Expert Review of Gastroenterology & Hepatology

ISSN: 1747-4124 (Print) 1747-4132 (Online) Journal homepage: www.tandfonline.com/journals/ierh20

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EXPERT REVIEW OF GASTROENTEROLOGY & HEPATOLOGY
2024, VOL. 18, NOS. 1–3, 25–36
https://doi.org/10.1080/17474124.2024.2321947

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REVIEW

An update on improving long-term outcomes for patients with chronic pancreatitis post-surgery

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ABSTRACT

Introduction: Chronic pancreatitis is a common inflammatory disease that severely impairs patients' quality of life, mainly due to abdominal pain which is the most frequent symptom. Current guidelines suggest medical therapy as the first line intervention based on a stepwise use of analgesics (i.e. NSAIDs followed by weak opioids and later by strong oppioids), which is rarely effective in improving pain and often leads to opioid addiction. Interventional procedures are therefore frequently needed. Endoscopic therapy is suggested as the second line of intervention, aiming at decompressing the main pancreatic duct via structure dilatation and ductal stone removal. Endoscopic therapy is usually effective in reducing pain in the short term, but its effects frequently decrease with time and multiple procedures are often required. Surgery is usually reserved as a last resource when medical and endoscopic therapy have failed. Pancreatic surgery is burdened with non negligible morbidity and mortality but is effective in reducing pain and improving quality of life in chronic pancratitis with long lasting effects.

Areas covered: Surgical treatment of chronic pancreatitis is based on resection of inflammatory head mass or decompression of the ductal system, alone or in combination, which can be performed using different techniques. In this paper we reviewed the current evidence on the long-term outcomes of this type of surgery in terms of pain relief, quality of life, exocrine end endocrine function, and long-term mortality.

Expert opinion: Quality of current evidence on this field is on average poor; a consensus to define clinically significant outcomes is needed in order to correctly design prospective studies that will enable gastroenterologists to understand which patients, and when, will benefit most from surgery and should therefore be referred to surgeons.

ARTICLE HISTORY
Received 26 November 2023
Accepted 19 February 2024

KEYWORDS
Chronic pancreatitis; endoscopic therapy; pain; quality of life; surgery

1. Background

Chronic pancreatitis (CP) is a chronic inflammatory disease of the pancreas that leads to a progressive deposition of connective tissue and a decrease in exocrine and endocrine function [1], often resulting in pancreatic exocrine insufficiency (PEI) and diabetes mellitus (DM). Pain is the main complaint in CP, being present in up to 97% of patients [2]. Pain in CP can present with different patterns that can be classified into three subtypes: type A: intermittent, infrequent attacks of pain or pancreatitis; type B intermittent severe pain with continuous pain between attacks; and type C: severe, constant pain without attacks of pain or pancreatitis [3]. It has been shown that pain is one of the main causes of reduced QoL in CP patients and that pain frequency correlates with reduced QoL more than pain intensity [4,5]. Because of this, current guidelines suggest that pain should be evaluated not only in terms of intensity but also in terms of its frequency and impact on QoL [1]. In particular, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire has been validated specifically for CP [6].

Historically the pathogenesis of pain in CP was largely attributed to three mechanisms:

- Inflammation of the pancreas;
- Tissue ischemia secondary to increased pancreatic pressure, mainly due to strictures and stones of the main pancreatic duct (MPD);
- Pancreatic or extra pancreatic complications, most frequently bile duct and duodenal strictures;

Based on these assumptions, therapies for pain relief in CP have always been mainly aimed at treating inflammation with medical therapy and strictures and stones with surgery or endotherapy. However, newer studies on this topic suggest that peripheral and central sensitization of the nervous system in CP patients leads to a lower pain threshold and a maladaptive response to pain [7–11]. This may explain why the structural changes of the pancreas do not always correlate well with the level of pain [12,13] and why a clear structural cause of pain is not identifiable altogether in a large group of patients (the so-called 'minimal change CP') [12].

The long standing paradigm regarding the natural history of CP was that as time passes pancreatic mass loss determines PEI and diabetes while progressively reducing pain, the so-called 'burn-out theory' [14]. More recent studies contradict this theory: the development of endocrine and/or exocrine dysfunction doesn't seem to be predictive of reduced pain [15,16] and a longer disease

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Article highlights

- Pain is the main complaint of CP patients for which medical and endoscopic therapy are rarely sufficient;
- Many different surgical techniques can be used to treat CP, all of which appear to yield similar results;
- Outcome definition in current literature is dishomogeneus, but overall surgery shows good results in terms of pain reduction and QoL improvement.
- Future research should strive to improve quality of evidence with prospective studies to define patients' and disease's characteristic that may be able to predict those who wil benefit the most from surgery

duration does not correlate with either reduced pain severity or frequency [5].

Current European guidelines on pain management in CP recommend a multimodal step-up approach [1]. Medical therapy is the first-line treatment and should be based on the WHO ladder (nonopioid analgesics followed by weak and later strong opioids [17]). Analgesics use in CP patients is ubiquitous and strong opioids are usually needed. Unfortunately, analgesics alone are rarely sufficient and interventional procedures are almost always needed.

Current guidelines suggest endotherapy as the preferred first-line interventional treatment to manage pain in these patients. Duct stenosis and ductal stones are frequently identifiable causes of pain and therefore represent good therapeutic targets. The usual approach for ductal stenosis is pancreatic sphincterotomy, stricture dilatation, and insertion of one or more stents in the main pancreatic duct (MPD). Stents are then electively changed after one year or when signs or symptoms of stent dysfunction are present, until the stenosis is resolved [18]. Stones in the MPD can be removed with direct endoscopic retrograde pancreatography, usually preceded by extracorporeal shock-wave lithotripsy (ESWL) for large stones (≥5/7 mm). Endotherapy is usually effective in terms of pain reduction in the short term, but the benefit tends to decrease significantly in the mid-long term and multiple procedures are usually needed [19].

As per current guidelines, surgery is regarded as a last option when all the previous strategies have failed. In recent years, though, there has been significant research on the matter of surgery timing. A recent randomized control trial investigated whether an early surgery strategy, as compared to the per guidelines step-up approach, could be beneficial [20]. The results showed that early surgery was superior in terms of pain control (expressed as integrated Izbicki score during follow-up) and that 30% of the patients randomized to the step-up approach ultimately ended up with having surgery after a median of 299 days. Supplementary data from the study underlines the importance of technical expertise of the endoscopist, as it showed that effective clearance of the MPD after endoscopy is a crucial predictor of pain relief: the rates of partial or complete pain relief were similar between patients from the endoscopy first approach group who achieved complete duct clearance and those from the early surgery group (52% and 57%, respectively) but much lower among those that did not achieve duct clearance (21%). This study did not show statistically significant differences in terms of pancreatic function and quality of life between the study and the control group, but a subsequent analysis of the trial results found that the early surgery approach may also be cost-effective [21].

A limitation of this study is that endotherapy was only performed with plastic stents, while in recent years the role of fully covered self-expandable metal stents (FC-SEMS) has emerged for the treatment of refractory MPD strictures. Two prospective studies evaluated the use of FC-SEMS in the treatment of MPD strictures refractory to plastic stenting with favorable results [22,23]. A recent review and meta-analysis on FC-SEMS vs. multiple plastic stents for CP related refractory MPD strictures found similar rates of pain improvement (88% vs 89%) and stricture recurrence (8% vs 11%), with FC-SEMS being superior in terms of a reduced number of ERCP needed at the cost of higher adverse event rate (39% vs 14%) [24]. Future studies investigating the role of FC-SEMS as first-line treatment of MPD strictures may change current therapeutic algorithms especially when a more durable stenting is needed, for example in patients that are likely to be non compliant with follow-up imaging and ERCP.

1.1. Types of surgery

Surgery can be divided between resective, decompressive, and mixed procedures. The choice of the procedure mainly depends on morphological changes of the pancreas: resective procedures are indicated in patients with an inflammatory mass of the head (usually defined as an enlargement ≥4 cm of the pancreatic head) which is thought to be the main driver of pain, whereas derivative procedures are most useful when strictures and stones are diffused throughout the MPD (and thus not treatable with endotherapy) [25].

- **Purely derivative procedures** → Lateral Pancreaticojejunostomy (LPJ): Partington-Rochelle or (Modified) Puestow Procedure. The MPD is incised longitudinally for its entire length in order to clear stones and strictures and then a lateral pancreaticojejunostomy is created with a Roux-en-Y anastomosis;
- **Purely resective procedures**:
  - **Pancreaticoduodenectomy (PD)**: the pancreas head is removed en-bloc with the duodenal C alongside the pylorus (Whipple procedure) or preserving the pylorus (pylorus preseving pancreaticodudenectomny, PPPD);
  - **Duodenum preserving pancreatic head resections** (DPPHR):
    - **Beger procedure**: the pancreatic head is resected leaving a small part of pancreatic tissue on the duodenum; a two-sided pancreatico-jejunostomy is then performed on the pancreas remnant and the remaining part of the head. Biliary anastomosis can be performed if a stenosis is present;
    - **Berne procedure**: a variation of the Beger procedure in which the pancreatic head isn't resected but cored out instead;
  - **Total Pancreatectomy with Islet Auto Transplantation (TPIAT)**: pancreas is entirely

removed and Islet Auto Transplantation is performed to maintain a certain degree of insulin and glucagon secretion and thus prevent Type 3c diabetes. This technique is mainly indicated for patients who fail to improve after other surgeries or those with intractable pain and small-duct or minimal change disease, in which no clear structural change is amendable to surgical intervention via drainage or resection [26]

- **Mixed procedures → Frey procedure**: combines a duodenum preserving head resection with drainage of the MPD of the body and tail;

Surgery for CP has been extensively studied in terms of peri-operative short-term outcomes. In general these procedures are technically demanding and carry significant risk of post-operative morbidity but usually with low mortality. Briefly, the most common complications after pancreatic surgery consist of post operative pancreatic fistula (POPF), delayed gastric emptying (DGE), intra-abdominal abscesses and drain or surgical site infections. A German retrospective study on a large cohort of 1125 patients that received different techniques of DPPHR found an overral morbidty of 25.4% and mortality of 2.4% [27]. A recent meta analysis compared PD with DPPHR and found the former to be superior in terms of 30-days morbidity (24.73% vs. 43.95% respectively), but no significant difference in mortality ermeged (1.5% vs. 0% respectively) [28].

2. Long-term outcomes of surgery

On 15th of September 2023 we conducted a search on PubMed for papers dealing with the long-term results of surgery for CP. Since most studies on the subject are based on patients' cohorts dating back to the 1980s we restricted the search to papers published after 2010 for which we could get access to an English full text using the search string '(long term outcome) AND (surgery) AND (chronic pancreatitis) AND ((“2010”[Date – Publication] : “2023”[Date – Publication])) AND (english[Language]).'

The search resulted in a total of 268 articles. We discarded all the reviews, meta-analyses, guidelines, expert opinions, letters to journals, and commentaries. We also focused on papers specifically dealing with surgical procedures, discarding studies on medical and endoscopic therapy. We did not include studies dealing specifically with a pediatric population or those analyzing a specific subset of CP (for example paraduodenal pancreatitis) and those with a cohort of less than 20 patients. We also excluded two studies on cohorts that spanned over 40 years of enrollment, as we deemed the cohorts to be exceedingly dishomogeneous given the evolution of surgery procedures during such a long span of time.

With the above mentioned criteria we selected 41 papers which characteristics are summarized in Table 1.

Table 1. Studies summary. IQR (interquartile range); RCT (randomized controlled trial); QoL (quality of life).

Population numerosity *median (IQR)*	85 (51–147)
Duration of follow-up (years) *median (IQR)*	5 (2–7,5)
Study design	
Retrospective *n (%)*	28 (68%)
Prospective, non randomized *n (%)*	8 (20%)
RCT n (%)	5 (12%)
Evaluated outcomes:	
Pain relief *n (%)*	35 (85%)
QoL *n (%)*	18 (44%)
Endocrine insufficiency *n (%)*	33 (80%)
Exocrine insufficiency *n (%)*	24 (59%)
Long term mortality *n (%)*	16 (39%)

2.1. Pain relief

As previously discussed, pain is the main complaint in CP patients and is also by far the most common indication for surgery. This was confirmed among all the studies that reported the indications for the procedure, with pain always being the major indication for surgery with percentage always over 90%. This being the case, one major concern regarding surgery for CP is whether these procedures are effective in reducing pain and, more importantly, if this benefit is sustained in the long term.

The first step in evaluating pain before and after surgery is to define and quantify it. Among the studies considered, pain was most commonly evaluated in ways not specifically designed for patients with CP such as Visual Analogue Scale (VAS) values [29], pain-related items in QoL scores and the frequency of use of narcotics and/or narcotic free status as a proxy of absence of pain.

Out of the 35 studies that evaluated pain as an outcome, only 7 used a score specifically developed for CP, the Izbicki score [30] (see Table 2). Since the impact of pain on the QoL of patients depends not only on its intensity but also on its frequency and impairment in daily activities, this score consists of a scale ranging from 0 (no pain) to 100 (worst pain) calculated as the mean of 4 subscores: frequency of pain attacks, VAS, analgesic medication used, and time of disease-related inability to work during last year.

Recently the COMPACT-SF score was presented as a new score specifically developed for CP patients evaluating five dimensions of pain: severity, pattern, provocation, spreading, and a qualitative description [31]. The authors showed that the COMPACT-SF score is strictly linked to hospitalizations rate and quality-of-life scores. Unfortunately this comprehensive tool for the evaluation of pain in CP is very recent and none of the studies in our review used it.

Table 2. The Izbicki pain score.

Frequency of pain attacks	Daily	100
	Several times a week	75
	Several times a month	50
	Several times a year	25
	None	0
VAS (Visual Analogue Scale)		0–100
Analgetic medication (morphine-related analgetic potency)	Morphine	100
	Buprenorphine	80
	Pethidine	20
	Tramadol	15
	Metamizol	3
	Acetylsalicylic acid	1
Time of disease related inability to work (last year)	Permanent	100
	<1 year	75
	<1 month	50
	<1 week	25
	none	0

Many studies have previously demonstrated that derivative and resective procedures are effective in reducing pain in CP patients, but most of them only evaluated it in the short term, usually up to a maximum of 12 months after surgery. Since CP is a chronic disease, how pain relief persists in mid- and long-term follow-up is of paramount importance. One limitation in comparing the results from the studies is the lack of standardization on how 'pain relief' is defined. Most of the studies reported the results as rate of 'complete pain relief,' others as 'complete or partial pain relief' and others only reported the mean VAS value before and after surgery, not specifying the rate of pain relief. In our opinion the most homogeneous endpoint in pain evaluation is 'complete pain relief' (usually defined as VAS ≤ 4, Izbicki score < 10 or independence from opiates). We found that at the end of follow-up the overall median rate of completely pain free patients across all the procedures was 62% (IQR 51,3%-73,1%). The only two procedures that have specific pain relief rates reported in a relevant number of papers are the Frey procedure (median 76%, IQR 62,0%-88,0%) and TPIAT (median 68%, IQR 65,5%-70,5%). Lower pain control for TPIAT, which should theoretically be the most effective among all the procedures, are probably due to the particularly long follow-up span of the studies on this procedure.

Many types of surgery and specific procedures were compared head to head either on retrospective or prospective studies: Frey vs. Beger [32], Frey vs. LPJ [33], Frey vs. PPPD [34], PPPD vs. DPPHR [35], DCP vs. DPPHR vs. distal pancreatectomy [36], derivative vs. resective procedures [37], pylorus preserving TPIAT vs. non pylorus preserving TPIAT [38], Berger vs. Berne [39]. None of the mentioned studies found a statistically significant difference in rates of pain relief in long-term follow-up between the compared procedures. This evidence supports the choice of procedure based on morphological elements of the patients (presence or absence of inflammatory head enlargement and/or MPD dilatation, presence and localization of strictures and intraductal calculi) and the preference and expertise of the center and surgeon on a specific procedure, as none of them has been shown to be clearly superior to the others in reducing pain in CP patients.

Another way to evaluate how pain relief is sustained in the long term is to look at how often patients who underwent surgery need redo operations. This outcome was reported in 18 studies with a median value of 9% (IQR 5.3%-11.8%), without any clear difference between different procedures. This data show how surgery is usually a more definitive treatment than endotherapy, which almost invariably consists of multiple consecutive procedures, both scheduled and unscheduled, especially considering that some of the redo operations were done for local complications or in general for indications other than pain recurrence.

Another important aspect is to identify patients' characteristics that correlate with better or worse pain relief. The most common reported risk factors for absent pain relief in multivariate analysis were long duration of disease, opiate usage and multiple endoscopic procedures prior to surgery [40–42]. These factors probably reflect a group of patients with a more advanced disease at time of surgery and further strengthen the argument for early surgery. Another factor indicative of advanced disease is the presence of local complications such as biliary obstruction (BO) but this factor wasn't predictive of worse pain relief in a study specifically designed to investigate the matter [43].

Another risk factor for pain persistence that recurs in various studies is persistence of alcohol abuse, which also strongly impairs QoL scores [27,34,44,45]. Two studies observed that a continuous pain pattern was associated with worse pain relief [42,45].

A recent work by Bachman et al. [27] proposed the Chronic Pancreatitis Pain Relief (CPPR) Score, which assigns a point for every pre-operative factor that the authors found to be linked with higher rates of pain relief: MPD dilatation >4 mm, inflammatory head mass >4 cm, alcohol related etiology. This score performed well as a prognostic marker for pain relief, which was shown to increase from 5%, to 65.8%, to 95.8% to 100% in patients that have 0, 1, 2 and 3 points, respectively. This score may be a useful tool to identify those patients which will most probably benefit from surgery and that shuld therefore taken in consideration for early intervention.

2.2. Quality of life (QoL)

If one had to choose a single outcome to determine the efficacy of a procedure, QoL would probably be the most suitable. CP patients are burdened with a number of symptoms and disease related complications that can directly or indirectly impact daily activities, and surgery for CP itself can determine consequences that can impair QoL. An overall evaluation of the QoL after surgery for CP is probably more meaningful than pain relief alone: a procedure that is effective in reducing pain but at the same time determines complications and/or physiological modifications could impair overall QoL, potentially more so than pain reduction actually improved it.

The main problem when dealing with QoL as an outcome rests in its intrinsic subjectiveness in definition and evaluation. The most common way to quantify QoL is the use of standardized scores, usually composed of several domains (for example physical, mental, social etc.). The two most commonly used QoL scores in studies dealing with surgery for CP are the SF-36 [46] and the EORTC QLQ-C30 [47].

Twenty (44%) of the studies we reviewed evaluated QoL results after surgery for CP, usually comparing scores values before and after surgery. The results from all the studies are consistent and find surgery effective in significantly improving QoL of patients with CP, although frequently post-op QoL is still lower than in the general population. Only a few studies found a difference in QoL scores between different procedures, but only limited to certain domains. Specifically, worse physical functioning domain scores were reported in Frey than in PPPD by Bachman et al. [34] and in DPPHR compared to PD and distal pancreatectomy [36]. Ahmed Ali et al. [41] found that a head resection correlated with lower mental composed scores. All the other studies found the different surgery types and specific procedures to be largely equivalent in both overall and specific subdomains of QoL.

A study from Wilson et al. applied a cost-effectiveness evaluation to QoL scores in a rather specific setting, TPIAT for minimal change CP. The authors compared this aggressive management with standard medical and endoscopic combined therapy and reported that early surgery not only appears to be economically more convenient because of reduced costs for hospitalization and repeated endoscopic procedures but also shows better results in terms of quality adjusted survival [48].

Only a handful of studies specifically tried to identify elements that correlate with better or worse results in terms of QoL improvement, with the most frequent unsurprisingly being post-operative pain reduction. The Hamburg group reported persistent alcohol abuse after surgery as a significant risk factor for reduced QoL, strongly impacting not only on pain scores but also cognitive, emotional and work functioning domains [34,49]. Ahmed Ali et al. [41] found pre-operative use of opioid and post-surgery complications needing relaparotomy to be predictive of reduced physical composed scores, with opioid use also impacting on mental composed scores. Surprisingly, two studies found no correlation between presence of PEI and diabetes mellitus (DM) and reduced QoL [50,51]. This results are in contrast with those from an older study on a German cohort of CP patients in which PEI appeared to be a relevant driver of reduced QoL [52] and can probably be explained by the more widespread use of PERT in recent years, which has been shown to significiantly improve QoL in CP patients [53,54].

2.3. Endocrine insufficiency

The evolution of the disease determines fibrosis and loss of function of the pancreas causing a progressive tendency to hyperglycemia and, ultimately, to the development of diabetes mellitus in a large number of CP patients. Pancreatogenic diabetes (or Type 3c diabetes) is characterized by rapid swings in glycemic levels, the so-called ‘brittle diabetes.’ This is due to the chronic damage to Langherans islets in CP patients that impairs the production of insulin but also of the main counter regulatory hormone, glucagon. Moreover, PEI makes absorption of glucides highly variable and susceptible to errors and forgetfulness of PERT intake and can thus need specific strategy to reduce glycemic variability [55].

Both derivative but especially resective surgery determine some extent of pancreatic tissue loss, with a predictable decrease of insulin production capacity and consequently a tendency to develop DM in non diabetic patients or to worsen the glycemic control in those already diabetic. Many of the studies we reviewed evaluate the pre- and post-surgery prevalence of DM. In particular, the median pre-operative prevalence of DM among all the studies is 28% (IQR 18–34%).

Apart from total pancreatectomy, which predictably determines diabetes in 100% of the patients, evaluating how different surgeries impact the development of DM post-operatively is difficult. Prevalence of DM in CP patients with longstanding disease is exceedingly high even in those treated with medical or endoscopic therapy alone. Many studies report post-operative prevalence of DM and some report the incidence of de novo DM, but in the long-term follow-up it is difficult to separate the impact of surgery from disease progression itself, especially since the already mentioned variability in duration of follow-up. Among the studies we evaluated (excluding those dealing with TPIAT) median post-operative DM prevalence was 57% (IQR 45–62%) over a median follow-up of 5.3 years (IQR 4.3–6.9). As expected among the results of these study there is a clear relation between the duration of follow-up and DM prevalence (R^2 = 0.572, Figure 1).

Only the Frey and TPIAT have specific post-op DM prevalence data reported in a relevant number of papers. Following Frey procedure the median prevalence of DM was 50% (IQR 38–61%) over a median follow-up of 4.65 years (IQR 4.23–6.15), again with a linear relation between prevalence and duration of FU (R^2 = 0.705, Figure 2).

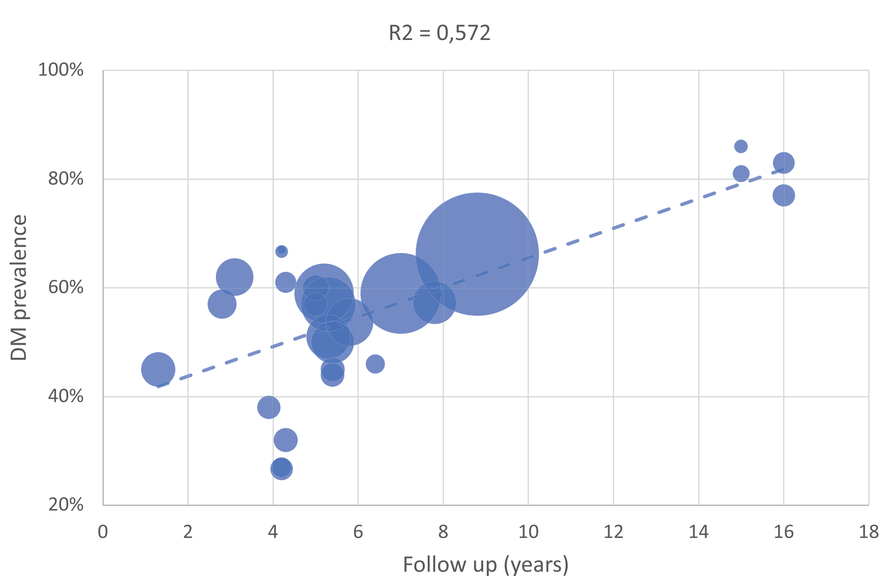

Figure 1. Diabetes prevalence and follow-up duration after any procedure (bubble area proportional to patient number).

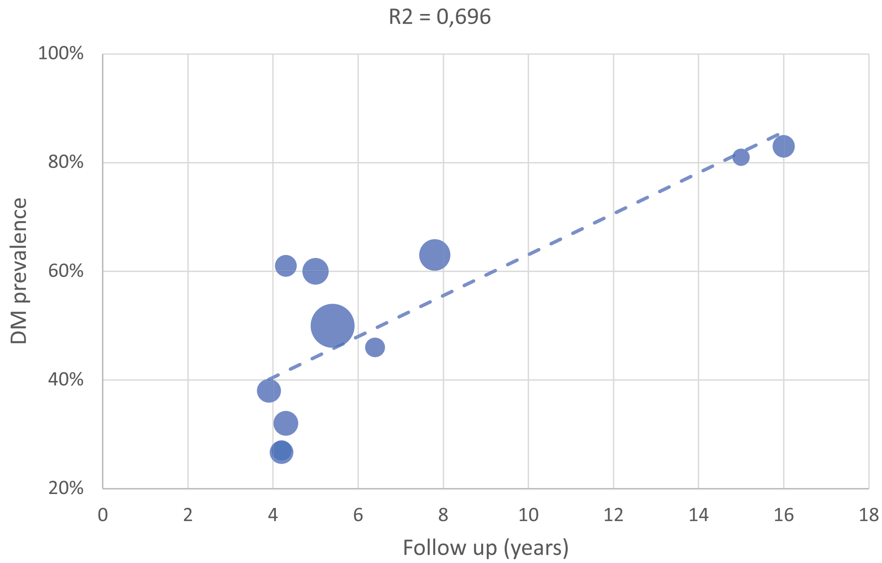

Figure 2. Diabetes prevalence and follow-up duration after Frey procedure (bubble area proportional to patient number).

Since DM is present in all patients after TPIAT, studies focused on this procedure evaluate the success of the islet auto transplantation with the rate of insulin dependent patients after the procedure. Three studies reported this data over a 5 year follow-up, two of them also reporting up to 10 years, resulting in an average insulin dependency rate at 5 and 10 years of 75% and 88%, respectively [56–58].

Many studies confronted DM prevalence following different procedures. Specifically, different techniques of head resection appear to have comparable outcomes, as one prospective study and two RCT showed no difference when confronting DM prevalence after PPPD vs. DPPHR [35], Beger vs. Berne [39] and DPPHR vs. PD [59]. On the contrary, three different papers found derivative procedures to be superior in terms of endocrine function preservation when compared to resective techniques [37,40,41]. This can easily be explained by the much more relevant loss in pancreatic tissue after head resections, with some patients even showing improved glycemic control after derivative procedures.

Frey procedure appears to be comparable to Beger's [32] while contrasting results emerge when confronted to purely derivative procedures, as two different retrospective studies with comparable population numerosity and follow-up duration found opposite results: Ray S. et al. showed a statistically significant lower prevalence of DM after derivative procedures vs. Frey's [42], while Kempeners et al. found comparable rates of diabetes after these two procedure [33].

Possible risk factors for development of DM after surgery were investigated only in four studies. Longer duration of disease [41–43], presence of biliary obstruction [43], re-operation because of any complication [40], or any postoperative complication in general [43] were associated with a higher prevalence of post-operative DM.

While DM development in patients that experienced post-op complications or re-operation can be directly linked to the effects of surgery, a worsening endocrine function in patients who underwent surgery after a longer duration of disease or in presence of biliary obstruction is probably related to a more advanced stage of disease, where parenchymal damage has become significant and the residual tissue after the resection is insufficient to maintain adequate glycemic control.

2.4. Exocrine insufficiency

Pancreatic exocrine insufficiency is a well-known complication of CP which is often already present in patients undergoing surgery. Similarly to diabetes, the loss of pancreatic tissue after surgical procedures often determines the development of de-novo PEI or the worsening of preexisting exocrine insufficiency. One of the main issue in evaluating the pre- and post-operative prevalence of this condition is that symptoms alone are not sensible nor specific to diagnose PEI. Current European guidelines therefore suggest an objective definition using fecal elastase (FE) levels < 200 ug/g as the preferred laboratory parameter [1,60]. Unfortunately, only three of the studies we reviewed adopted this definition for PEI while all the others defined it as the presence of related clinical signs (steatorrhea, bloating etc.) and/or use of PERT.

The studies we reviewed reported a median pre-operative prevalence of PEI of 49%, (IQR 42–63%) while at the end of follow-up the median prevalence among all the procedures was 72% (IQR 37%-82%). The prevalence after Frey alone is higher but also shows a higher variability (median 72%, IQR 37–79%). Surprisingly, the duration of follow-up seems to be less related with the prevalence of PEI than to the prevalence of DM (Figures 3 and 4).

Contrasting evidence emerges from the direct comparison between different surgery types. Ahmed Ali et al. [41] found that head resection appears to be a risk factor for worse exocrine function while a distal pancreatectomy correlated with lower PEI prevalence, which could be explained by the different amount of pancreatic tissue removed during these

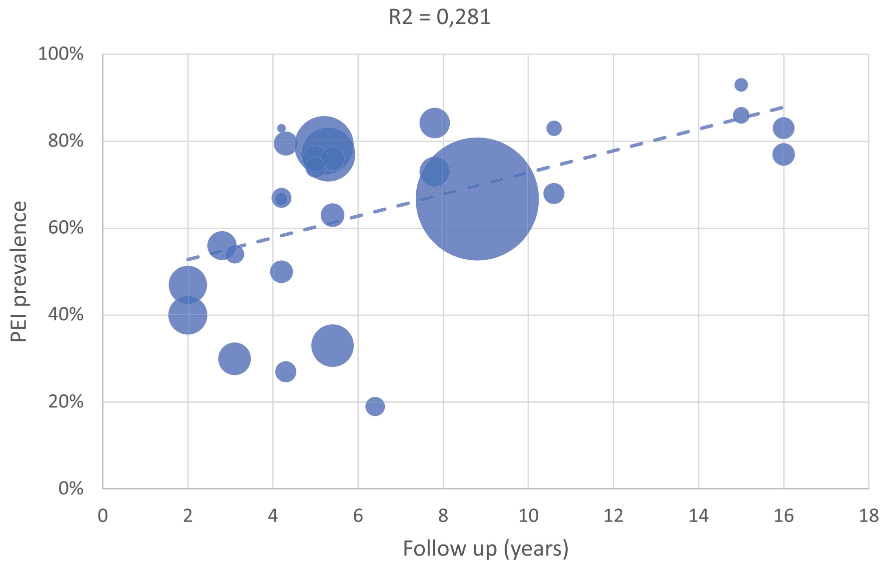

Figure 3. PEI prevalence and follow-up duration after any procedure (bubble area proportional to patient number).

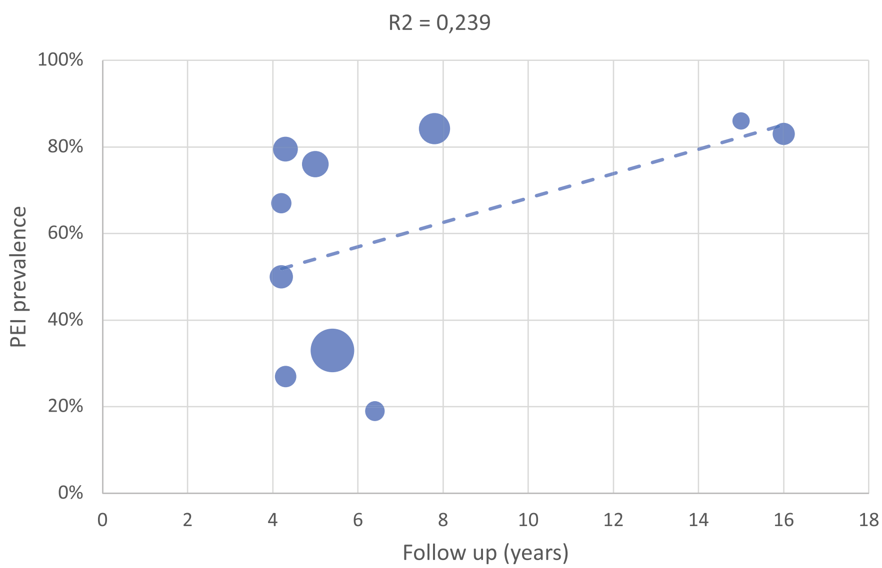

Figure 4. PEI prevalence and follow-up duration after Frey procedure (bubble area proportional to patient number).

different procedures. On the contrary, in a recent paper Matsumoto et al. [37] found a trend, although not statistically significant, for lower PEI prevalence among patients that underwent resective rather than drainage procedures. These counterintuitive results could be imputed to patient selection bias in this retrospective study with a relatively small sample size (20 patients for resective, 69 for drainage).

Frey procedure was compared to other surgery types by many authors and no significant difference in terms of PEI prevalence was found when compared to Beger [32,49], PPPD [34] and LPJ [33,42]. Among resective surgeries, no difference was found between DPPHR and PD [34,59].

Unfortunately, apart from the effect of different surgery types, no study evaluated if any patient or disease factor is associated with higher or lower prevalence of PEI following surgery.

2.5. Survival

It is well known that CP patients have a higher mortality and lower life expectancy than the general population. A Danish study from 2010 estimated a 4.5 times higher mortality rate than the general population [61] while a population study from the U.S.A. found a two fold higher mortality [62].

Many of the studies we selected document long term survival of patients undergoing surgery for CP, but survival is rarely the focus of the study and the way the outcome is defined is highly variable. 5 or 10 year survival rate is the most commonly reported outcome, being respectively 86% (SD 6%) and 62% (SD 7%) on average with a mean age of death of 54 years (SD 2.8). Three studies [34,63,64] reported the mean survival after surgery which was on average 14 years (SD 2.3) [50].

Only a few studies compared the results of different procedures. The Hamburg group showed a statistically significant better overall survival for the Frey procedure over PPPD (14,5 vs. 13,3 years, respectively) but comparable to Beger's procedure [34,49]. Diener et al. compared DPPHR and PD and found no difference in mortality rates [59].

The most complete work on long-term survival after surgery for CP was recently published by Murruste et al. The authors prospectively followed 161 patients and found an overall standardized mortality rate (SMR, i.e. the ratio of observed deaths compared to an aged matched general population) of 1,8. The strongest risk factor for lower survival was continued alcohol abuse after surgery: patients that stopped drinking actually had a mortality rate similar to the general population while those who kept drinking had a SMR as high as 2,7. Smoking and malnutrition (BMI <18.5 kg/m2) were also detrimental factors as well as the presence of multiple comorbidities (Charlson's index ≥ 2). A recent work of Wilson et al. [64] showed that alcohol abuse is a risk factor for reduced survival also if consumed prior to surgery, as patients with CP of alcoholic etiology show a higher mortality rate than patients with CP of other etiology. The authors also reported a negative effect of persistent opioid use after surgery.

We mentioned before how DM and PEI development don't seem to worsen QoL of patients, but when investigating risk factors for long-term mortality a study from Winny et al. interestingly found that the presence of insulin dependent DM and absence of PERT at time of discharge after surgery are risk factors for reduced long term survival [44]. This shows that although patients don't seem to be much impacted in their daily lives by endocrine and exocrine insufficiency the preservation of pancreatic function is actually important in terms of long-term survival, as it decreases the incidence of complications of long-standing diabetes and malnutrition. This evidence supports the diffuse practice of prescribing PERT indiscriminately after pancreatic surgery, even though it must be said that an objective diagnosis of PEI with the measurement of FE-1 levels can be useful, especially in managing digestive symptoms that can arise after surgery and are not always only related to exocrine insufficiency.

In the specific setting of TPIAT, Bellin et al. found obesity (BMI >30 kg/m^2) to be a risk factor for worse survival [57], which can easily be explained by the higher incidence of metabolic comorbidities that come with obesity. Interestingly the authors found that a longer duration of disease prior to surgery correlates with a longer survival, which is in contrast with the previously mentioned worse results in terms of pain relief and QoL for these patients.

The effect of behavioral aspects on mortality after surgery for CP is well shown by the actual causes of death of these patients. With the limitation of missing data on the cause of death in many patients, especially in retrospective studies, CP related deaths seem to be a minority. The most frequently reported causes of death are infection, liver disease, cardiovascular disease, substance abuse related deaths and non-pancreatic cancer [34,39,49,50,56,57,63,64]. Both liver and cardiovascular disease are well known consequences of alcohol abuse that are worsened by the presence of diabetes, which itself is poorly managed in patients with ongoing alcohol abuse. Smoking is also frequent in CP patients, representing a major risk factor for cancer and exposing them to a higher risk of pulmonary infections. This data underlines the importance of treating alcohol abuse and promoting smoke cessation in CP patients.

Unfortunately, little data is found among these studies about pancreatic cancer risk after surgery for CP. Only one study reported deaths from pancreatic cancer, which occurred in 3 patients (2% of the deaths) [64]. Four studies didn't report any death from pancreatic cancer [34,39,50,63] and one reported 19% of deaths because of cancer of unspecified origin [49]. No pancreatic cancer deaths were of course reported in the studies dealing with TPIAT [56–58].

2.6 Risk factors

As reported above, only a handfull of studies evaluated risk factors for the different outcomes. We summarized the evidence on risk factors present in the included papers in Table 3.

Table 3. Risk factor for worse outcomes. QoL (quality of life), PPPD (pylorus preserving pancreaticoduodenectomy), PD (pancreaticoduodenectomy), DM (diabetes mellitus), PEI (pancreatic exocrine insufficiency), LPJ (lateral pancreaticojejunostomy), PERT (pancreatic enzyme replacement therapy), DPPHR (duodenum preserving pancreatic head resection).

Outcome	Procedure type	Pre surgery risk factors	Post surgery risk factors
Pain	No difference	Long duration of disease Opiate usage Multiple endoscopic procedures Continuous pain pattern	Persistence of alcohol abuse
QoL	Overal QoL: no difference Physical functioning: Frey (vs. PPPD); DPPHR (vs. PD and DP) Mental composed scores: head resection (vs. derivative)	Opioid use	No pain relief Persistent alcohol abuse Complications needing relaparotomy *DM and PEI: not related to worse QoL*
DM	Resective (vs. derivative) PD = DPPHR Beger = Berne Frey = Beger Frey vs. LPJ: contrasting results	Longer duration of disease Biliary obstruction	Re-operation because of any complication Any postoperative complication
PEI	Derivative vs. resective: contrasting results Frey = Beger, PPPD and LPJ	n.a.	n.a.
Survival	PPPD (vs. Frey) Frey = Beger DPPHR = PD	Smoking BMI <18.5 Multiple comorbidities Alcohol abuse	Persistent alcohol abuse Insulin dependent DM at discharge No PERT at discharge

3. Conclusions

In conclusion, in recent years many studies on long-term outcomes after surgery for CP have been published, but the strength of the findings is limited by many factors that make it difficult to compare results between different studies.

The starting point of this paper was to analyze the outcomes of surgery in a long-term prospective but we observed that a significant source of heterogeneity lies in the definition of 'long-term follow-up' itself, which in the selected studies ranges from just 1 to up to 15 years: such a large difference in follow-up time can determine significant discrepancies in the results, especially when dealing with outcomes such as PEI and DM development that are inherently time dependent due to the evolutive nature of CP. Of note, in many studies long-term outcomes, or a part of them, are only available for a fraction of the study population, therefore introducing bias in the statistical analysis on the effects of surgery and further reducing the overall strength of the results.

Most of the studies we reviewed were retrospective: many of them selected patients from a database of surgery recipients and only included those with an available follow-up of a certain duration; others sent follow-up questionnaires to all the surgery recipients, often receiving them back just from a fraction of patients. Both these study designs clearly introduce a relevant bias in patient selection. Another matter is how reliable can retrospectively compiled forms for QoL and pain be considered. Even among the prospective studies many were purely descriptive, without any statistical analysis of the post-surgery outcomes, and only a handful were proper randomized controlled trials. Moreover, half of the studies included less than 90 patients: not infrequently some outcomes presented remarkable differences between different groups but couldn't reach statistical significance because of the limited numerosity.

Another problem we encountered reviewing the data from these studies is heterogeneity in the classification of the procedures. In the introduction of this paper we described them as either derivative, resective or mixed; unfortunately, certain studies classify Frey's among resective procedures, thus making it difficult to compare results with other studies that separate it from purely resective procedures such as DP or DPPHR.

We also encountered heterogeneity in the reported outcomes on PEI and DM. Only three out of all the studies correctly defined PEI based on fecal elastase < 200ug/g as suggested by current guidelines on CP and exocrine insufficiency. All the others defined PEI as the presence of related clinical signs (steatorrhea, bloating etc.) and/or use of replacement therapy. This definition can underdiagnose PEI if the clinician isn't accurate on investigating symptoms preoperatively and can overestimate it postoperatively, since it's common practice in many centers to prescribe PERT in all patients after resective surgery, thus making impossible to have a reliable quantification of post-operative PEI prevalence. On the contrary, all the studies correctly define DM as per current guidelines, but some of them only report insulin-dependent patients, making it difficult to compare results with others that report all the diabetic patients irrespective of the antidiabetic therapy.

When dealing with exocrine and endocrine function we willingly only considered the reported prevalence of PEI and DM at the end of follow-up, and not the reported rates of 'de novo' PEI and DM. Not all the studies reported this outcome and, more importantly, among those that did the incidence is not calculated and defined homogeneously. Many papers calculated the incidence over the totality of surgery recipients, including those already diabetic/with PEI, and often it's not clear at what time point this rate is calculated: the more time passes between surgery and quantification of de-novo DM and PEI the more difficult it is to distinguish between the effect of surgery and the progression of the disease. In our opinion the clinically more useful outcome is how many non diabetic/non PEI patients pre-surgery will develop DM or PEI following surgery. We propose that de-novo PEI/DM should then be calculated as the number of patients that have PEI/DM at day 30 after surgery among those that did not have it at time of surgery. Comparing this incidence with the long-term overall prevalence of PEI and DM among CP patients could provide some insight on the actual impact of surgery over the natural course and progression of the disease.

4. Expert opinion

Pain is a relevant cause of reduced QoL for CP patients and all efforts should be made to improve its management. A common error in clinical practice is to stubbornly offer more and more repeated endoscopic procedures for patients that are already chronic opiates users, with practicable underwhelming results. Surgery is often seen by clinicians as kind of a 'defeat' of their efforts, and this is somewhat emphasized by current guidelines that propose surgery as a last resort only to be used when sure that anything else has been tried. Things probably need to change and a more proactive approach toward surgery is needed.

In the last decades significant improvement has been made in surgery for chronic pancreatitis. Many different techniques have been proposed and several studies tried to establish which of them could be the better choice. These studies usually focused on short-term outcomes from a strictly surgical point of view, such as evaluating differences between different techniques in terms of surgery duration, length of hospital stay, intraoperative blood loss, morbidity and mortality etc. All these parameters are of course important for surgeons but for us as gastroenterologists, the specialists who are usually caring for CP patients before and after surgery, this isn't enough. Our attention should be focused on three main questions: which patient will benefit most from surgery? When is it best indicated during the natural history of the disease? What will the long-term outcomes be for these patients after surgery? Answering these questions is the only way we will be able to make evidence-based decisions to offer our patients the best possible treatment, at the most appropriate time. As we've shown, the quality of evidence regarding these matters is on average quite low. In our opinion a consensus focused on the definition of clinically relevant outcomes should be pursued as it is much needed to improve the quality of the research in this field. As of today there are plenty of retrospective series but prospective studies, ideally randomized controlled trials, are in our opinion essential to reduce biases in patients selection and to produce more reliable results on subjective outcomes such as pain and QoL. Past studies mainly focused on describing and comparing outcomes between different procedures but as we've seen the results are rarely significantly different and, in the end, the choice between different techniques is probably to be made based on the surgeon's expertise. What studies should strive for in the future is to find patients' characteristics that are able to predict better or worse outcomes after surgery. The latest evidence in the field points toward the benefits of early surgery as opposed to its use as a last resource when other strategies have failed, but we cannot ignore the physical and psychological burden that such invasive procedures put on patients, which is particularly significant when dealing with a benign condition such as CP. It is thus crucial to be able to identify patients that will probably benefit most from surgery and can consequently be proposed with early intervention. Especially until those questions will be answered by solid evidence based data, a multidisciplinary approach involving gastroenterologists, interventional endoscopists, surgeons, and radiologists will be key. Only a shared decision-making process among different specialists allows to competently evaluate every possible therapeutical option for our patients, avoiding the risk of individual specialists only proposing patients the treatment options they're most used to or that they personally perform. In other terms, the choice between surgery, endoscopy or other treatments shouldn't be based solely on the patient being followed by a surgeon or by an endoscopist, but on a shared decision process among them, the patient and all the other figures involved in their care.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Löhr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPaneu). United Eur Gastroenterol J. 2017;5(2):153–199. doi: 10.1177/2050640616684695
   •• Current European guidelines on the management of CP.
2. Tanaka M, Matsumoto I, Shinzeki M, et al. Short- and long-term results of modified Frey's procedure in patients with chronic pancreatitis: a retrospective Japanese single-center study. Kobe J Med Sci. 2014;60:E30–6.
3. Vege SS, Chari ST, Solomon CG. Chronic pancreatitis. N Engl J Med. 2022;386(9):869–878. doi: 10.1056/NEJMcp1809396
4. Olesen SS, Juel J, Nielsen AK, et al. Pain severity reduces life quality in chronic pancreatitis: implications for design of future outcome trials. Pancreatology. 2014;14(6):497–502. doi: 10.1016/j.pan.2014.09.009
5. Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut. 2011;60(1):77–84. doi: 10.1136/gut.2010.213835
6. Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. Eur J Cancer. 1999;35(6):939–941. doi: 10.1016/S0959-8049(99)00047-7
7. Liu P, Lu CL, Wang C, et al. Spinal microglia initiate and maintain hyperalgesia in a rat model of chronic pancreatitis. Gastroenterology. 2012;142(1):165–173.e2. doi: 10.1053/j.gastro.2011.09.041
8. Poulsen JL, Olesen SS, Malver LP, et al. Pain and chronic pancreatitis: a complex interplay of multiple mechanisms. World J Gastroenterol. 2013;19(42):7282–7291. doi: 10.3748/wjg.v19.i42.7282
9. Drewes AM, Gratkowski M, Sami SAK, et al. Is the pain in chronic pancreatitis of neuropathic origin? Support from EEG studies during experimental pain. World J Gastroenterol: WJG. 2008;14(25):4020. doi: 10.3748/wjg.14.4020
10. Bouwense SAW, Olesen SS, Drewes AM, et al. Is altered central pain processing related to disease Stage in Chronic pancreatitis Patients with pain? An exploratory study. PLoS One. 2013;8(2):e55460. doi: 10.1371/journal.pone.0055460
11. Buscher HCJL, Wilder-Smith OHG, Van Goor H. Chronic pancreatitis patients show hyperalgesia of central origin: a pilot study. Eur J Pain. 2006;10(4):363. doi: 10.1016/j.ejpain.2005.06.006
12. Drewes AM, Krarup AL, Detlefsen S, et al. Pain in chronic pancreatitis: the role of neuropathic pain mechanisms. Gut. 2008;57(11):1616–1627. doi: 10.1136/gut.2007.146621
13. Wilcox CM, Yadav D, Ye T, et al. Chronic pancreatitis pain pattern and severity are Independent of Abdominal Imaging Findings. Clin Gastroenterol Hepatol. 2015;13(3):552. doi: 10.1016/j.cgh.2014.10.015
14. Ammann RW, Buehler H, Muench R, et al. Differences in the natural history of idiopathic (nonalcoholic) and alcoholic chronic pancreatitis. A comparative long-term study of 287 patients. Pancreas. 1987;2(4):368–377. doi: 10.1097/00006676-198707000-00002
15. Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. Gastroenterology. 1999;116(5):1132–1140. doi: 10.1016/S0016-5085(99)70016-8
16. Layer P, Yamamoto H, Kalthoff L, et al. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. Gastroenterology. 1994;107(5):1481–1487. doi: 10.1016/0016-5085(94)90553-3
17. Ventafridda V, Saita L, Ripamonti C, et al. WHO guidelines for the use of analgesics in cancer pain. Int J Tissue React. 1985;7(1):93–96.
18. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) guideline – updated August 2018. Endoscopy. 2019;51(2):179–193. doi: 10.1055/a-0822-0832
19. Tadenuma H, Ishihara T, Yamaguchi T, et al. Long-term results of extracorporeal shockwave lithotripsy and endoscopic therapy for pancreatic stones. Clin Gastroenterol Hepatol. 2005;3(11):1128–1135. doi: 10.1016/S1542-3565(05)00530-6
20. Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. JAMA - J Am Med Assoc. 2020;323(3):237–247. doi: 10.1001/jama.2019.20967
21. Kempeneers MA, Issa Y, Bruno MJ, et al. Cost-effectiveness of early surgery versus endoscopy-first approach for painful chronic pancreatitis in the ESCAPE trial. Ann Surg. 2023;277(4):E878–E884. doi: 10.1097/SLA.0000000000005240
   •• A recent trial on the benefits of early surgery in CP.
22. Tringali A, Vadalà di Prampero SF, Landi R, et al. Fully covered self-expandable metal stents to dilate persistent pancreatic strictures in chronic pancreatitis: long-term follow-up from a prospective study. Gastrointest Endosc. 2018;88(6):939–946. doi: 10.1016/j.gie.2018.08.019

• **Long term efficacy of FC-SEMS for refractory MPD strictures.**
23. Matsubara S, Sasahira N, Isayama H, et al. Prospective pilot study of fully covered self-expandable metal stents for refractory benign pancreatic duct strictures: long-term outcomes. Endosc Int Open. 2016;4(11):E1215–E1222. doi: 10.1055/s-0042-115934
24. Sofi AA, Khan MA, Ahmad S, et al. Comparison of clinical outcomes of multiple plastic stents and covered metal stent in refractory pancreatic ductal strictures in chronic pancreatitis- a systematic review and meta-analysis. Pancreatology. 2021;21(5):854–861. doi: 10.1016/j.pan.2021.03.017
25. Bouwense SAW, Kempeneers MA, Van Santvoort HC, et al. Surgery in chronic pancreatitis: indication, timing and procedures. Visc Med. 2019;35(2):110–118. doi: 10.1159/000499612
26. Jabłońska B, Mrowiec S. Total pancreatectomy with autologous islet cell transplantation—the Current indications. J Clin Med. 2021;10(12):2723. doi: 10.3390/jcm10122723
27. Bachmann K, Melling N, Groteluschen R, et al. Morphologic factors predict pain relief following pancreatic head resection in chronic pancreatitis description of the chronic pancreatitis pain relief (CPPR) score. Ann Surg. 2021;273(4):800–805. doi: 10.1097/SLA.0000000000003439
28. Zhao X, Cui N, Wang X, et al. Surgical strategies in the treatment of chronic pancreatitis: an updated systematic review and meta-analysis of randomized controlled trials. Medicine. 2017;96 (9):e6220. doi: 10.1097/MD.0000000000006220
29. McCormack HM, Horne DJDL, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med. 1988;18 (4):1007–1019. doi: 10.1017/S0033291700009934
30. Bloechle C, Izbicki JR, Knoefel WT, et al. Quality of life in chronic pancreatitis—results after duodenum-preserving resection of the head of the pancreas. Pancreas. 1995;11(1):77–85. doi: 10.1097/00006676-199507000-00008
31. Kuhlmann L, Teo K, Olesen SS, et al. Development of the comprehensive pain assessment tool short form for chronic pancreatitis: validity and reliability testing. Clin Gastroenterol Hepatol. 2022;20: e770–e783. doi: 10.1016/j.cgh.2021.05.055
• **A new comprehensive tool for evaluating pain in CP.**
32. Keck T, Wellner UF, Riediger H, et al. Long-term outcome after 92 duodenum-preserving pancreatic head resections for chronic pancreatitis: comparison of beger and frey procedures. J Gastrointestinal Surg. 2010;14(3):549–556. doi: 10.1007/s11605-009-1119-9
33. Kempeneers MA, Van Hemert AKE, Van Der Hoek M, et al. Short- and long-term outcomes of selective use of Frey or extended lateral pancreaticojejunostomy in chronic pancreatitis. Br J Surg. 2022;109(4):363–371. doi: 10.1093/bjs/znab473
34. Bachmann K, Tomkoetter L, Kutup A, et al. Is the whipple procedure harmful for long-term outcome in treatment of chronic pancreatitis? 15-years follow-up comparing the outcome after pylorus-preserving pancreatoduodenectomy and Frey procedure in chronic pancreatitis. Ann Surg. 2013;258(5):815–821. doi: 10.1097/SLA.0b013e3182a655a8
35. Keck T, Adam U, Makowiec F, et al. Short- and long-term results of duodenum preservation versus resection for the management of chronic pancreatitis: a prospective, randomized study. Surgery (United States). 2012;152:S95–S102. doi: 10.1016/j.surg.2012.05.016
36. Benzing C, Hau HM, Atanasov G, et al. Surgical therapy of chronic pancreatitis: clinical results and health-related quality of life. Z Gastroenterol. 2018;56(11):1354–1364. doi: 10.1055/a-0713-0873
37. Matsumoto I, Kamei K, Murase T, et al. Surgical treatment for chronic pancreatitis: a single-center retrospective study in Japan. J Hepatobiliary Pancreat Sci. 2020;27:632–639. doi: 10.1002/jhbp.795
38. Shahbazov R, Yoshimatsu G, Haque WZ, et al. Clinical effectiveness of a pylorus-preserving procedure on total pancreatectomy with islet autotransplantation. Am J Surg. 2017;213(6):1065–1071. doi: 10.1016/j.amjsurg.2016.09.051
39. Klaiber U, Alldinger I, Probst P, et al. Duodenum-preserving pancreatic head resection: 10-year follow-up of a randomized controlled trial comparing the beger procedure with the berne modification. Surgery (United States). 2016;160(1):127–135. doi: 10.1016/j.surg.2016.02.028
40. Van Der Gaag NA, Van Gulik TM, Busch ORC, et al. Functional and medical outcomes after tailored surgery for pain due to chronic pancreatitis. Ann Surg. 2012;255(4):763–770. doi: 10.1097/SLA.0b013e31824b7697
41. Ahmed Ali U, Nieuwenhuijs VB, Van Eijck CH, et al. Clinical outcome in relation to timing of surgery in chronic pancreatitis: a nomogram to predict pain relief. Arch Surg. 2012;147(10):925–932. doi: 10.1001/archsurg.2012.1094
42. Ray S, Das K, Khamrui S, et al. Short- and long-term outcome of Frey procedure for chronic pancreatitis in adults. Am J Surg. 2021;222(4):793–801. doi: 10.1016/j.amjsurg.2021.02.006
43. Cauchy F, Regimbeau JM, Fuks D, et al. Influence of bile duct obstruction on the results of Frey's procedure for chronic pancreatitis. Pancreatology. 2014;14(1):21–26. doi: 10.1016/j.pan.2013.10.008
44. Winny M, Paroglou V, Bektas H, et al. Insulin dependence and pancreatic enzyme replacement therapy are independent prognostic factors for long-term survival after operation for chronic pancreatitis. Surgery (United States). 2014;155(2):271–279. doi: 10.1016/j.surg.2013.08.012
45. Negi S, Singh A, Chaudhary A. Pain relief after Frey's procedure for chronic pancreatitis. Br J Surg. 2010;97(7):1087–1095. doi: 10.1002/bjs.7042
46. Ware JE. SF-36 health survey update. *Spine (Phila Pa 1976)*. 2000;25 (24):3130–3139. doi: 10.1097/00007632-200012150-00008
47. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–376. doi: 10.1093/jnci/85.5.365
48. Wilson GC, Ahmad SA, Schauer DP, et al. Cost-effectiveness of total pancreatectomy and islet cell autotransplantation for the treatment of minimal change chronic pancreatitis. J Gastrointestinal Surg. 2015;19(1):46–55. doi: 10.1007/s11605-014-2612-3
49. Bachmann K, Tomkoetter L, Erbes J, et al. Beger and frey procedures for treatment of chronic pancreatitis: comparison of outcomes at 16-year follow-up. J Am Coll Surg. 2014;219(2):208–216. doi: 10.1016/j.jamcollsurg.2014.03.040
50. Rückert F, Distler M, Hoffmann S, et al. Quality of life in patients after pancreaticoduodenectomy for chronic pancreatitis. J Gastrointestinal Surg. 2011;15(7):1143–1150. doi: 10.1007/s11605-011-1539-1
51. Hildebrand P, Duderstadt S, Jungbluth T, et al. Evaluation of the quality of life after surgical treatment of chronic pancreatitis. JOP. 2011;12(4):364–371.
52. Wehler M, Nichterlein R, Fischer B, et al. Factors associated with health-related quality of life in chronic pancreatitis. Am J Gastroenterol. 2004;99(1):138–146. doi: 10.1111/j.1572-0241.2004.04005.x
53. Czakó L, Takács T, Hegyi P, et al. Quality of life assessment after pancreatic enzyme replacement therapy in chronic pancreatitis. Can J Gastroenterol. 2003;17(10):597–603. doi: 10.1155/2003/515848
54. De La Iglesia-García D, Huang W, Szatmary P, et al. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. Gut. 2017;66(8):1354.1–1355. doi: 10.1136/gutjnl-2016-312529
55. Campagnola P, de Pretis N, Zorzi A, et al. Chronic pancreatitis and nutritional support. Best Pract Res Clin Gastroenterol. 2023;101823:101823
• **A recent update on the overall management of nutrition in CP.**
56. Turner KM, Delman AM, Donovan EC, et al. Total pancreatectomy and islet cell autotransplantation: a 10-year update on outcomes and assessment of long-term durability. HPB. 2022;24(11):2013–2021. doi: 10.1016/j.hpb.2022.07.001
57. Bellin MD, Beilman GJ, Sutherland DE, et al. How durable is total pancreatectomy and intraportal islet cell transplantation for treatment of chronic pancreatitis? J Am Coll Surg. 2019;228(4):329–339. doi: 10.1016/j.jamcollsurg.2018.12.019
58. Wilson GC, Sutton JM, Abbott DE, et al. Long-term outcomes after total pancreatectomy and islet cell autotransplantation: is it a durable operation? *Ann Surg*. 2014;260(4):659–667. discussion 665-7 doi: 10.1097/SLA.0000000000000920

59. Diener MK, Hüttner FJ, Kieser M, et al. Partial pancreatoduodenectomy versus duodenum-preserving pancreatic head resection in chronic pancreatitis: the multicentre, randomised, controlled, double-blind ChroPac trial. Lancet. 2017;390(10099):1027–1037. doi: 10.1016/S0140-6736(17)31960-8
60. Arvanitakis M, Ockenga J, Bezmarevic M, et al. ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. Clin Nutr. 2020;39(3):612–631. doi: 10.1016/j.clnu.2020.01.004
61. Nøjgaard C, Bendtsen F, Becker U, et al. Danish patients with chronic pancreatitis have a four-fold higher mortality rate than the Danish population. Clin Gastroenterol Hepatol. 2010;8(4):384–390. doi: 10.1016/j.cgh.2009.12.016
62. Yadav D, Timmons L, Benson JT, et al. Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. Am J Gastroenterol. 2011;106(12):2192–2199. doi: 10.1038/ajg.2011.328
63. Murruste M, Kirsimägi Ü, Kase K, et al. Long-term survival, risk factors and causes of mortality in surgically treated chronic pancreatitis. Pancreatology. 2021;21(4):714–723. doi: 10.1016/j.pan.2021.03.003
64. Wilson GC, Turner KM, Delman AM, et al. Long-term survival outcomes after operative management of chronic pancreatitis: two decades of experience. J Am Coll Surg. 2023;236(4):601–610. doi: 10.1097/XCS.0000000000000575