



International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis

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ABSTRACT

Background/objectives: Chronic pancreatitis (CP) is a complex inflammatory disease with pain as the predominant symptom. Pain relief can be achieved using invasive interventions such as endoscopy and surgery. This paper is part of the international consensus guidelines on CP and presents the consensus guideline for surgery and timing of intervention in CP.

Methods: An international working group with 15 experts on CP surgery from the major pancreas societies (IAP, APA, JPS, and EPC) evaluated 20 statements generated from evidence on 5 questions deemed to be the most clinically relevant in CP. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the level of evidence available for each statement. To determine the level of agreement, the working group voted on the 20 statements for strength of agreement, using a nine-point Likert scale in order to calculate Cronbach's alpha reliability coefficient.

Results: Strong consensus was obtained for the following statements: Surgery in CP is indicated as treatment of intractable pain and local complications of adjacent organs, and in case of suspicion of malignant (cystic) lesion; Early surgery is favored over surgery in a more advanced stage of disease to achieve optimal long-term pain relief; In patients with an enlarged pancreatic head, a combined drainage and resection procedure, such as the Frey, Beger, and Berne procedure, may be the treatment of choice; Pancreaticoduodenectomy is the most suitable surgical option for patients with groove pancreatitis; The risk of pancreatic carcinoma in patients with CP is too low (2% in 10 year) to recommend active screening or prophylactic surgery; Patients with hereditary CP have such a high risk of pancreatic cancer that prophylactic resection can be considered (lifetime risk of 40–55%). Weak agreement for procedure choice in patients with dilated duct and normal size pancreatic head: both the extended lateral pancreaticojejunostomy and Frey procedure seems to provide equivalent pain control in patients.

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Conclusions: This international expert consensus guideline provides evidenced-based statements concerning key aspects in surgery and timing of intervention in CP. It is meant to guide clinical practitioners and surgeons in the treatment of patients with CP.

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Introduction

Chronic pancreatitis (CP) is a complex inflammatory disease with pain as the most dominant symptom. Pain reduction is the main goal of treatment since it is the most important factor that influences the quality of life in patients with CP [1]. Lifestyle management, including cessation of alcohol use and smoking, and medical therapy (including opioid analgesics) are the first line treatment for CP but are often not sufficient to relieve pain. A large percentage of patients with symptomatic CP have morphological abnormalities such as a ductal obstruction due to ductal strictures, ductal stones, inflammatory pancreatic (head) mass and/or pseudocysts [2–4]. The rationale of endoscopic and surgical pain treatment is that pain relief will be achieved by reducing ductal pressure by removing the obstruction and/or resecting of an inflammatory pancreatic mass.

Invasive pain treatment includes both endoscopic and surgical techniques, and in current clinical practice, endoscopy is often attempted first before surgical treatment is performed. For years, the optimal treatment of CP related pain has been debated, especially regarding the timing of endoscopy and surgery in the course of CP. This has resulted in inconsistency in several recently published guidelines, since some guidelines recommend surgery as the most effective treatment, whereas others advise a step-up approach with surgery as last treatment option [5–7].

Although there are several different treatment guidelines for CP in circulation, the aim of the International Guidelines on Chronic Pancreatitis was to create a consensus guideline that is truly international and multidisciplinary, covering from development and early diagnosis to progression and treatment of CP. To develop the first international guidelines on CP, John Neoptolemos, David Whitcomb, Carlos Fernandez-Del Castillo, and Tooru Shimosegawa started at the EPC 2016 on a joint venture with endorsement from the international societies: International Association of Pancreatology (IAP), American Pancreatic Association (APA), Japan Pancreas Society (JPS) and the European Pancreatic Club (EPC). International experts were identified to have a multidisciplinary representation within subgroups focusing on 16 key topics of CP. The first major step was the agreement on a new mechanistic definition of CP [8]. Thereon several other parts of the consensus guidelines were published, covering the early diagnosis of CP, imaging of CP and understanding and management of pain [9–11]. This manuscript is another part of the international consensus guidelines, covering the topic on surgery and timing of intervention in CP and is meant to guide the clinical practitioners and surgeons in the treatment of patients with CP.

Methods

For this key topic ‘Surgery and timing of intervention in CP’ a team of fifteen worldwide experts on surgery in CP and additional research fellows was composed, with MAB appointed as chair of the group. Based on a review of data from the relevant literature all experts presented their perspectives on the role of surgery and timing of intervention in the treatment of CP. The method of the systematic literature review on articles on CP was previously

described [8]. For this surgical topic, the international experts evaluated 20 statements generated from evidence on 5 questions deemed the most clinically relevant in CP.

Grading

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the level of evidence per statement (see <http://www.uptodate.com/home/gradingtutorial>). Quality assessment of evidence was graded as ‘high’ if there was (very) low probability of further research substantially changing the conclusions, ‘moderate’ if further research might completely change the conclusions, and ‘low’ if further research was likely to completely change the conclusions. The strengths of the recommendation were graded as ‘strong’ if it was very certain that benefits outweigh risks and burdens, ‘weak’ if risks and burdens appear to be finely balanced, or when benefits, risks, and burdens are closely balanced or uncertain, or ‘conditional’ if it was in between strong and weak recommendation.

Consensus

After grading, the working group of international experts voted on the 20 statements for strength of agreement, using a nine-point Likert scale. Out of the results, a Cronbach’s alpha reliability coefficient was calculated for each statement (<http://hdl.handle.net/1805/344>). The voting results were classified for agreement as either; ‘strong’ if 80% of votes were 7 or above, ‘conditional’ if 65% of votes were 7 or above, and ‘weak’ less than 65% of votes were 7 or above. In addition, comments to each question and statements were compiled to explain the surrounding issues, supported by key references. An overview of results of most important studies were tabulated and presented in the supplementary appendix. All statements and comments were reviewed by all authors to ensure the general relevance and applicability of the conclusions. Eventually a final draft of the document was generated and circulated to all authors for final editing and approval.

Results

Question 1: what are the indications for surgery in CP?

Statement

1.1 The most common indication for surgery for CP is intractable pain

Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 86%).

1.2 Other indications for surgery are a suspicion of neoplasm

Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 100%).

1.3 Other indications for surgery are local complications of adjacent organs, such as duodenal or common bile duct stenosis, pseudoaneurysm or erosion of the large vessels, large pancreatic pseudocysts and internal pancreatic fistula.

Quality assessment: moderate; Recommendation: conditional; Agreement: strong (alpha-score 86%).

Comments

At present, conservative management is always the first step, even in patients with clear morphological changes. Longitudinal studies show that of all CP patients, 40–75% will require surgery in the course of the disease [12–14]. Progression to severe and intractable pain is considered necessary before invasive treatment is considered [15].

The most common indication for surgery for CP is intractable pain. Traditionally, a long period of medical pain management (opioid analgesics) and multiple endoscopic interventions precede surgery. When both medical management as endoscopic interventions fails to provide pain relief, surgery is the last option. For example, in an expert center a large cohort of patients with CP underwent surgery for CP after a median period of 40 months (10th – 90th percentile; 12–132 months) after start of pain complaints and after a median of 2 (ranging 0 to 29) endoscopic procedures [16]. This approach can be questioned, because evidence suggests that early surgical intervention can mitigate the disease progression, achieve pain control, and preserve the pancreatic function.

A small proportion of patients undergoing repetitive endoscopy do not have pain when stents are changed regularly (progressive stenting). In these patients, pain reduction and complete duct clearance without stents should be obtained after several endoscopic procedures, since multiple endoscopic interventions are associated with reduced success with respect to long term pain relief after surgery (evidence regarding early surgery is reviewed in question 2) [17].

Other indications for surgery are a suspicion of neoplasm and local complications of adjacent organs, such as duodenal or common bile duct stenosis, pseudoaneurysm or erosion of the large vessels, large pancreatic pseudocysts and internal pancreatic fistula. Pancreatic pseudocysts can be treated either by endoscopic (transmural or transpapillary) or surgical intervention. Percutaneous drainage is not recommended. Surgical drainage tend to have a higher success rate, but endoscopic drainage has a somewhat lower mortality. Therefore a multidisciplinary treatment approach is recommended [7,18].

The primary goal of surgery for CP is long-term pain relief and control of the complications associated with CP. The optimal surgical procedure should manage the pain, preserve a maximum of endocrine and exocrine function still present, lead to reduction or cessation of opioid use, restore quality of life, and in some cases resolve complications of adjacent structures whenever possible (e.g., duodenal stenosis). Several surgical strategies are available for the treatment of pain in CP, and can be categorized into three major categories of procedures: decompression (focusing on ductal hypertension), resection (focusing on inflammatory masses in the pancreatic head), and mixed techniques.

In part, the type of surgical procedure is chosen based on the presence of morphological features of the pancreas (e.g., inflammatory mass of head or tail, strictures/dilatation of the PD, duct disruption) and involvement of adjacent structures (e.g., duodenal or CBD stenosis, portal hypertension with newly formed vascular collaterals). The effectiveness for pain control weighed against the risk of complications is also important when choosing a particular surgical procedure. This evidence reviewed and dealt with is question 3.

Question 2: what is the optimal timing of surgery?

Statement

2.1 Surgery early in the disease process of CP is favored over surgery in a more advanced stage of disease to achieve optimal long-term pain relief.

Quality assessment: moderate; Recommendation: strong; Agreement: strong (alpha-score 100%).

2.2 The risk of developing pancreatic exocrine insufficiency is lower after early surgery for CP than after surgery performed in an advanced disease stage. Pancreatic resection techniques have a higher risk for PEI than drainage techniques.

Quality assessment: low; Recommendation: conditional; Agreement: conditional (alpha-score 79%).

2.3 No recommendation can be drawn from the evidence regarding the effect of early surgery on developing endocrine pancreatic function during follow-up due to few and contradicting studies.

Quality assessment: low; Recommendation: none; Agreement: weak (alpha-score 64%).

2.4 Long-term quality of life is improved after early surgery (<3 years of onset) compared to surgery in a more advanced stage of disease

Quality assessment: low; Recommendation: conditional; Agreement: conditional (alpha-score 79%).

Comments

In current clinical practice, surgery is often offered in late phase of treatment, after a long period of medical pain management and multiple endoscopic interventions. The delay in surgical intervention, with subsequent prolonged periods of pain and opioid use leads to opioid dependency and eventually to the development of neuropathic pain. When this neuropathic pain has developed, the pain is very difficult to treat [19]. Several observational studies showed that early surgery leads to more pain relief and less postoperative opioid use compared to late surgery [17,20–25]. An Individual Patient Data Meta-Analysis (IPDMA) of raw data of two randomized controlled trials including 406 patients focused on complete pain relief after surgery [25–27]. In this study, early surgery was associated with an increased likelihood of complete pain relief (RR 1.67 (1.09–2.56), $P = 0.02$). Early surgery was associated with a reduced risk of pancreatic insufficiency and low re-intervention rates. In a cross-sectional study of Ahmed Ali et al., 266 patients were included with a mean follow-up of 62 months. Pain relief after surgery was associated with a short preoperative period of pain (≤ 3 vs. > 3 years; OR 1.81 (1.02–3.37), $P = 0.03$), no preoperative opioid use (OR 2.14 (1.23–3.96), $P = 0.006$), and less than 5 endoscopic interventions before surgery (OR 2.46 (1.10–6.27), $P = 0.04$) [17]. See the supplementary appendix [Tables S1 and S2](#) for an overview of studies comparing early and late surgery.

Progressive inflammation and fibrosis caused by CP leads to destruction of the pancreatic function cells. Development of pancreatic insufficiency increases over time and after 12 years of CP 50% of patients have developed pancreatic exocrine insufficiency [14]. It has been suggested that surgery in the early phase can prevent for development of exocrine insufficiency as it could limit inflammation through resection of an inflammatory mass or

drainage of an obstructed pancreatic duct [22–24]. In a cross-sectional study of 224 patients, early surgery (within 3 years) was compared with late surgery (after >3 years). Development of exocrine insufficiency on long term was less in the early surgery group compared with the late surgery group (OR 2.47 (1.38–4.41), $P = 0.002$) [23].

Endocrine insufficiency develops later in the disease process compared with exocrine insufficiency. After 20 years of disease, 50% of patients develop diabetes mellitus [28]. Several studies investigated the effect of timing of surgery on endocrine insufficiency; in which a small and even none effect of early surgery on the preserving endocrine function was found [17,22–24]. Potentially no effect of early surgery on endocrine insufficiency is present since this insufficiency develops late in the disease progress and most of the surgery is already performed before the development of endocrine insufficiency. Table S2 provides an overview of studies investigating the effect of timing of surgery on pancreatic exocrine and endocrine insufficiency.

A lower quality of life in CP is most associated with pain and pain-related disability [1]. Surgery performed in the early phase of the disease, may lead to greater pain relief and pain-related disability compared to surgery performed in a later stage of the disease. This is confirmed in one study investigating the timing of surgery on quality of life [17]. In that study, long-term preoperative opioid use was also associated with a lower quality of life for both the physical and mental components.

Remark

There is currently an ongoing RCT, that recently finish accrual, designed to examine the benefits of early surgery versus optimal current step-up practice for CP [29].

Question 3: what are the surgical options for the treatment for CP?

What operative technique should be used for patients with CP and enlarged pancreatic head?

Statement

3.1 In patients with CP and an enlarged pancreatic head, performing a combined drainage and resection, such as Frey, Beger, and Berne procedure may be the treatment of choice. The combined procedure such as Frey or Beger procedure have been shown to be superior to pancreaticoduodenectomy (PD) or pylorus-preserving pancreaticoduodenectomy (PPPD) in terms of postoperative complications; with comparable results in pain relief results. The Frey and Berne procedures have similar results when compared to each other and to the Beger procedure from which they are both derived. The Frey and Berne procedures have however a lower morbidity rate with a comparable effect on pain control and quality of life.

Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 86%).

Short-term results (up to 2 years of follow-up)

DPPHR versus PD. The available data show that the DPPHR and PD procedures are equally effective in relieving post-operative pain. Specifically, no differences are seen for DPPHR versus PD for post-operative pain relief, overall mortality and morbidity up to two years of follow-up. Intraoperative blood replacement, hospital stay, weight gain, occupational rehabilitation, and quality of life are significantly improved after DPPHR. Endo- and exocrine insufficiency are comparable after both strategies in the short-term

assessment. However, the two procedures are not strictly comparable as a high proportion of patients with an inflammatory mass in the head of the pancreas and involvement of surrounding vessels may not be able to undergo a PD procedure, but can still undergo a DPPHR (*Quality assessment: high*).

Modifications of DPPHR. The Beger and Berne procedures are equal in terms of pain relief, postoperative morbidity and mortality. The operating time and time of hospital stay for the Berne procedure is significantly shorter (GRADE 1B).

There is no difference between the Frey and Beger procedures in terms of pain relief, postoperative mortality and operating time. Compared to the Beger procedure, intraoperative blood replacement and postoperative morbidity are significantly improved for the Frey procedure (*Quality assessment: high*).

Long-term results (up to 15 years of follow-up)

DPPHR versus PD. The available long-term data show continued pain relief in the majority of patients, with no differences between surgical procedures for pain and quality of life outcomes. Occupational rehabilitation remains significantly better with DPPHR (*Quality assessment: high*). There is a non-significant trend towards improved long-term mortality with DPPHR (*Quality assessment: moderate*). Endo- and exocrine insufficiency were comparable after both strategies in the long-term assessment.

Modifications of DPPHR. There are no differences in long-term outcomes between the Frey, Beger, and Berne procedures (*Quality assessment: high*).

Comments. Surgical procedures for CP can be categorized into three major groups: drainage procedures (e.g., pancreaticojejunostomy), procedures combining drainage and resection (Frey or Beger procedure), and resectional procedures (e.g., PD or PPPD). In the patients who have an inflammatory mass in the pancreatic head and have dilation of the main pancreatic duct, the Frey, Beger or Berne procedure may be the treatment of choice [30–33]. The DPPHR procedures are aimed at drainage of the pancreatic duct and have the theoretical advantage of removal of the inflammatory mass in the pancreatic head and resolution of the biliary tract obstruction in a single operation [34]. The Frey, Beger and Berne procedures have similar results when compared to each other. However, in patients with an inflammatory mass in the pancreatic head and strictures or stones in the more distal pancreatic duct (corpus or tail), a Frey procedure is advised over the Beger and Berne procedure since latter procedures do not drain the entire length of the pancreatic duct.

The preserving (DPPHR) procedures and the resectional (PD and PPPD) procedures are not entirely comparable as a high proportion of patients with an inflammatory mass in the head of the pancreas and involvement of surrounding vessels cannot undergo a resectional procedure but can still undergo a DPPHR. As reported in the original report of the Berne variation this procedure can be used in “patients with portal hypertension and dilated collateral veins” but the actual experience in these kinds of cases in that report was very limited [33]. None of the randomized trials has considered this difference, as the eligibility criteria include the requirement that the patient is suitable to undergo either procedure in question.

Several randomized controlled trials have been performed comparing a DPPHR procedure with PD, showing overall no significant differences [35–42]. A multicenter randomized controlled trial compared DPPHR techniques with PD/PPPD in a pragmatic design. It demonstrated no differences in quality of life between both interventions 24 months after surgery. In addition, no differences in mortality, morbidity and the new onset of pancreatic insufficiency was seen. DPPHR resulted in a shorter operating time compared to PD, but patients treated with DPPHR were more frequently readmitted to the hospital during follow-up due to CP,

although it should be noted that only 296 (65.8%) of the 450 patients randomized were actually included in the analysis [36]. Additionally, a small RCT which compared the Beger procedure with PD or PPPD mentioned that incidence of delayed gastric emptying after Beger procedure was less frequent than that after PPPD [40]. Another small RCT, which compared the Frey procedure with PPPD, showed that the overall morbidity rate in the Frey procedure was lower than that in PPPD (19% vs 53%, $p < 0.05$) and that quality of life was improved by 71% in Frey procedure and by 43% in PPPD ($p < 0.01$) [37]. RCTs which evaluated long-term follow-up revealed that there was no difference between the Frey or the Beger procedure and PPPD in terms of pain relief, quality of life and pancreatic function [38,41,42]. A systematic review and meta-analysis [43] of 4 RCTs [35,37,39,44] comparing DPPHR (Frey and Beger procedures and modifications) with PD demonstrated no significant differences in terms of postoperative pain relief, overall morbidity, postoperative pancreatic fistula development, or operating time. Only for the Frey procedure, a significant reduction of operating time, delayed gastric emptying, duration of hospital stay, and need for perioperative blood transfusion were observed compared to PPPD. Furthermore, the DPPHR group had a higher quality of life, postoperative weight gain, and more exocrine function impairment compared with the PD group [34,43].

The results of both the Frey and Beger procedures in terms of pain relief and quality of life seem to be comparable [45]. Forty-two patients with an inflammatory mass in the head of the pancreas for CP allocated randomly to either the Beger ($n = 20$) or the Frey ($n = 22$) procedure found no significant differences in pain relief (morbidity: 20% vs 9%, decrease of pain scores: 95% vs 94%, overall increase of quality of life: 67% vs 67%) [46]. This same study continued to recruit patients until 74 patients were included [47]. In 2005, the long-term results of these 74 patients with a median follow-up of 104 months were reported [48]. No significant differences between the groups with regard to pain scores, global quality of life, late mortality, and pancreatic exocrine and endocrine insufficiency were found [48]. A non-randomized comparison of 42 Beger, and 50 Frey procedures with a median follow-up almost 5 years found that pain control after the Frey procedure was better than that after the Beger procedure (complete pain relief: 62% vs 50%) and there was no difference in term of morbidity (30% vs 40%), incidence of new-onset of diabetes mellitus (60% vs 57%) and rate of exocrine insufficiency (76% vs. 74%) [49]. A systematic review and meta-analysis [50] of 2 RCTs [38,48] comparing the Frey with the Beger procedures showed no difference in post-operative pain, mortality, morbidity, exocrine insufficiency and endocrine insufficiency. A 5-year long-term outcome analysis of fifty-one patients with head resection for CP (PD = 24; DPPHR = 27) documented superiority of the Beger duodenum-preserving technique over the classic Whipple procedure in terms of quality of life and pain intensity as self-assessed by the patients [45]. A RCT on the evaluation of Berne and Beger procedures showed that Berne procedure provided significantly shorter operation times (323 vs 369 min, $p = 0.02$) and hospital stays (11 vs 15 days, $p = 0.015$), while the quality of life was identical [51]. However, ten-year follow-up did not show any differences between Berne and Beger procedures in term of complete pain relief (55% vs 56%, $p = 0.94$), new-onset of DM (55% vs 33%, $p = 0.31$) and exocrine insufficiency (68% vs 83%, $p = 0.46$) [52].

What operative technique should be used for patients with CP and a dilated pancreatic main duct and a documented normal size pancreatic head?

Statement

3.2 In adult patients, a main duct diameter of 5 mm or more in the pancreatic body seems amenable to ductal drainage for the

majority of pancreatic surgeons. This threshold of 5 mm could be proposed as definition of a “dilated main duct”.

Quality assessment: low; Recommendation: conditional; Agreement: conditional (alpha-score 71%).

3.3 Both, the extended lateral pancreaticojejunostomy on a Roux-en-Y loop and Frey procedure seems to provide equivalent pain control in patients with main duct dilatation and normal size pancreatic head, but studies with a direct comparison of the two techniques are lacking. For patient with painful CP and a dilated duct and normal size pancreatic head, an extended lateral pancreaticojejunostomy on a Roux-Y loop and Frey procedure provide comparable pain control (low quality of evidence). No preference can be made which is the best surgical technique of the two in these patients.

Quality assessment: low; Recommendation: conditional; Agreement: weak (alpha-score 50%).

Comments

In adult patients, a main duct diameter of 5 mm or more in the pancreatic body seems amenable to ductal drainage for the majority of pancreatic surgeons. This threshold of 5 mm could be proposed as definition of a “dilated main duct”. Different thresholds used in studies to define a dilated main duct in CP, ranging from 3 mm by Izbicki et al. to 8 mm by Nealon et al. [22,26,29,37,53–61] However, in most of the recent studies, a pancreatic duct of more than 5 mm is defined as dilated (Table S3).

In the literature published from 1993, patients with dilated pancreatic main duct and documented normal size pancreatic head were mainly treated by a lateral pancreaticojejunostomy (Table S4) [16,26,53,54,57,59,60,62–74]. Several techniques of the lateral pancreaticojejunostomy are alternately used in the literature, of which the lateral pancreaticojejunostomy according to Partington & Rochelle is most commonly described. According this procedure, the dilated pancreatic duct is longitudinally opened toward the tail and somewhat to the right of the mesenteric vessels. The opened pancreatic duct is then covered by a Roux-en-Y loop [75]. However, the majority of the obstructed ducts at the pancreatic head are left undrained. To overcome this pitfall, the *extended* lateral pancreaticojejunostomy is recommended in which the pancreatic duct is opened to within 1–2 cm of the splenic hilum and within 1 cm of the duodenum to decompress the complete pancreatic duct including the ducts of Wirsung and Santorini [16,68]. In patients with an isolated obstruction of the distal pancreatic duct, an extended lateral pancreaticojejunostomy is preferred over a distal pancreatectomy. A distal pancreatectomy unnecessarily increases the risk of developing endocrine insufficiency and should therefore be avoided in patients with chronic pancreatitis [76]. The Beger procedure was evaluated in patients with ductal obstruction in only one retrospective study [77]. Findings were evaluated according to head size: a good result (opiate withdrawal) was observed in 3 of 11 (27%) patients without head enlargement and 13 of 16 patients (81%) with head enlargement, respectively ($p = 0.018$) [77]. In some recent series, patients received lateral pancreaticojejunostomy and/or Frey procedure according to the surgeon's preference or the study period. Characteristics of studies and results of lateral pancreaticojejunostomy and Frey procedure are given in Table S4 (series including patients with an enlarged pancreatic head were excluded).

Question 4: what is the role of surgery in groove pancreatitis?**Statement**

4.1 Surgery should be performed when medical and endoscopic options have failed. Surgery should be aimed at pain relief and/or complete pain resolution, and to solve the malnutrition status

Quality assessment: very low; Recommendation: conditional; Agreement: conditional (alpha-score 71%).

4.2 Initial treatment of groove pancreatitis should involve medical treatment and occasionally, endoscopic drainage procedures may be helpful. If these approaches fail, the patient should be referred for surgery.

Quality assessment: very low; Recommendation: conditional; Agreement: conditional (alpha-score 71%).

4.3 In expert hands, pancreaticoduodenectomy is the most suitable surgical option for patients with groove pancreatitis.

Quality assessment: very low; Recommendation: conditional; Agreement: strong (alpha-score 86%).

Comments

No RCTs on this topic were found, hence all the studies considered are observational cohort studies or retrospective analyses (Table S5) [78–82]. The quality of the evidence is predictably low and influenced by selection bias. Nor did any study compare medical, endoscopic and surgical treatments. There are no studies comparing pancreas-preserving vs. pancreas-sparing procedures. The pancreas-sparing procedures have been described as surgical options when only the duodenum is involved and pancreatic involvement can be ruled out. An additional argument in favor of pancreaticoduodenectomy is that there is a small, but yet unquantifiable risk of pancreatic cancer in patients with presumed groove pancreatitis. See Table S5 for an overview of all studies investigating surgery in groove pancreatitis.

Question 5: how to assess the risk of pancreatic cancer in a patient with CP? Is there a role for prophylactic (cancer) surgery?**Statement**

5.1 Surgical resection should be chosen for a suspected malignant cystic lesion.

Quality assessment: high; Recommendation: strong; Agreement: strong (alpha-score 100%).

5.2 The risk of pancreatic carcinoma is somewhat higher in patients with CP but still too low to recommend active screening or prophylactic surgery.

Quality assessment: moderate; Recommendation: conditional; Agreement: strong (alpha-score 93%).

5.3 Patients with hereditary CP have such a high risk of pancreatic cancer that prophylactic resection can be considered.

Quality assessment: moderate; Recommendation: conditional; Agreement: weak (alpha-score 57%).

Comments

Background risk for pancreatic cancer in patients with CP. Evidence has recently been reviewed in a publication by Issa et al. [83] A significant association exists between smoking and pancreatic cancer, with a 2- to 3-fold increased risk of pancreatic cancer for patients who smoke [84]. The cumulative risk of pancreatic cancer in patients with CP after 10 years and 20 years is 2% and 4%, respectively [85,86]. Raimondi et al. found an increased RR of developing pancreatic cancer of 5.1 in patients with unspecified pancreatitis, 13.3 in patients with CP and 69.0 for patients with hereditary pancreatitis in a meta-analysis that included 22 studies [87]. Patients with hereditary pancreatitis due to autosomal dominant PRSS1 mutations have a high cumulative lifetime risk of developing pancreatic cancer of 40–55% [88,89]. Besides smoking, obesity and dietary factors (such as high intake of red meat) are associated with an increased risk of pancreatic cancer [90–92]. These environmental factors are important for future research - especially in combination with the rapidly developing field of next generation DNA sequencing, gut and oral microbiota analyses and microRNA testing - for creating more reliable screening tools to determine the subgroup of patients with CP at high risk of developing pancreatic cancer [93,94]. In conclusion, patients with CP have a small but increased risk of developing pancreatic cancer. Screening of patients with CP for pancreatic cancer cannot be recommended yet, as cost-effectiveness data of surveillance are lacking.

How to assess the presence of pancreatic cancer in the presence of CP? Three different scenarios are possible: 1) risk for pancreatic cancer associated with CP; 2) the need to differentiate between central intraductal papillary mucinous neoplasms (IPMN) and CP for adequate treatment and need for surveillance; and 3) the need to differentiate between an autoimmune pancreatitis and CP for adequate treatment. The estimated prevalence of pancreatic pseudocysts in CP is 20 and 40%. Of the cystic lesions, which are not pancreatic pseudocysts but genuine cystic neoplasms that are resected, 30% are benign serous cystadenomas, 45% are mucinous-cystic neoplasms and 25% intraductal papillary mucinous neoplasms [7]. The improvement in diagnostic tools (EUS + FNA, CT, MRI, PET, histology, laboratory tests) allows the correct diagnosis in most cases of malignancy suspicion. Diagnostic needle aspiration of a pseudocyst with the aid of EUS helps in differentiating between premalignant cystic neoplasms, cystic malignancies and pseudocysts. However, if the suspicion of cancer cannot be ruled out, a (partial) pancreatic resection is needed, as what is required is both a curative resection and adequate tissue removal for a definite histological diagnosis. Delay in diagnosis reduces the likelihood of curative resection.

Does surgery for CP reduce the incidence of pancreatic cancer in CP patients? Of a Dutch cohort of patients who had undergone surgery for CP, overall 6 of 223 patients (2.7%) were diagnosed with pancreatic cancer during long-term follow-up, among which were 4 of 146 (2.7%) after drainage surgery and 2 of 37 (8%) after tail resection [16]. In a Japanese study of patients after surgery for CP, the standardized incidence ratio of pancreatic cancer was 11.8 (7.1–18.4) [95]. The incidence of pancreatic cancer was significantly lower in patients who had received surgery for CP than in those who had not undergone surgery (HR 0.11; 95% CI, 0.0014–0.80; P = 0.03). Patients who continued to drink alcohol after diagnosis of CP showed a significantly higher incidence of pancreatic cancer than those who stopped drinking after diagnosis of CP (hazard ratio, 5.07; 95% CI, 1.13–22.73; P = 0.03) [95].

Extension of resection criteria in pancreatic malignancies and our current knowledge of specific disease entities of the pancreas,

such as IPMNs, which are premalignant lesions often affecting the whole pancreas-require TP [96–98]. In addition, patients with a family history of hereditary pancreatic cancer, patients suffering from hereditary CP, and patients with other known diffuse premalignant lesions in the pancreas have a considerable risk of developing pancreatic cancer during their lifetime [99]. Patients with hereditary CP due to PRRS1 mutations have a clearly increased risk of developing pancreatic cancer compared with a control population. TP can be a prophylactic measure in high-risk populations, used to eliminate the risk of cancer development [100]. However, the fact that TP leads to insulin-dependent diabetes mellitus induction, with subsequent secondary diabetes-related morbidity and poor quality of life, makes prophylactic TP without islet auto transplantation questionable. TP with islet auto transplantation is increasingly adopted worldwide and can potentially protect from complete endocrine function loss leading to a difficult to regulate diabetes mellitus. However, after TP with islet auto transplantation, still more than two-third of the patients develops insulin-dependent diabetes mellitus. Robust evidence is lacking [101,102]. This is further considered in the ICGP Guideline on the 'Role of Total Pancreatectomy and Islet Auto Transplantation in the Management of Chronic Pancreatitis.'

A screening program for patients with hereditary CP has been recommended [103,104]. Although there is no clear consensus on how to conduct pancreas cancer screening, many centers recommend the use of EUS, based on its ability to identify pancreatic masses smaller than 1 cm [105]. In fact, the differential diagnosis between inflammatory and malignant masses and early detection of malignancy in patients with known CP remains a difficult task for all diagnostic imaging techniques [104]. EUS may not be the most appropriate screening technique in patients with CP and is considered in further detail in two separate ICGCP Guidelines on the 'Role of Diagnostic Endoscopic Ultrasound in the Management of Chronic Pancreatitis' and 'Surveillance for Pancreatic Cancer in Chronic Pancreatitis.'

Summary

Surgery in CP is indicated as treatment of intractable pain and local complications of adjacent organs. Early surgery is favored over surgery in a more advanced stage of disease to achieve optimal long-term pain relief. In patients with an enlarged pancreatic head, a combined drainage and resection procedure, such as the Frey, Beger and Berne procedures, may be the treatment of choice. In patients with a dilated duct but a normal size pancreatic head, an extended lateral pancreaticojejunostomy on a Roux-en-Y loop and Frey procedure may provide equivalent pain control. The management of pain in advanced end-stage pancreatitis is complex and a number of non-surgical and surgical approaches still need further evaluation [9,16–18,106,107]. For patients with groove pancreatitis, pancreaticoduodenectomy is the most suitable surgical option. Surgical resection is indicated in a suspected malignant (cystic) lesion, and in patients with hereditary CP, prophylactic resection can be considered since they have such a high risk of pancreatic cancer.

Declaration of competing interest

Each of the authors has declared that they do not have any conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2019.12.005>.

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