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The role of surgery in chronic pancreatitis

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Summary

Background Chronic pancreatitis (CP) remains a complex condition resulting in significant morbidity and suffering in patients, often over a long period of time. Treatment is mostly centred on a conservative approach, with a variety of more aggressive options being trialled over the years utilising numerous endoscopic and surgical techniques.

Methods This review provides an overview of current treatment options for CP, the literature search was performed via PubMed. Personal experiences from the authors on how to approach the disease from the surgeon's perspective are added. The outline includes pathophysiologic aspects, classifications and patient-centred surgical approaches.

Results There has not been a standardized treatment for CP so far as clinical and radiological appearance of the disease have a wide range due to great heterogeneity of this complex disease; therefore, level 1 evidence for treatment of CP remains low. More recently, different approaches to surgical management have been trialled. With personalized surgery, long-term pain relief is achievable in up to 90% with low morbidity. Autologous islet cell transplantation is a feasible option in selected patients to avoid endocrine insufficiency.

Conclusion A tailored approach to CP patients is mandatory in this heterogeneous disease. Surgery provides good outcomes especially as prophylaxis for

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and treatment of chronic pain. A multidisciplinary approach is mandatory, including physicians, pancreatic surgeons, endoscopists, dieticians and radiologists.

Introduction

Chronic pancreatitis (CP) remains a challenging condition to manage, despite its establishment as a clinical entity almost 80 years ago [1]. Although most studies demonstrate incidence and prevalence rates of around 7 per 100,000 and 28 per 100,000, respectively, the morbidity associated with the disease causes a disproportionate impact on healthcare systems worldwide [2–5]. Despite advances in understanding the pathophysiology, technological advances in endoscopic techniques and improvement in outcomes in pancreato-biliary surgery, management remains unstandardised with contention in approaches, of which some were more recently addressed by clinical trials [6, 7]. These precedents may lead to difficulties for clinicians in decision making for patients with CP.

The heterogeneity of the pancreas and its multi-functionality results in the complex pathophysiology at play in CP. A series of mechanisms have been postulated as to the pathophysiology, including (i) the direct effect of toxic metabolites (e.g. tobacco, alcohol) on acinar cells, (ii) a "two-hit" model in which an episode of acute pancreatitis causes activation of pancreatic stellate cells with subsequent fibrosis, (iii) ductal dysfunction causing obstruction secondary to formation of protein plugs, (iv) oxidative stress in acinar cells secondary to free radicals promoting fusion of lysosomes and (v) a necrosis-fibrosis sequence as

a result of repeated episodes of acute pancreatitis [8]. As demonstrated by the numerous proposed pathophysiological mechanisms, definitive understanding of the predominant process remains poor.

Pain remains the key symptom of clinical presentation and the primary focus of clinical management. It has been hypothesized that recurrent episodes of pain are due to progressive pancreatic fibrosis [9]. Delays in diagnosis from the onset of symptoms to establishment of diagnosis may range from 62 to 81 months. Following repeated attacks of pain, the pancreas may undergo full fibrosis leading to a painless state over a period of years [10]. However, not all patients with CP present with pain or develop symptoms of exocrine/endocrine insufficiency. Thus, from a clinical viewpoint, patient subgroups exist within the spectrum of CP for which different treatment combinations may be required. The challenge for the pancreatic surgeon is to identify this subgroup of CP patients who will benefit from operative intervention at the appropriate juncture.

Diagnosis and classification of chronic pancreatitis

The presence of relevant aetiological risk factors should be sought early in clinical assessment, such as alcohol abuse, nicotine use, gallstones and family history in order to prevent delayed diagnosis. Episodes of intermittent abdominal pain likely represent repeated attacks of acute pancreatitis which may go undiagnosed. It is now widely accepted that a single episode of clinically diagnosed acute pancreatitis may represent a sentinel event which results in CP [12, 13]. In addition to these aforementioned clinical presentations, patients may be asymptomatic and detected incidentally following imaging for other reasons. The resultant mix of possible presentations causes difficulties in identifying cases, monitoring and trialling treatments.

Computed tomography (CT) remains the best initial imaging modality to diagnose CP, with the findings of pancreatic duct dilatation, pancreatic atrophy, pancreatic mass, calcification and/or recurrent pseudocyst formation [11]. However, normal pancreatic morphology may also be observed on CT imaging with early CP, making diagnosis particularly challenging.

It is commonly known that longstanding pre-existing CP is a risk factor for pancreatic cancer. Although only 1.8% of these patients will develop pancreatic cancer within 10 years from the diagnosis and 4% after 20 years [14], it may be very difficult to rule out pancreatic cancer in the presence of a pancreatic mass. There have been a number of developments in imaging and molecular technologies to aid in differentiating benign from malignant mass lesions in patients with chronic pancreatitis. While some such as EUS-FNA (endoscopic ultrasound/fine needle aspiration) and advanced CT/MRI (magnetic resonance imaging) techniques are already in clinical use, technologies like CE EUS (contrast enhanced endoscopic ultrasound), EUS elastography and digital image analysis require development of standardised protocols, consensus and operator training facilities before they can be inducted into regular clinical use [15]. The molecular techniques are still in the early stage of development. Continued research and development are required to help in the correct diagnosis of this challenging condition.

The desire to organise and classify patients with CP has led to development of multiple classification systems over the years, including the Marseille, Cambridge, Zurich and TIGAR-O systems amongst others [16–19]. More recently, the M-ANNHEIM classification has sought to unify these systems and permit aetiology and clinical severity to be included in stratification [20]. Whilst these systems have contributed greatly to the study of CP, none of them are specifically focussed on a surgical approach. Although patients may be classified by these systems as "probable pancreatitis" (Zurich system), "moderate changes" (Cambridge system) or "M-ANNHEIM C", this does not assist the surgeon in making management decisions. With the increasing evidence to support surgery in treatment of CP, there is a need to stratify patients differently to aid the operative decision-making process [21].

Timing of surgery

It is widely accepted that the primary indication for surgery is the presence of pain. As discussed previously, however, the majority of patients will present with pain and this large patient subgroup needs further assessment. Medical management should be optimised to address the risk factors by reducing diabetic complications, diet/supplement administration for exocrine insufficiency, psychiatric support and analgesia for pain management prior to the consideration for surgical intervention using a multidisciplinary team approach. Once the aetiology of CP has been addressed, surgery can be considered under the proviso that basic assessment of fitness for operation has been met.

The traditional management approach to CP favoured a classical pathway of medical treatment followed by endoscopic intervention and, finally, surgery if previous treatments had failed [22]. The primary objective for surgery is to avoid a state of chronic, intractable pain which leads to a state of continual analgesic abuse and dependence. Pain specialists should be involved early and guide the use of effective analgesic control; however, once typical analgesia management has failed, techniques such as endoscopic coeliac plexus block/neurolysis can be applied and have been shown to provide effective pain relief in 50% of patients [23]. This procedure can be repeated safely but caution should be exer-
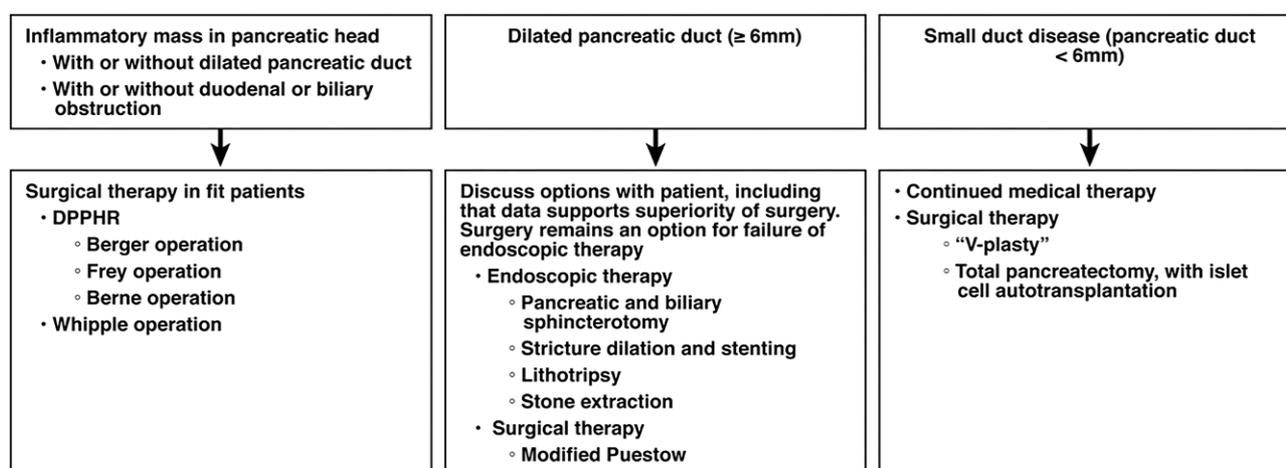
Inflammatory mass in pancreatic head • With or without dilated pancreatic duct • With or without duodenal or biliary obstruction	Dilated pancreatic duct (≥ 6mm)	Small duct disease (pancreatic duct < 6mm)

Surgical therapy in fit patients
• DPPHR
  ◦ Berger operation
  ◦ Frey operation
  ◦ Berne operation
• Whipple operation
	Discuss options with patient, including that data supports superiority of surgery. Surgery remains an option for failure of endoscopic therapy
	• Endoscopic therapy
	  ◦ Pancreatic and biliary sphincterotomy
	  ◦ Stricture dilation and stenting
	  ◦ Lithotripsy
	  ◦ Stone extraction
	• Surgical therapy
	  ◦ Modified Puestow
		• Continued medical therapy
		• Surgical therapy
		  ◦ "V-plasty"
		  ◦ Total pancreatectomy, with islet cell autotransplantation

Fig. 1   Different types of CP appearance and potential treatment algorithms. *DPPHR* duodenum preserving pancreatic head resection

cised. Whilst patients are suffering with symptoms, the underlying cause of the pain, for example ductal obstruction secondary to calculus, would not be addressed. The result may be progressive destruction of pancreatic parenchyma and loss of function, making surgery technically more challenging, therefore worsening outcomes. It is the authors' belief that patients should not be progressed from standard analgesics to complex analgesic administration indefinitely without an overall plan for future treatment. The goal should be to avoid a state of analgesic abuse and to use such endoscopic techniques as a bridging therapy to definitive treatment [24].

Numerous endoscopic and interventional radiological techniques now exist to manage chronic pancreatitis, including endoscopic retrograde cholangiopancreatography (ERCP) and pancreatic duct stenting, endoscopic cystogastrostomy and percutaneous drainage of pseudocysts under image guidance. All these techniques play a role in patient management for chronic pancreatitis. However, in patients with chronic intractable pain secondary to CP, evidence now supports proceeding to surgery earlier over endoscopy due to superiority in success rate, pain relief and quality of life. Surgery may need to be considered at an earlier phase than it is now, preferably within 3 years of symptomatic CP [24–27].

One of the primary problems in an endoscopy-based treatment regime is that whilst treatments may be successful, their duration may be short lived, necessitating multiple procedures causing complications, which could have been avoided with a single intervention. Nevertheless, endoscopic techniques do have a role in patients who are unfit for surgery. In all other cases, they should serve as an adjunctive treatment modality in the overall patient management rather than as definitive therapy.

Moreover, early surgery may help to correct exocrine insufficiency, which commonly develops 5 to 10 years after the onset of CP but tends to be under-diagnosed and is under-treated in CP patients. CP may also lead to type 3c diabetes mellitus and early stage surgery in CP may reduce this risk [28].

Surgical options

The rationale for surgical treatment in CP has traditionally focused primarily on addressing the mechanical obstruction secondary to pancreatic parenchymal calcification, and its local complications secondary to pancreas parenchymal fibrosis causing biliary or duodenal obstructions, and pseudocyst formation due to recurrent inflammation and/or head of pancreas duct obstruction [29–31]. Whilst the presence of macroscopic complications plays a key role in the decision for surgical intervention, clinical symptoms must be considered in conjunction at the decision process.

Evidence thus far supports surgery over endoscopic intervention in treatment of CP and indicates that the timing of surgery should be carefully considered [24–27]. Most clinicians favour an early surgical intervention in a recent survey [32]. The subject of surgical treatment of CP has been extensively reviewed in the literature from a surgical perspective [33, 34]. However, it is still unclear regarding the optimal choice of the type of surgical technique. This variation of practice was highlighted in a recent survey of 288 pancreatologists from 47 countries. It concluded that the majority of CP management is based on local expert opinion, rather than evidence-based guidelines [32].

We hereby describe four common clinical scenarios, where most CP patients are likely to be categorized, and attempt to discuss various surgical options available for each scenario (see Fig. 1).

Group 1a—inflammatory pancreatic mass with suspicious features

Differentiation between CP and malignancy has proven to be difficult prior to surgery, especially

Fig. 2 Schematic drawing of duodenum-preserving pancreatic head resection (DPPHR) procedures. Extent of resection is shown for Beger's operation (**a**) and Frey's operation (**b**), as well as the Berne modification (**c**). Panels **d–f** show the corresponding surgical sites after reconstruction. © Republished with permission of Elsevier, from Muller et al. [35]); permission conveyed through Copyright Clearance Center, Inc. This figure is not included under the Creative Commons CC BY license of this publication
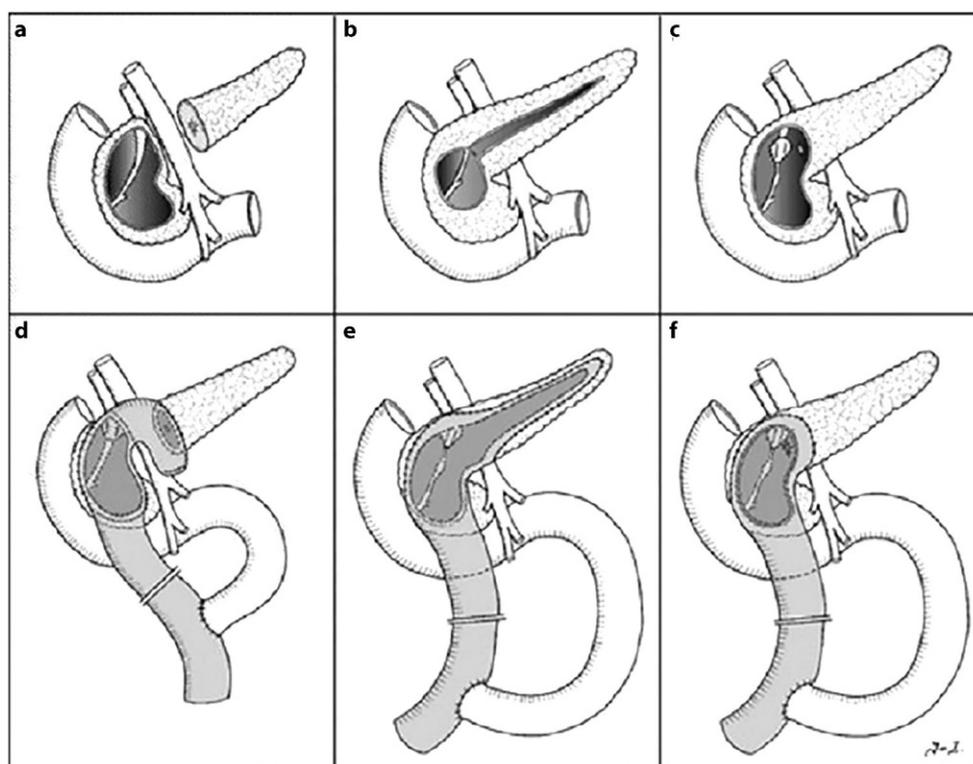
when there is a distinctive pancreatic mass identified on cross-sectional imaging [33]. Pancreatic biopsy with a frozen section should be performed at the time of surgery to establish the diagnosis of malignancy. If positive for malignancy, formal oncological resection with curative intent should be performed at the same setting.

Group 1b—inflammatory pancreatic mass with benign appearance

The identification of a pancreatic mass with benign appearance requires very careful history and examination of the recurrent inflammatory process, gradual changes of pancreas parenchyma on cross-sectional imaging over a period of time and expert radiologist interpretation. The potential false-negative diagnosis of a pancreatic mass as benign appearance has a significant impact on patient outcome.

An inflammatory mass located at the pancreatic head can cause obstruction to the pancreatic duct, bile duct and gastric outflow. The presence of such complications and intractable pain are indications to proceed to surgery, ideally prior to the commencement of opiate analgesia [32].

Notably, however, such an inflammatory mass may also be associated with chronic pain in the absence of mechanical obstruction. This is likely secondary to the postulated theory that the head of the pancreas serves as a "pacemaker", driving the process of intractable pain [34–36]. Whilst surgery has been offered to such patients, there is no body of evidence on

the benefit of surgery for this particular patient group versus medical management. This is due to the small numbers of case series and the inclusion of a rather heterogeneous patient population.

Where obstruction is present, duodenum-preserving pancreatic head resection (DPPHR) and pancreaticoduodenectomy (PD) are the two most common surgical interventions. There are various techniques for DPPHR, but the most commonly performed techniques are Beger's operation, Frey's operation or Berne modification procedures. The differences in terms of their technical aspects are illustrated in Fig. 2.

Several single-centre clinical trials compared PD and DPPHR and had favoured the DPPHR approach [30, 31]. However, a multi-centre double-blinded randomised controlled superiority ChroPac trial comparing PD vs. DPPHR for chronic head pancreatitis was recently reported. The primary endpoint focused on long-term quality of life over a 24-month period following either of the two surgical interventions. The study did not demonstrate any difference in quality of life, mortality and morbidity between the interventions [6]. Based on this finding, authors therefore recommend that the choice of DPPHR or PD procedure should be based on the merit of each individual case and surgeon's preference.

Group 2—isolated dilated pancreatic duct disease

Dilatation of the pancreatic duct in CP may arise secondary to a variety of mechanisms such as ductal obstruction by calculi, ductal compression by parenchy-

mal inflammation or mass, or localised fibrosis. If, however, the dilatation is isolated without mass in the pancreatic head, the gland can be decompressed by a drainage procedure, rather than surgical resection. This clinical scenario is best demonstrated on cross-sectional imaging as the classic "chain of lakes" appearance. Drainage procedures minimise resection of any aspect of the pancreas, thereby focussing on preservation of remnant pancreatic function and minimised morbidity. However, they are contraindicated in patients with significant changes to pancreatic parenchyma where resection is normally required.

Puestow and Gillesby first described a side-to-side pancreaticojejunostomy with a distal pancreatectomy to drain the dilated pancreatic duct in patients with CP [37]. In 1960, this procedure was modified by Partington and Rochelle who performed only a side-to-side pancreaticojejunostomy without a distal pancreatectomy (colloquially known as "Puestow" procedure). This procedure addresses CP in patients with a dilated pancreatic duct (≥6 mm) and no inflammatory mass in the head of the pancreas. When performed adequately, long-term pain relief has been reported in the region of 60–98%, with low morbidity [38].

Group 3—small pancreatic duct disease

Small-duct CP remains rare and may be related to parenchymal gland inflammation or fibrosis causing narrowing of the pancreatic duct (PD) to <3 mm [39]. Diagnosis may be difficult as typical imaging may demonstrate mild abnormalities, which can be potentially overlooked by an inexperienced radiologist. Definitive diagnosis can be sought and confirmed by secretin testing. Endoscopic ultrasound (EUS) should be considered to exclude a pancreatic ductal neoplasm. Having confirmed the diagnosis of CP, patients should proceed to surgery for symptom control.

Some anecdotal evidence suggests that a "V-plasty" operation is the procedure of choice, with reasonable safety and median- to long-term pain relief [40–42]. However, one contraindication to offering "V-plasty" in this group of patients is the suspicion of malignancy, where an aggressive oncological resection would be much more appropriate.

Group 4—atypical presentation of CP

Cases of CP presenting differently to the above-described grouping will require an alternative/bespoke approach. A total pancreatectomy (TP) may also be offered to CP patients with endocrine insufficiency. However, the brittle diabetes resulting from TP (due to loss of glucagon as well as insulin secretion) will require careful titration of insulin administration by endocrinologists.

The long-term morbidity caused by TP can be reduced by autologous islet transplantation (TPIAT) for patients without diabetes mellitus. A meta-analysis of 12 published articles indicated that TPIAT is safe, with a 30-day mortality of 2.1% and a long-term mortality of 1.09 per 100 person-years, which is comparable with TP alone. Increasing severity of pancreatic fibrosis correlates positively with poor yield of islets (<300,000) and insulin dependence. C-peptide-negative diabetes, type I diabetes, portal vein thrombosis and portal hypertension/significant liver disease are considered contraindications to TPIAT [43].

Two systematic reviews which carried out meta-analyses reported pooled insulin independence rates of 27% (95% CI: 21–33%) and 28.4% (95% CI: 15.7–46.0) at one year and 21% (95% CI: 16–27%) and 19.7% (95% CI: 5.1–52.6%) at two years, respectively [44, 45].

Conclusion

The complex, heterogenous nature of the pancreas results in CP manifesting in a variety of clinical presentations. Treatment of CP should follow a multidisciplinary approach involving physicians, pain specialists, endoscopists and pancreatic surgeons. Evidence now favours early surgery as the preferable treatment for patients with intractable pain over endoscopic management. Head-dominant CP has been addressed through the latest clinical trials. However, further clarity is still required for the management of non-head-dominant disease.

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