing increased pancreatic intraductal and intra-

parenchymatous pressure as well as symptomatic pseudocysts.[4] An increasingly discussed hypothesis is that pancreatic neuropathy due to neuronal hypertrophy and neuritis causing altered nociception with peripheral and central sensitization of the nervous system may contribute to the pathogenesis of pain.[8] The phenomenon of central sensitization may explain the persistent pain experienced by some patients despite undergoing total pancreatectomy (TP) in which the root cause of pain should be removed in its entirety.[9] It is also suggested that the inflammatory mass in the head of the pancreas is the 'pacemaker' of pain and can only be addressed surgically.[10]

Management of CP is complex and should be undertaken in a multidisciplinary approach including surgeons, gastroenterologists, radiologists and pain management physicians.[11] In current clinical practice conservative management is employed as a first-line approach before considering more invasive therapy such as endoscopic intervention or surgery.[2] This approach is being questioned by increasing evidence showing that early surgery should be favoured over surgery at a more advanced stage of the disease.[2,12] At present, there are various surgical techniques available for the treatment of CP and multiple randomized trials comparing the procedures have been conducted. Although, each procedure has its significance and applicability, lack of a uniform operative management exists between centres and the procedure of choice differs.[13] It is not fully established whether the classical pancreatoduodenectomy (PD) or the newer parenchyma-sparing duodenum-preserving pancreatic head resection (DPPHR) should be the preferred surgical option in the management of CP with an inflammatory head mass. In this article, we aimed to give an overview of the different surgical procedures currently available for CP, with an emphasis on comparing the outcomes of these procedures and discussing the optimal timing of surgery. For the purpose of this review, we included the most recent highest-evidence literature, with a focus on randomized controlled trials (RCT), on adult patients with CP undergoing surgery (Table 2).

STEP-UP APPROACH AND SURGICAL INDICATIONS

Currently, the first line-treatment for CP is conservative therapy that is, medical analgesics in accordance with the 'pain relief ladder' provided by the World Health Organization.[14] In addition, pancreatic enzyme replacement therapy to combat malnutrition-related problems and lifestyle changes such as cessation of alcohol and smoking are all part of the initial management.[15] Notably, opioids fail to achieve pain relief in up to 50% of patients with chronic pain[2] and adverse effects such as abuse potential, opioid-induced hyperalgesia and risk of painful narcotic bowel syndrome with prolonged usage should be taken into consideration.[16] Hence, more invasive measures (endoscopic—and/or surgical intervention) may be more effective in ameliorating pain compared to the conservative approach.[17]

Endoscopic therapy (ET), such as endoscopic retrograde cholangiopancreatography (ERCP), is indicated in patients with an obstructive form of CP due to stones or strictures in the main pancreatic duct (MPD). ET can be effective in alleviating pain by decompressing the pancreatic duct through stone removal, dilatation, and stenting of strictures.[2,18] Lesions of the pancreatic duct are found in nearly half of the patients[18] and successful ET is defined as patients remaining pain-free during the year following stent removal.[19] A multicenter study conducted by Rösch et al.[20] of 1018 CP patients undergoing ET with a long-term follow up of 2–12 years (mean 4.9 years) found that ET offered pain relief in 65% of cases while 25% had to undergo surgery. The HaPanEU/UEG evidence-based guidelines on the management of CP published in 2017,[2] recommend ET for uncomplicated CP and dilated MPD after failed medical therapy. If ET fails to achieve any pain relief at 6–8 weeks, a new discussion in a multidisciplinary team meeting is warranted and surgical options should be considered.

Extracorporeal shock wave lithotripsy (ESWL), which is often combined with ET, is the procedure of choice for larger obstructive radiopaque stones (≥5 mm) in MPD.[2] An observational study on 146 patients with painful obstructive CP found that ESWL was successful in 76% of patients after 6 months follow-up, which meant complete resolution of pain, no analgesic treatment and no surgical treatment.[21] EUS-guided coeliac plexus block, used for pain control for pancreatic cancer pain, is effective only for 50% of CP patients and only 10% remain pain free after 24 weeks.[22]

When the abovementioned strategies fail, surgery is considered. The most common indication for surgery is intractable pain. Other indications for surgery include a suspicion of neoplasm as well as local complications of adjacent organs such as duodenal or common bile duct stenosis.[11] The main goals of surgical intervention are achieving long-term pain relief as well as treating CP-associated complication, improving of quality of life (QoL) and achieving maximum preservation of pancreatic function.[11] It is estimated that 40%–75% of all patients will require some form of surgical intervention during the course of the disease.[11] An experienced high volume pancreatic centre is recommended for the surgical treatment of CP.[2] At present, surgical intervention for CP results in excellent long-term pain relief ranging from 70% to 90% as well as low in-hospital mortality rate <1%; however, the non-negligible post-operative morbidity (up to 40%) calls for careful patient selection in a multidisciplinary setting.[23,24] The incidence of pancreatic cancer is also lower in patients who undergo surgery compared to those receiving a non-surgical treatment.[11]

SURGICAL THERAPY

The surgical options for CP are divided into three categories: drainage, resection and a combination of drainage and resection procedures, DPPHR. Generally, the type of surgical therapy depends largely on the morphological changes of the pancreas (e.g., inflammatory mass in the pancreatic head/tail or dilated MPD) and complications in adjacent organs (e.g., duodenal and biliary stenosis).[11] However, differences in surgical practice exist and the procedure of choice for an enlarged head of the pancreas is still a point of

TABLE 1 Indications for different surgical procedures in the treatment of CP.

Surgical procedures	Indications
Drainage	
Partington-Rochelle	Dilated MPD and absence of an inflammatory mass in the pancreatic head
Pancreatic resections	
PD	Presence of an inflammatory mass or suspicion of malignancy in the pancreatic head. Local complications of CP such as duodenal or common bile duct stenosis
DP	Isolated inflammation, symptomatic pseudocysts or suspected malignancy in the pancreatic body or tail
TP/TP-IAT	Reserved as end-of-the-line treatment when previous surgical interventions have failed. Useful in the setting of intractable pain and small MPD (e.g., small duct disease). It is occasionally used as a prophylactic measure for pancreatic cancer in patients with hereditary CP
DPPHR	
Beger procedure	Inflammatory mass in the pancreatic head with MPD dilatation and low suspicion of malignancy
Frey procedure	Similar to the Beger procedure, with the addition that this modification can be performed even in the presence of portal hypertension or thrombosis
Berne procedure	Similar to the Frey procedure

Abbreviations: CP, chronic pancreatitis; DP, distal pancreatectomy; DPPHR, duodenum-preserving pancreatic head resection; MPD, main pancreatic duct; PD, pancreatoduodenectomy; TP, total pancreatectomy; TP-IAT, total pancreatectomy with islet autotransplantation.

contention, which will be further discussed below. The various surgical procedures and their indications are presented in Table 1.

Drainage procedures

Partington-Rochelle

Partington-Rochelle, also known as lateral pancreaticojejunostomy, is a purely surgical drainage procedure and is the favoured procedure recommended for patients with a dilated MPD, of 5 mm or more, and no inflammatory mass in the pancreatic head (Figure 1a).[2] In this procedure the MPD is cut open from the tail to the head and a Roux-en-Y loop of jejunum is anastomosed side-to-side along the length of the pancreas, creating a pancreaticojejunostomy. This technique was first described by Partington and Rochelle in 1960[26] and is an optimization and modification of the Puestow method in which, in addition to the lateral pancreaticojejunostomy, splenectomy and distal pancreatectomy (DP) are performed.[27] An advantage of Partington-Rochelle is the potential for preservation of the pancreatic parenchyma by mitigating the risk of hastening exocrine and endocrine insufficiency postoperatively.[28] This procedure is safe and technically easier to perform than pancreatic head resections. It is associated with low morbidity and 30-day postoperative mortality <5%.[29] Overall, short-term pain relief is reported to occur in 50%–90% of patients; however, adequate pain relief diminishes over time and a up to 30% of patients develop recurrent pain with a significant number requiring reoperation.[29] The principal cause of long-term pain relapse is the failure of this procedure to address the pancreatic head which is hypothesized pacemaker in CP.[30] Another disadvantage is that this procedure does not allow for histological verification of the dignity of the mass in the head of the pancreas.

Pancreatic resections

Pancreatoduodenectomy

In about one-third of the CP patients, the disease is primarily located in the head of the pancreas,[23] an issue addressed by PD also known as the Whipple procedure (introduced by Kausch-Whipple)[31] and the modified version, pylorus preserving pancreatoduodenectomy (PPPD) introduced by Traverso and Longmire in 1978 (Figure 1b).[32] These procedures are still the treatment of choice when there is a suspicion of malignancy in the pancreatic head in CP patients.[33] Other indications are duodenal obstruction or common bile duct stenosis caused by an enlargement (diameter of >4 cm) of the pancreatic head secondary to an inflammatory mass.[11] In the Whipple procedure, the head of the pancreas is resected along with the duodenum, the gallbladder, bile duct and distal part of the stomach. Afterwards, three jejunal anastomoses are made, resulting in pancreatico-, hepatico- and gastrojejunostomy.[31] The Whipple procedure and PPPD are comparable in terms of long-term pain relief and other surgical/non-surgical endpoints.[34] PDis safe and effective providing pain relief in 67%–90% of cases after a follow-up of 1–5 years, and with an in-hospital mortality less than 1%.[23,35] However, both procedures have been shown to carry a significant rate of postoperative morbidity (ranging from 40% to 51%) as well as significant loss of endocrine and exocrine pancreatic function.[23,24]

TABLE 2 Randomized controlled trials comparing different surgical approaches for CP.

Reference	Year	Procedures	Patients (*n*)	Mean follow-up (months)	Perioperative mortality (%)	Postoperative morbidity (%)	Pain relief (%)	QoL[a] (%)
Büchler et al.[52]	1995	Beger	20	6	0	15	**75**	NA
		PPPD	20		0	20	**40**	NA
Izbicki et al.[43]	1995	Frey	22	18	0	**9**	94	67
		Beger	20		0	**20**	95	67
Izbicki et al.[44]	1997	Frey	36	30[b]	0	**22**	93	67
		Beger	38		0	**32**	95	67
Izbicki et al.[53]	1998	Frey	31	24[b]	3	**19**	94	**71**
		PPPD	30		0	**53**	95	**43**
Farkas et al.[23]	2006	Berne	20	12	0	**0**	85	NA
		PPPD	20		0	**40**	90	NA
Köninger et al.[49]	2008	Berne	33	24	0	21	NA	71
		Beger	32		0	20	NA	66
Keck et al.[35]	2012	DPPHR[c]	42	66	0	33	67	34
		PPPD	43		0	30	67	34
Diener et al.[54]	2017	DPPHR[d]	125	24	4[e]	64	69	73
		PD	125		2	52	65	75

Note: Bold values denote statistical significance ($p < 0.05$).

Abbreviations: DPPHR, duodenum-preserving pancreatic head resection; NA, not available; PD, pancreatoduodenectomy; PPPD, pylorus preserving pancreatoduodenectomy; QoL, quality of life.

[a]Improvement in QoL.

[b]Median follow-up (months).

[c]DPPHR procedures including Beger and Frey.

[d]DPPHR procedures including Beger, Frey and Berne.

[e]Mortality within 6 months.

Distal pancreatectomy

DP is reserved for patients with complications confined to the body or tail of the pancreas. Such complications, caused by obstruction of the MPD, include segmental inflammation in the pancreatic tail and symptomatic pseudocysts.[36] DP is also appropriate when there is a suspicion of malignancy in patients with CP.[36] This procedure yields good results with long-term pain relief ranging from 50% to 81% and low perioperative mortality. Nevertheless, a recent study by Siegel et al.[37] on 138 CP patients undergoing DP reported a high morbidity rate of 44% with a high frequency of postoperative pancreatic fistula. Following DP, nearly half of the patients develop some element of pancreatic insufficiency.[36]

Total pancreatectomy

TP has two main indications in the treatment of CP. Firstly, as a salvage procedure in refractory CP in which endoscopic -and surgical interventions have either failed to offer pain relief or resulted in complications.[38] Secondly, TP is indicated in patients with concomitant intractable pain and absence of MPD dilatation, known as small duct disease.[2] Additionally, patients with hereditary pancreatitis have a considerable risk of developing pancreatic cancer and TP is indicated as a prophylactic procedure on such occasions.[11] There is a relatively high threshold to perform TP in isolation as it would result in complete insulin deficiency with a brittle form of diabetes with frequent and unpredictable episodes of hypoglycaemia that is often difficult to manage.[39] Thus, a combination procedure of TP with an intraportal islet autotransplant (TP-IAT) was designed to preserve beta islet mass and mitigate postoperative diabetic complications.[39] In this procedure, the entire pancreas is removed along with the duodenum, distal bile duct, and spleen followed by gastrointestinal reconstructions. Afterwards, the islet cells are extracted from the pancreas and reimplanted into the patient's portal vein.[39]

The first TP-IAT for painful CP was performed in 1977 at the University of Minnesota Medical School and a total of 581 TP-IATs were performed at this centre from 1977 to 2014. Pain relief was reported in 92.6% of cases at 1-year follow-up and only four in-hospital deaths occurred within 30 days during the entire study period.[9] TP-IAT also provides excellent long-term results with 90% pain relief at 15 years follow-up.[40] This surgical strategy has been

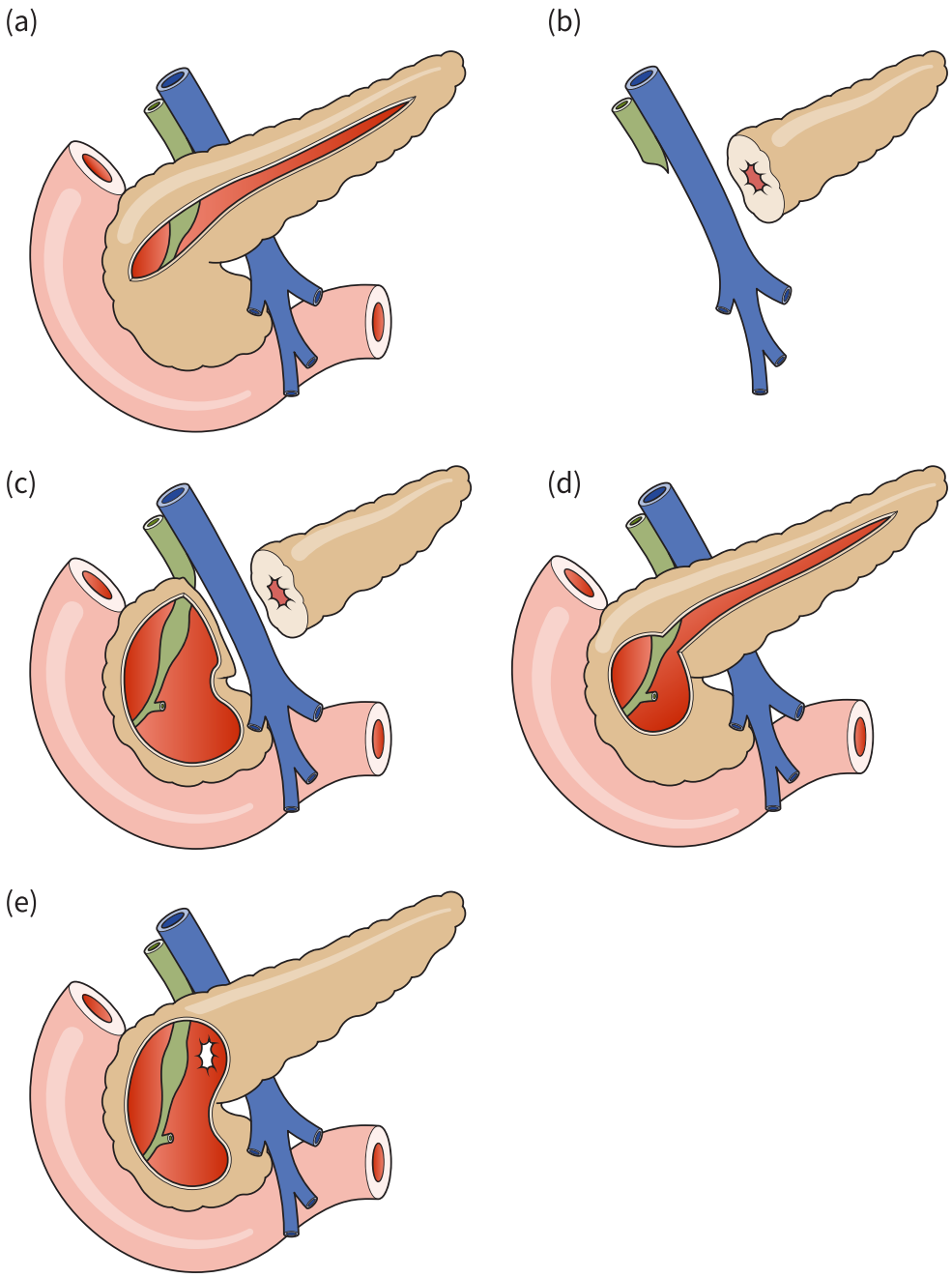

FIGURE 1 Schematic view of different surgical procedures for chronic pancreatitis. (a) Drainage procedure (Partington-Rochelle or modified Puestow). (b) Pancreatoduodenectomy (Kausch-Whipple or Pylorus-preserving) (c) Duodenum-preserving pancreatic head resection, DPPHR (Beger procedure). (d) DPPHR modification (Frey procedure). (e) DPPHR modification (Berne procedure). *Source*: Mihaljevic et al. (2008, pp. 167–181), reproduced with permission.[25]

shown to be even more effective in the paediatric population and patients with hereditary forms of CP (who run greater risk of developing pancreatic ductal adenocarcinoma).[9,39] Nevertheless, perioperative morbidity is still relatively high (up to 41%)[39] and even in the setting of high islet yield (≥200,000 islets) TP-IAT is associated with significantly higher endocrine insufficiency rates than limited surgery within the first 2–10 years, with 13% maintaining insulin independence at 10 years.[40,41] Careful patient selection remains paramount for TP-IAT.[39]

Combined drainage and resection

Beger procedure

In 1972, Hans Beger performed the first DPPHR, which was the first resection procedure specifically designed to manage CP (Figure 1c).[42] The Beger procedure, was developed as an alternative surgical technique to PD in patients with an inflammatory mass in the pancreatic head and concomitant MPD dilatation.[30]

This procedure is performed by a subtotal resection of the pancreatic head leaving a small remnant of pancreatic tissue to the adjacent duodenum, followed by a transection of the gland above the portal and superior mesenteric vein. Finally, a jejunal Roux-en-Y loop is then used to perform a two-sided pancreaticojejunostomy to the transected pancreatic neck and to the head remnant.[30] In contrast to the PD procedure, DPPHR offers the advantage of preserving the extrahepatic biliary tree, the stomach and the duodenum, with the preservation of the latter resulting in preserved endocrine function early after surgery due to its role in the hormonal axis and postprandial regulation of the digestive process.[30] Beger et al.[30] revealed a hospital mortality rate of 0.8% during their 26-year experience of this procedure in 504 patients with CP. After an observation period of up to 14 years, 91.3% of the patients were considered pain-free, endocrine function was improved in 11% and QoL was significantly improved. The Beger procedure is associated with acceptable postoperative morbidity ranging from 20% to 32%.[43,44]

Frey procedure

The Frey procedure was first described by Frey and Smith in 1987 (Figure 1d).[45] This method is a modification of the DPPHR (according to Beger), and combines a coring out of the pancreatic head tissue, leaving a small remnant along the duodenum wall, with a longitudinal incision of the MPD. Finally, a lateral pancreaticojejunostomy is performed draining the cored-out head and the opened duct using a Roux-en-Y jejunal limb.[46] As such, the indications for this procedure include dilated MPD in the setting of an inflammatory mass in the head of the pancreas that is not amenable to drainage with other drainage techniques such as Partington-Rochelle.[11] The Frey procedure is seen as technically less demanding than the Beger procedure since no transection of the pancreatic neck is necessary, which reduces the risk of haemorrhagic complications in the presence of portal hypertension. The risk of anastomotic leakage is also reduced in the Frey technique by the fact that only a single jejunal anastomosis is required compared to the Beger procedure, which requires two anastomoses.

The Frey procedure can be performed with a low perioperative mortality (<1%) and morbidity (28%–31%). Long-term pain control is achieved in 91%–93% of patients and the development of new-onset diabetes after surgery ranges from 31% to 37%, which appears to be less significant compared to other resection procedures.[46,47] For patients with painful CP and a dilated MPD and documented normal sized pancreatic head, Partington-Rochelle and the Frey procedure seem to provide equivalent pain control and due to the lack of direct comparison, no preference of either procedure can be made.[11] A disadvantage of the Frey procedure is that the narrow rim of pancreatic tissue left on the duodenum and adjacent portal and mesenteric veins could potentially contain active disease.

Berne procedure

The Berne procedure is a further modification of the previously introduced variations of DPPHR (Beger and Frey), and was described by Gloor et al.[48] at the University of Bern (Figure 1e). This procedure solely focuses on the head of the pancreas and involves the excision of the enlarged pancreatic head, almost in its entirety, leaving behind only a thin bridge of pancreatic tissue, and an opened common bile and pancreatic duct. Finally, a Roux-en-Y end to side pancreaticojejunostomy is performed to drain the resulting cavity.[48] The rationale behind the Berne modification is that it combines the advantages of the Beger and Frey procedure by focussing solely on the head of the pancreas, consistent with the principle that this area is the pacemaker for the inflammatory process in CP. Subsequently, by avoiding the transection of the pancreas above the portal vein (Beger procedure) and the ductomy with longitudinal pancreaticojejunostomy (Frey procedure), the operative trauma can be minimized.[48] The Berne variation carries an acceptable rate of postoperative morbidity and mortality of 21% and 1%, respectively.[49] At 10-year follow-up, 55% of the patients experienced sustained pain-relief, and 68% reported improved QoL.[50]

Comparison of the different surgical procedures

DPPHR versus PD

There is currently no consensus on the surgical procedure of choice for patients with CP and enlargement of the pancreatic head. The choice of procedure seems to reflect institutional or regional preferences, highlighted by the fact that most American surgeons prefer PD whereas DPPHR is the preferred surgical technique in Germany.[51] Several RCTs have been conducted comparing different variants of DPPHR with PD,[23,52–54] which are summarized in Table 2. Büchler et al.[52] concluded in their trial that the Beger procedure was superior to PPPD regarding pain relief (75% vs. 40%, $p < 0.05$), postoperative QoL, endocrine function (glucose tolerance and insulin secretion) and weight gain after 6 months. However, after a long-term follow-up of up to 14 years, the initial advantages of the Beger procedure were no longer present.[55] The authors speculated that this might be due to the natural history of the disease with a burn out of the gland which is inevitable and can only be delayed by the DPPHR. Similarly, Izbicki et al.[53] randomized 74 CP patients to receive either DPPHR (Frey) or PPPD. Again, the DPPHR compared favourably with PPPD in terms of short-term outcomes including postoperative morbidity (19% vs. 53%, $p < 0.05$), improved QoL (71% vs. 43%, $p < 0.01$), better preservation of pancreatic function and professional rehabilitation with 68% of patients in the DPPHR group and 43% in the PPPD group ($p < 0.05$) returning to regular daily work. Again, long-term follow-up (median of 7 years) revealed comparable outcomes between both groups regarding pain control, QoL

and pancreatic function.[56] Farkas et al.[23] randomized 40 patients to the Berne modification of DPPHR or the PPPD group. At the 1-year follow-up examination, complete pain relief did not differ between the groups (85% for DPPHR vs. 90% in the PPPD group). However, the Berne procedure was associated with significantly shorter operating time, duration of hospital stay, lower morbidity and increased weight gain in comparison with the PPPD group.

The most recent RCT (ChroPac trial) on this topic was performed in a multicenter setting and included 226 patients with CP (115 in the DPPHR [Beger, Frey and Berne] group and 111 in the PD group).[54] There was no difference between the two groups with respect to short-and long-term (2 years follow-up) outcomes; thus, the superiority of DPPHR was not confirmed. Nevertheless, Zhao et al.[57] demonstrated in their updated systematic review and meta-analysis of 7 RCTs significantly improved short-term outcomes (including operative times, blood transfusions, hospital stays and postoperative morbidity) as well as intermediate and long-term outcomes (including QoL, weight gain and occupational rehabilitation) for CP patients who underwent DPPHR compared with PD. The authors concluded that the DPPHR procedure is a more favourable surgical option.

Frey versus Beger versus Berne

The results of RCTs comparing the different modifications of DPPHR with each other are shown in Table 2. Izbicki et al.[43] conducted the first prospective randomized trial comparing the most common techniques of DPPHR (Beger and Frey), 42 patients were randomly allocated to either Beger procedure ($n = 20$) or Frey procedure ($n = 22$) with a mean follow-up of 1.5 years. Both procedures proved to be equally effective and comparable with regard to complete pain relief (95% vs. 89%, for Beger vs. Frey, respectively), QoL and preservation of pancreatic function. Mortality rate was zero for both procedures; however, postoperative morbidity was significantly lower in the Frey group (9% vs. 20%, $p < 0.05$). In the 16-year follow-up reported by Bachmann and colleagues,[58] no significant differences were detected between the two treatment groups in terms of pain control, mortality, rates of endocrine and exocrine insufficiency, or other somatic parameters.

Only 1 RCT has compared the Berne variation of DPPHR with the original Beger technique.[49] In the short-term follow-up, after 24 months, both techniques were equally effective regarding QoL. Largely due to the simpler design, the Berne modification provided a significant reduction in operation time (323 vs. 369 min, $p = 0.02$) and shorter duration of hospital stay (11 vs. 15 days, $p = 0.015$). However, in the long-term (10-year follow-up)[50] the Berne and Beger procedure yielded similar results regarding complete pain relief (55% vs. 56%, $p = 0.94$), improved QoL (68% vs. 89%, $p = 0.15$), exocrine insufficiency (68% vs. 83%, $p = 0.46$) and new-onset diabetes mellitus since the index operation (55% vs. 33%, $p = 0.31$). A systematic review and meta-analysis,[59] which included 2 RCTs, assessing the outcomes in patients with CP undergoing various forms of DPPHR, showed that all procedures were equally effective in the management of painful CP. The authors concluded that the choice of procedure should be determined by the presence of secondary complications of pancreatitis and intra-operative findings.

TIMING OF SURGERY

The timing of surgical intervention in the management of CP remains a dilemma.[60,61] Currently, surgical intervention is kept as a last resort when medical treatment and multiple endoscopic interventions have failed.[11] Several observational studies found that daily opioid use and high numbers of endoscopic attempts prior to surgery are associated with suboptimal outcomes with failure to achieve adequate long-term pain relief and improved QoL in patients with CP.[9,24] It is suggested that the postponement of surgical intervention results in prolonged periods of pain and a more advanced disease stage, with the potential to produce central sensitization and neuropathic pain, which is very difficult to treat.[11] Ali et al.[60] concluded in their cross-sectional study of 266 patients with painful CP that early surgery (within 3 years) of symptom onset was correlated with better QoL, lower rates of endocrine insufficiency and more pain relief. Moreover, the author found that surgery prior to opioid usage and multiple endoscopic treatments (five or fewer) was associated with higher rates of pain relief in a mean follow-up of 62 months. These findings were corroborated by a different study suggesting that early surgical intervention of 26.5 months or less of CP diagnosis was associated with pain control and preservation of pancreatic function.[62]

Cahen et al.[61] performed a randomized trial comparing endoscopic ($n = 19$) and surgical drainage (Partington-Rochelle) ($n = 20$) in patients with CP and pancreatic-duct obstruction. The study was preterminated by the safety committee after an unscheduled interim analysis on the basis of significantly lower Izbicki pain scores, after a median of 2 years follow-up, in the surgical group compared to those who were treated endoscopically (25 vs. 51, $p < 0.001$). Pain relief was achieved in 75% of patients assigned to surgical drainage compared with 32% receiving endoscopic treatment ($p = 0.007$). Finally, the surgical patients also required fewer procedures (a median of 3 vs. 8, $p < 0.001$), implying that surgical drainage was associated with more effective decompression. After a long-term follow-up period of 7-year, the surgically treated group still experienced more pain relief (80% vs. 38%, $p = 0.042$), which was mostly accomplished in a single operation, whereas the endoscopically treated group had to undergo multiple procedures.[63] Based on these outcomes (short-and long-term), the authors suggested that surgery is superior to endoscopic treatment in patients with advanced painful CP. In light of this accumulating evidence concerning the timing of surgery for CP, Issa et al.[12] conducted the ESCAPE trial in 2020. In this multicenter trial, 88 patients with CP were randomly allocated to either the early surgery group or the endoscopy-first approach (undergoing the current step-up practise with medical treatment, endoscopy and surgery if needed). In contrast to the previously mentioned trial, DPPHR and resectional procedures were included in this study as well as patients with an enlarged pancreatic head. At the

end of 18 months follow-up period, the group randomized to early surgery had a lower reported Izbicki pain score compared with the group receiving the endoscopy first-approach (37 vs. 49, $p = 0.02$). The early surgery group also required fewer number of interventions (median 1 vs. 3, $p < 0.001$). Interestingly, one-third of the patients from the endoscopic-first approach were referred to undergo surgery during the study-period and the medical pain management as a first-step treatment in this group failed in nearly all patients. Simply put, these studies are making a good argument against the current step-up approach for the treatment of CP and advocating earlier surgical intervention. Despite this, clinical practice has not yet changed since ET is still preceding surgery in many cases.[12]

MINIMAL INVASIVE SURGERY

Minimally invasive surgical techniques are widely used for various surgical disorders, and although nearly all of the previously described open surgical procedures have been performed in a minimally invasive fashion, its application in CP is disproportionally low.[64] The primary reason for the limited adoption is thought to be the inherent technical difficulties and risk of intraoperative haemorrhage due to the distortion of the anatomy of the vessels caused by the pancreatic inflammation and fibrosis.[64] Nonetheless, multiple case series and some observational studies have demonstrated the feasibility and favourable short-term outcomes after the laparoscopic Partington-Rochelle procedure and the Frey modification.[65,66] Senthilnathan et al.[66] reported their results on 54 patients with CP undergoing Partington-Rochelle ($n = 39$) and Frey procedure ($n = 15$). Both procedures achieved pain relief in 91%, 89% and 88% after 1, 3 and 5 years of follow-up, respectively. Three patients were converted to open surgery because of non-identification of the duct, which is seen as the most critical step in the minimally invasive approach in these surgical procedures. Both procedures were equally effective and safe, with results comparable to those for open surgery. The advent of robotic-assisted surgery for all general surgical procedures has increased the use and demand for minimally invasive procedures. More importantly, robotic surgery in patients with CP is gaining momentum and has shown promising results in terms of safety and feasibility.[64] However, definite conclusions regarding minimally invasive surgical treatment are not possible due to the limited quality of available evidence. It is likely that minimally invasive surgery for CP will gain more traction in the coming years as more pancreatic surgeons become comfortable with these techniques.

LIMITATIONS AND FUTURE ASPECTS

There are some limitations that should be considered when interpreting the reviewed studies. First, the heterogeneity in the reported assessment of pain relief, QoL and the variability in follow-up durations are notable limitations in the current literature. Second, the excellent functional results provided by DPPHR in the European setting may not be generalized to outcomes at centres in countries with less expertise such as the United States, where only a small number of senior surgeons practice this procedure.[67]

The optimal timing of surgery remains a clinical management dilemma and further research is needed. A new prospective Dutch study which is currently taking place around Europe titled 'European practice and outcome of Surgery for Chronic Pancreatitis (ESCOPA): A Prospective, International Modified Snapshot Study', might shed some additional light on the importance of early surgery for CP. Furthermore, randomized studies comparing TP-IAT with other surgical treatments are lacking and need to be assessed in future clinical trials to ascertain which surgical approach results in more favourable short-and long-term outcomes. Future studies should also aim to evaluate and compare laparoscopic and robotic procedures with open surgical techniques in the treatment of CP.

CONCLUSION

Surgical management of CP is indicated in patients with intractable abdominal pain and pancreatitis-related complications of adjacent organs. Around 50% of patients will require surgical intervention during their lifetime. Current surgical armamentarium consists of drainage, resection and hybrid surgical procedures (DPPHR). These procedures are safe and effective in providing long-term pain relief and improved QoL. Surgery is superior to endoscopic treatment in patients with advanced CP not only based on short-term outcomes but also in the long-term. In cases of less extensive disease, ET may still be a valuable option due to its less invasive approach. Medical pain management should only be used as a short bridging period to interventional therapy. Correct patient selection in a multidisciplinary setting with early referral to surgery is of paramount importance to a successful outcome. In patients with an inflammatory mass in the pancreatic head, known to act as the 'pacemaker' of pain, both DPPHR and PD are excellent treatment options with comparable long-term pain relief and QoL. However, based on the available literature, DPPHR offers superior short-term outcomes and should be considered the procedure of choice in centres with experience. The different modifications of DPPHR provide equivalent outcomes.

CONFLICT OF INTEREST STATEMENT

We declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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