Cystic dystrophy in heterotopic pancreas

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Highlights

• Cystic Dystrophy in Ectopic Pancreas (CDEP) primarily affects the duodenum of middle-aged, smoker/drinkers with chronic pancreatitis (CP). It results in symptoms of pancreatic pain, severe weight loss, and vomiting due to duodenal obstruction.

• The pathophysiology of CDEP is linked to the toxic effects of alcohol and tobacco leading to repeated episodes of acute pancreatitis that affect heterotopic pancreatic tissue located in the duodenal wall and in the pancreatic-duodenal groove, and then to chronic obstructive pancreatitis by obstruction of small channels resulting in the appearance of cystic dilatations within this heterotopic tissue.

• Diagnosis of CDEP is based on the demonstration by imaging (CT, MRI, echo-endoscopy) of marked thickening and multiple small cysts in the wall of the second portion of the duodenum.

• A therapeutic strategy in successive stages is usually indicated-- first-line conservative and/or endoscopic treatment, with surgical treatment reserved for failures of previous treatments, often consisting of pancreato-duodenectomy.

SUMMARY

Cystic dystrophy in ectopic pancreas (CDEP), or paraduodenal pancreatitis, is a rare and complicated presentation involving heterotopic pancreatic tissue in the duodenal wall. This condition is present in 5% of the general population but disease mainly affects middle-aged alcoholic-smoking men with chronic pancreatitis (CP). It may be purely duodenal or segmental (pancreatico-duodenopathy).

Its pathophysiology arises from alcohol toxicity with obstruction of small ducts of heterotopic pancreatic tissue present in the duodenal wall and the pancreatic-duodenal sulcus, leading to repeated episodes of pancreatitis. The symptomatology includes episodes of acute pancreatitis, weight loss, and vomiting due to duodenal obstruction. Imaging shows thickening of the wall of the second portion of the duodenum with multiple small cysts.
A stepwise therapeutic approach is preferred. Conservative medical treatment is favored in first intention (analgesics, continuous enteral feeding, somatostatin analogues), which allows complete symptomatic regression in 57% of cases associated with a 5% rate of complications (arterial thrombosis and diabetes). Endoscopic treatment may also be associated with conservative measures. Surgery achieves a complete regression of symptoms in 79% of cases but with a 20% rate of complications. Surgery is indicated in case of therapeutic failure or in case of doubt about a malignant tumor. Pancreato-duodenectomy and duodenal resection with pancreatic preservation (PPDR) seem to be the most effective treatments. PPDR has also been proposed as a first-line treatment for purely duodenal CDEP, thereby preventing progression to an extended segmental form.

KEYWORDS
Cystic dystrophy in heterotopic pancreas; paraduodenal pancreatitis; chronic calcifying pancreatitis; pancreatic cyst; cephalic pancreatico-duodenectomy; duodenal resection with pancreatic preservation

INTRODUCTION

Cystic dystrophy in ectopic pancreas (CDEP) is a rare duodenopancreatic pathology, whose nosology was belatedly clarified, which means that even today its diagnosis remains difficult and management is poorly codified.

CDEP is a complication of pancreatic heterotopia, first described in 1970 by Potet and Duclert [1]. Other terms such as “pancreatic duodenal hamartoma”, “paraduodenal wall cyst”, “myoadenomatosis” or groove pancreatitis have been used to describe this entity. The different histological aspects were unified by Adsay and Zamboni in 2004 under the term “paraduodenal pancreatitis” [2].
CDEP is defined histologically by:
1/ the presence of fibrous inflammatory tissue located in the duodenal wall, the pancreato-duodenal groove or sulcus (thin zone between the pancreas, the common bile duct and the duodenum) and the distal main bile duct),
2/ thickening of the duodenal wall with the presence of intramural cysts and
3/ hyperplasia of Brunner's glands and fragments of ectopic pancreatic tissue associated with infiltration of the duodenal wall by myoid cells [2].

The purely duodenal form of CDEP is relatively rare, representing less than 20% of cases [3]. It corresponds to fibrous and cicatricial alterations of the duodenal wall and of the pancreato-duodenal groove without associated damage to the pancreatic parenchyma. The segmental form (80%) is characterized by fibrous changes in both the pancreato-duodenal groove, and by stigmata of chronic pancreatitis (CP) in the head of the pancreas or throughout the entire gland [3]. Some authors have also divided CDEP into "cystic" or "solid" forms depending on whether fibro-inflammatory thickening of the duodenal wall is accompanied by cystic transformation (cystic form) or not (solid form). The cystic form comprises the majority, while the solid form is only observed in approximately 30% of patients [3].

PATHOPHYSIOLOGY

Pancreatic embryogenesis involves two primitive buds, the dorsal bud and the ventral bud, which arise respectively from the duodenum and the base of the liver, at the 5th week of gestation. During the 7th week of gestation, the two buds merge: the ventral part gives rise to the head of the pancreas and the uncinate process, while the dorsal part gives rise to the body and the tail of the pancreas [1]. Pancreatic heterotopia develops during embryogenesis and is defined by the presence of mature pancreatic tissue containing endocrine and exocrine parenchyma outside the confines of the pancreas, with no anatomical or vascular connection to the orthotopic pancreas [1]. This phenomenon is caused by either metaplasia of multipotent endodermal cells, or by migration of embryonic pancreatic cells within adjacent structures [4].

The prevalence of pancreatic heterotopia in the literature varies from 0.5% to 2% in various autopsy series [5], but can reach up to 14% [4,6,7]. In more than half of the cases, the ectopic pancreatic tissue is located in the mucosa or muscularis of the duodenum, jejunum, or stomach wall. It can also develop within the serosa of the gastrointestinal tract. Finally, other anatomical sites may rarely be involved: ileum, liver, spleen, bile ducts, mesentery and umbilicus [4]. Ectopic pancreatic tissues lacking acinar and endocrine cells have been termed myoepithelial hamartoma, adenomyosis, or adenomyoma. Despite its congenital nature, this condition is usually discovered in adulthood when complications develop [8].

The pathophysiology of CDEP is, to date, imperfectly understood but is presumed to be based on the following mechanisms [2,9-11]:

- Obstructive mechanism:

CDEP may be secondary to the presence of small, disorganized aberrant ducts within the exocrine lobules of the ectopic pancreas, resulting in obstruction of pancreatic secretion, phenomena of recurrent acute pancreatitis, development of cysts, and of obstructive lesions of CP. This mechanism could explain the

occurrence of CDEP in patients with neither chronic alcoholism nor CP of the orthotopic pancreas.

- Toxic mechanism:

Toxic effects of alcohol and tobacco metabolites may lead to pancreatitis lesions that develop within the ectopic pancreatic tissue and consequently the appearance of cystic transformation zones of the duodenal wall, or in the form of one or more pseudocysts in the periampullary region. Over time, the periampullary region becomes involved in an inflammatory process responsible for obstructive CP lesions that also may affect the orthotopic pancreas.

These obstructive and toxic mechanisms are probably synergistic. Although a strong correlation with excessive alcohol consumption has been demonstrated, the existence of cases of CDEP associated with non-alcoholic CP suggests the possibility of other, non-toxic causes of CP. Some authors have suggested that abnormalities of the minor papilla could also be involved [11]. Disturbance in the flow of pancreatic juice through the duct of Santorini [2,12] may result in ductal dilation and upstream pancreatitis. Nevertheless, several surgical, anatomopathological and radiological studies make this hypothesis debatable; no increase in the prevalence of minor papilla anomalies has been demonstrated in several series of patients with CDEP compared to the general population [13,14].

EPIDEMIOLOGY, CLINICAL PRESENTATION AND NATURAL HISTORY

The prevalence of CDEP in the general population is still unknown. The available epidemiological data are mainly from patients with associated CP, where the prevalence of CDEP reaches 6% [15]. The natural history of CDEP and its epidemiological link with chronic alcoholism and CP are poorly established and usually reported through surgical series [1]. The first prospective medical-surgical series that focused on the natural history of CDEP was published in 2007 by Rebours *et al.* [9]. The diagnosis of CDEP was based on previously validated radiological and echo-endoscopic (EE) criteria. These criteria were based on the association of a localized thickening of the digestive

wall without disorganization of the different layers, and the presence of one or more cystic formations located within the *muscularis propria* layer [16,17]. This series of 105 patients included 91% men and 86% chronic alcoholics with a median age of 46 years. CP of the orthotopic pancreas was also present in 71% of cases. An alcoholic origin was established in 93% of the patients, while 7% had no identified etiology despite an exhaustive investigation. Among the 29% of patients without CP, 67% had chronic alcoholism. In total, only 9% had neither CP nor chronic alcoholism. In this cohort, the initial symptoms were dominated by pancreatic pain (91%), significant weight loss often greater than 10% of body weight (73%), acute pancreatitis (45%), vomiting (30%), steatorrhea (23%), diabetes (20%), jaundice (13%) and upper gastrointestinal bleeding (5%). The median time between the first symptoms and the diagnosis of CDEP was one year. Inflammatory syndrome and cholestasis were present in 35% and 33% of patients, respectively. Symptoms related to pancreatic insufficiency (diabetes, steatorrhea) were more frequent in patients with CP. A retrospective study from 2011 [10] and a 2017 literature by Kager *et al.* [18] that analyzed 335 cases of CDEP confirmed the previous data and provided additional information on the prevalence of smoking amounting to 94% in patients with CDEP.

IMAGING DIAGNOSIS

Diagnosis of CDEP is based mainly on imaging, including computed tomography (CT), magnetic resonance imaging (MRI), and echoendoscopy (EE) [17].

Computed tomography (CT) (Figures 1 and 2)
CDEP presents as a hypodense lesion that enhances slightly compared to the orthotopic pancreatic parenchyma, lying between the pancreatic head and the duodenum. The weak enhancement is mainly due to the fibrous character of the lesion, arterial vasoconstriction and the cystic component [19]. Three major diagnostic elements have been identified [17]:

1/ the presence of multiple cysts located in the wall of the second portion of the duodenum,

2/ these cysts are generally small in size,

3/ they are associated with marked thickening of the duodenal wall.

Inflammatory changes in the second portion of the duodenum that extend to the anterior pararenal space may be suggestive of CDEP, without being specific since these abnormalities are encountered in other situations, particularly pancreatitis without associated CDEP. Rebours *et al.* [9] observed that the cysts were located in the second portion of the duodenum in 91% of cases and were multiple in 75% of cases, with a median of three cysts and a median diameter of the largest cyst of 10mm. Dilatation of the common bile duct (CBD) and spleno-portal venous thrombosis occurred in 26% and 10% of cases, respectively, with or without associated CP. Procaci *et al.* [16] defined two forms of CDEP: “cystic” and “solid”. The "cystic" form is the most frequent and is characterized by the presence of cysts of more than 10mm in the wall of the second portion of the duodenum, while the "solid" form is characterized by a fibrous thickening of the duodenal wall with cysts of less of 10mm. Non-specific abnormalities such as upstream dilatation of the CBD or stomach, secondary to duodenal stenosis, may be observed. Pancreatic calcifications, dilatation of the main pancreatic duct or the presence of pseudocysts are common when there is associated CP.

Several semiological elements can help distinguish CDEP-specific cysts from extra-pancreatic pseudocysts located in the duodenal wall, which are more typically encountered in CP: the multiple nature of the cysts and their small size are in favor of CDEP cysts, whereas extra-pancreatic pseudocysts located in the duodenal wall are more often single, large, tubular in shape extending along the duodenum and flattening abruptly at the edge of the duodenal lumen [17].

Finally, the distinction between CDEP and a malignant lesion is not always easy since these two entities may share similar radiological signs [20]. A recent study reported a prevalence of malignant lesions of 26% in patients presenting with a lesion consistent with CDEP on imaging [21]. Elements in favor of a malignant lesion were the presence of jaundice, abrupt changes in the caliber of the CBD

and the presence of suspicious cytology. In contrast, the presence of intramural cysts was more frequently associated with CDEP.

Magnetic Resonance Imaging (MRI) (Figures 1 and 2)

Aspects similar to those visualized on CT can be observed on MRI in the form of a hypointense and poorly enhancing mass on T1 between the head of the pancreas and the duodenum, associated with delayed enhancement of the thickened duodenal wall. Cysts may be present in the pancreato-duodenal groove as hyperintense T2 lesions. MRI can be supplemented with magnetic resonance cholangio-pancreatography (MRCP) images to obtain images non-invasively that are similar to those of endoscopic retrograde cholangiopancreatography (ERCP). The diagnostic value of MRI is superior to that of CT in the evaluation of biliary structures in paraduodenal pancreatitis [10].

Endoscopic and echo-endoscopic (EE) aspect

Upper GI endoscopy is usually warranted since the symptomatology of CDEP (epigastric pain, severe weight loss, vomiting) can be mistaken for upper GI malignant and non-malignant processes. Rebours *et al.* [9] showed that endoscopy could be normal in 36% of patients, contrasting with the severity of vomiting, or could show duodenal stenosis in 52% of cases (complete 6%, incomplete 46%). In this study, duodenal biopsies were performed in 24 patients: the results were normal in 11 patients, heterotopic pancreas was observed in one patient, and non- specific inflammatory lesions in 12 patients. Duodenal biopsies therefore rarely seem informative for making a positive diagnosis of CDEP, but their performance should be systematic to rule out a malignant tumor process.

The diagnosis of CDEP can be confirmed by EE, which allows the most precise and reliable analysis of the bilio-pancreatic structures and can easily be complemented by a fine needle aspiration for cytological analysis when a malignant lesion is suspected. By identification of a hypoechoic zone between the duodenal wall and the pancreatic parenchyma, EE allows the detection of

cysts localized within the submucosa or the muscularis of the duodenal wall [16], which may be responsible for narrowing of the duodenal lumen, CBD or pancreatic duct.

Endoscopic retrograde cholangiopancreatography (ERCP)

Diagnostic ERCP has been supplanted by MRCP. ERCP is currently used mainly for therapeutic sphincterotomy [22].

MANAGEMENT

A recent literature review published by Kager *et al* [18] that collated eight studies on 335 patients with CDEP showed that therapeutic management was conservative in 29% of cases, endoscopic in 12% of cases and surgical in 59% of cases. To date, no prospective randomized study has compared the different therapeutic strategies, thus precluding the development of clear consensus. Table 1 summarizes the main published series of patients presenting with CDEP.

Conservative treatment

Conservative treatment, always the first-line treatment, includes: analgesics, addictology (ethyl and tobacco cessation), nutritional management (avoidance of high-fat foods, exclusive continuous enteral feeding) to benefit from its analgesic effect), enzyme replacement therapy, and specific treatment with somatostatin analogues if necessary. The success rate of conservative management reported by Kager *et al.* [18] was 70% (49% complete regression of symptoms, 21% incomplete regression). Somatostatin analogues caused complete and incomplete regression of symptoms in respectively 57% and 16% of the 37 patients who had this treatment with a treatment duration (often by parenteral depot injections) varying from 1 to 24 months with a 5% complication rate. Although there are few prospective data on the use of somatostatin analogues in CDEP, several retrospective studies report their efficacy for this indication [23,24]

and their simple and widespread use in other pathologies make it an attractive first-line treatment for CDEP with a very favorable risk profile. The retrospective multicenter study by Tarvainen *et al.* [25] on 33 cases of CDEP reaffirmed the effectiveness of optimal conservative medical management performed on more than one third of the patients in the cohort and allowing a 50% decrease in symptoms at one year and their virtual disappearance at five years. Nevertheless, this is a highly selected group of patients with no diagnostic doubt with cancer nor complications that would require intervention or surgery.
It is difficult to assess the long-term results of the conservative medical treatment given that the majority of published series are surgical series, and that that recurrence is difficult to assess in patients treated medically in a conservative manner. Nevertheless, in the study by Ooka *et al*. of 48 cases of CDEP treated medically with a median follow-up of five years, the mortality rates related to pancreatitis, pancreatectomy, and re-admission for pancreatitis were 4.2%, 14.6% and 68.8%, respectively [26]. In addition, although no study has prospectively evaluated the long-term functional results of the conservative strategy, it seems legitimate to estimate the failure rate of this strategy (lack of improvement and worsening of symptoms) at 30% while 30-40% of the patients who were improved by exclusive medical treatment will present a secondary recurrence of symptoms requiring a more invasive strategy. Finally, some authors suggest that the role of initial medical treatment would be, above all, to improve the patient's nutritional status and reduce loco-regional inflammation in order to facilitate surgery and improve post-operative results.

Endoscopic treatment

In the review by Kager *et al.* [18], endoscopic treatment consisted of endoscopic drainage of the cysts (63%), dilation/stenting of the pancreatic duct (24%) or the CBD (16%), duodenal dilatation (8%) or placement of a duodenal stent (2%). Endoscopic treatment was associated with complete regression of symptoms in 57% of cases and with a 13% complication rate without associated mortality.

Placement of a pancreatico-biliary stent prosthesis was often of little benefit in patients with CDEP without extensive CP, which suggests that the pancreatic duct and CBD are only affected in a minority of these patients. Under the hypothesis that anomalies of the minor papilla contribute to the pathophysiology of CDEP, several teams have been interested in drainage of the duct of Santorini. Isayama *et al.* [27] published a case of complete and prolonged regression of symptoms in a patient treated by stenting of the minor papilla. Similar results were observed in the work of Chantarojanasiri *et al.* [28] where seven patients underwent stented drainage of the duct of Santorini, resulting in clinical and imaging improvement in the majority of cases. Moreover, by analogy with the endoscopic treatment of pseudocysts in pancreatitis, endoscopic fenestration with cysto-duodenostomy makes it possible to obtain satisfactory results in cases of CDEP with large cysts [29,30].
Finally, once again, the assessment of the long-term prognosis of endoscopic treatment is difficult given the limited published data in the literature. Nevertheless, in the study by Arvanitakis *et al*., the overall survival rate at 54 months was 94% for 41 patients who mainly benefited from endoscopic treatment [29].

Surgical treatment

Surgical management should be considered if first-intention conservative and/or endoscopic treatment fails or when a malignant lesion cannot be excluded. Nevertheless, recourse to surgery is frequent in the literature (between 25 and 85% depending on the series) [3,19,26,31], but certainly overestimated, given the fact that these are often surgical series with a need for definitive histological proof. In the systematic review by Kager *et al.* [18], surgical treatment was associated with complete regression of symptoms in 79% of cases and incomplete regression in 16%, with a complication rate of 20%. In this study, pancreato-duodenectomy (CPD) was the most commonly performed procedure (77%) and the most effective, but was burdened by a mortality of 2% to 3% and

substantial morbidity (35% to 45%). In 2021, Egorov *et al.* [19] published a retrospective study comparing the results of several surgical techniques performed for CDEP: pancreatico-digestive drainage by pancreatico-jejunal anastomosis and cysto-jejunostomy (n = 8), cephalic pancreatectomy with duodenal preservation (duodenum preserving pancreatic head resection= DPPHR, n = 6), CPD (n = 44), and duodenal resection with preservation of the pancreas (PPDR) (n = 15) (Figure 3). The rate of severe post-operative morbidity (Dindo-Clavien ≥ III) [32] was 12%, 34%, 16% and 7%, respectively. No deaths within 90 days were observed in operated patients. Weight gain was significantly higher after CPD and PPDR compared to the other interventions. Complete pain control was achieved significantly more often after PPDR (93%) and CPD (84%) compared to the other interventions (18%). As expected, *de novo* diabetes and pancreatic exocrine insufficiency occurred after CPD (31% and 14% respectively) but not after PPDR. Thus, in this study, the authors ultimately proposed PPDR as the surgical treatment of choice for pure forms of CDEP. This proposal was based on the fact that PPDR seemed to be at least as effective (if not more so) than CPD in controlling pain while avoiding all the complications induced by resection of the head of the pancreas, which, by definition, is uninvolved in this pure form of CDEP. This choice is all the more indicated in the early forms of the disease, taking into account the fact that prolonged duration of evolution and prolonged conservative treatment could lead to the development of a segmental form with extension of the inflammation into the pancreatic head or even throughout the pancreas. Evolution from the pure to the segmental form could therefore deprive patients of localized duodenal resection and lead ultimately to greater morbidity, mainly related to the development of secondary diabetes. As a result, the latest consensus of 2019 [33] to establish the place of surgery in CP still recommends CPD today as the reference surgical treatment for CDEP, while still retaining, a poorly-defined role for PPDR for forms of CDEP involving only the duodenum, due to the lack of prospective studies. Finally, as an alternative to pancreatic and/or duodenal resection, and in particular CPD, some teams have resorted to creating digestive

and biliary diversions, mainly proposed when there is a duodenal or biliary obstruction without marked pain. In the study by Rebours *et al.* [9], 12 patients underwent digestive and biliary diversion for this indication and none of these patients subsequently required pancreatic and/or duodenal resection. This observation suggests that these procedures are effective in preventing the obstructive complications induced by CDEP, while, on the other hand, admitting that lack of knowledge regarding the physiopathology of this disease and discrimination of which symptoms should be attributed to CDEP or to the often-associated CP. This imbroglio between CP and CDEP management is all the more true since a large Italian series of 120 patients with CDEP showed that 21% of operated patients ultimately benefited from a pancreatico-jejunal diversion despite the presence of CDEP [3]. Nevertheless, the performance of a diversion in this context requires complete certitude about the absence of a neoplastic origin whose differential diagnosis is sometimes difficult.

Therapeutic strategy (figure 4)

A recent retrospective study [34] compared the results of surgical and medical management of CDEP in terms of pain control, quality of life and pancreatic insufficiency; in 75 patients with CDEP (median follow-up of 60 months), 63% underwent CPD and 37% had medical treatment. The results were similar in terms of steatorrhea (45% and 53%), quality of life and pain control but not in terms of the onset of diabetes, which was more common after surgery (60% *vs.* 11%) and is associated with difficulties in self-management of this diabetes in often young patients. Consequently, a therapeutic strategy in progressive stages seems to be the most appropriate for CDEP, with initial conservative and/or endoscopic treatment, reserving surgical treatment, particularly CPD, for failure of conservative management. Moreover, for the pure form of CDEP, particularly at an early stage, PPDR may be preferable to prolonged conservative treatment to prevent evolution to segmental CDEP with CP.

CONCLUSION

Cystic dystrophy in ectopic pancreas (CDEP), or paraduodenal pancreatitis, is a rare complication of pancreatic heterotopia that mainly affects alcoholic and smoking middle-aged males, who also suffer from CP in the orthotopic pancreas. Symptomatology frequently associates pancreatic pain, weight loss, vomiting and episodes of acute pancreatitis. Pathophysiology is related to alcohol toxicity as well as to obstruction of small ducts of heterotopic pancreatic tissue. Diagnosis is based on imaging demonstration of several small cysts in the second portion of the duodenum and duodenal thickening. A therapeutic strategy in successive stages seems logical, with initial conservative and/or endoscopic treatment. Surgical treatment is reserved for failure of conservative management or when there is concern about the possibility of a malignant tumor. On the other hand, for cases of the pure form of CDEP, PPDR could be preferred to a prolonged conservative treatment.

CDEP is a rare disease and studies with a high level of evidence are lacking, particularly with regard to its therapeutic management.

Additional studies are needed to refine the profile of the best responders to conservative, endoscopic or surgical treatment. The current therapeutic management of CDEP must therefore be part of a multidisciplinary approach involving gastroenterologists, addictologists, nutritionists, radiologists, interventional endoscopists and digestive surgeons, in order to best determine the treatment with the best risk-benefit ratio for the patient.

Disclosure of interest

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ABBREVIATION

MRCP: Magnetic resonance cholangio-pancreatography

ERCP: Endoscopic retrograde cholangio-pancreatography

CDEP: Eystic dystrophy in ectopic pancreas

CPD: Cephalic pancreato-duodenectomy

EE: Echo-endoscopy

MRI: Magnetic resonance imaging

EN: Exclusive parenteral nutrition

CP: Chronic pancreatitis

PPDR: Pancreas preserving duodenal resection

CT: Computed tomography

REFERENCES

1. Potet F, Duclert N. [Cystic dystrophy on aberrant pancreas of the duodenal wall]. Arch Fr Mal App Dig. 1970 Mar; 59(4): 223–38.
2. Adsay NV, Zamboni G. Paraduodenal pancreatitis: a clinico-pathologically distinct entity unifying “cystic dystrophy of heterotopic pancreas,” “para-duodenal wall cyst,” and “groove pancreatitis.” Semin Diagn Pathol. 2004 Nov; 21(4): 247–54.
3. de Pretis N, Capuano F, Amodio A, Pellicciari M, Casetti L, Manfredi R, *et al.* Clinical and Morphological Features of Paraduodenal Pancreatitis: An Italian Experience With 120 Patients. Pancreas. 2017 Apr; 46(4): 489–95.
4. Dolan RV, ReMine WH, Dockerty MB. The fate of heterotopic pancreatic tissue. A study of 212 cases. Arch Surg Chic Ill 1960. 1974 Dec; 109(6): 762–5.
5. Duff GL. Primary carcinoma of the infra-ampullary portion of the duodenum: with example of probable origin from aberrant pancreatic tissue Arch Surg. 1943 Apr 1; 46(4): 494.
6. Kung JW, Brown A, Kruskal JB, Goldsmith JD, Pedrosa I. Heterotopic pancreas: typical and atypical imaging findings. Clin Radiol. 2010 May; 65(5): 403–7.
7. Lai EC, Tompkins RK. Heterotopic pancreas. Review of a 26 year experience. Am J Surg. 1986 Jun; 151(6): 697–700.
8. Burke GW, Binder SC, Barron AM, Dratch PL, Umlas J. Heterotopic pancreas: gastric outlet obstruction secondary to pancreatitis and pancreatic pseudocyst. Am J Gastroenterol. 1989 Jan; 84(1): 52–5.
9. Rebours V, Lévy P, Vullierme MP, Couvelard A, O’Toole D, Aubert A, *et al.* Clinical and Morphological Features of Duodenal Cystic Dystrophy in Heterotopic Pancreas. Am J Gastroenterol. 2007 Apr; 102(4): 871–9.
10. Pezzilli R. Cystic dystrophy of the duodenal wall is not always associated with chronic pancreatitis. World J Gastroenterol. 2011; 17(39): 4349.
11. Chatelain D, Vibert E, Yzet T, Geslin G, Bartoli E, Manaouil D, *et al.* Groove pancreatitis and pancreatic heterotopia in the minor duodenal papilla. Pancreas. 2005 May; 30(4): e92-95.

12. Shudo R, Obara T, Tanno S, Fujii T, Nishino N, Sagawa M, *et al.* Segmental groove pancreatitis accompanied by protein plugs in Santorini's duct. J Gastroenterol. 1998 Mar 10; 33(2): 289–94.
13. Wagner M, Vullierme MP, Rebours V, Ronot M, Ruszniewski P, Vilgrain V. Cystic form of paraduodenal pancreatitis (cystic dystrophy in heterotopic pancreas (CDHP)): a potential link with minor papilla abnormalities? A study in a large series. Eur Radiol. 2016 Jan; 26(1): 199–205.
14. Egorov VI, Vankovich AN, Petrov RV, Starostina NS, Butkevich AT, Sazhin AV, *et al.* Pancreas-preserving approach to "paraduodenal pancreatitis" treatment: why, when, and how? Experience of treatment of 62 patients with duodenal dystrophy. BioMed Res Int. 2014; 2014: 185265.
15. Frulloni L, Gabbrielli A, Pezzilli R, Zerbi A, Cavestro GM, Marotta F, *et al*. Chronic pancreatitis: report from a multicenter Italian survey (PanCroInfAISP) on 893 patients. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2009 Apr; 41(4): 311–7.
16. Procacci C, Graziani R, Zamboni G, Cavallini G, Pederzoli P, Guarise A, *et al.* Cystic dystrophy of the duodenal wall: radiologic findings. Radiology. 1997 Dec; 205(3): 741–7.
17. Vullierme MP, Vilgrain V, Fléjou JF, Zins M, O'Toole D, Ruszniewski P, *et al.* Cystic Dystrophy of the Duodenal Wall in the Heterotopic Pancreas: Radiopathological Correlations: J Comput Assist Tomogr. 2000 Jul; 24(4): 635–43.
18. Kager LM, Lekkerkerker SJ, Arvanitakis M, Delhaye M, Fockens P, Boermeester MA, *et al.* Outcomes After Conservative, Endoscopic, and Surgical Treatment of Groove Pancreatitis: A Systematic Review. J Clin Gastroenterol. 2017 Sep; 51(8): 749–54.
19. Egorov V, Petrov R, Schegolev A, Dubova E, Vankovich A, Kondratyev E, *et al.* Pancreas-preserving duodenal resections *vs* pancreatoduodenectomy for groove pancreatitis. Should we revisit treatment algorithm for groove pancreatitis? World J Gastrointest Surg. 2021 Jan 27; 13(1): 30–49.
20. Jun JH, Lee SK, Kim SY, Cho DH, Song TJ, Park DH, *et al.* Comparison

between groove carcinoma and groove pancreatitis. Pancreatol Off J Int Assoc Pancreatol IAP Al. 2018 Oct; 18(7): 805–11.

21. Lekkerkerker SJ, Nio CY, Issa Y, Fockens P, Verheij J, Busch OR, *et al.* Clinical outcomes and prevalence of cancer in patients with possible groove pancreatitis. J Gastroenterol Hepatol. 2016 Nov; 31(11): 1895–900.

22. Itoh S, Yamakawa K, Shimamoto K, Endo T, Ishigaki T. CT findings in groove pancreatitis: correlation with histopathological findings. J Comput Assist Tomogr. 1994 Dec; 18(6): 911–5.

23. Pessaux P, Lada P, Etienne S, Tuech JJ, Lermite E, Brehant O, *et al.* Duodenopancreatectomy for cystic dystrophy in heterotopic pancreas of the duodenal wall. Gastroenterol Clin Biol. 2006 Jan; 30(1): 24–8.

24. Jouannaud V, Coutarel P, Tossou H, Butel J, Vitte RL, Skinazi F, *et al.* Cystic dystrophy of the duodenal wall associated with chronic alcoholic pancreatitis. Clinical features, diagnostic procedures and therapeutic management in a retrospective multicenter series of 23 patients. Gastroenterol Clin Biol. 2006 Apr; 30(4): 580–6.

25. Rahman SH, Verbeke CS, Gomez D, McMahon MJ, Menon KV. Pancreatico-duodenectomy for complicated groove pancreatitis. HPB. 2007; 9(3): 229–34.

26. Tison C, Regenet N, Meurette G, Mirallié E, Cassagnau E, Frampas E, *et al.* Cystic dystrophy of the duodenal wall developing in heterotopic pancreas: report of 9 cases. Pancreas. 2007 Jan; 34(1): 152–6.

27. Rebours V, Lévy P, Vullierme MP, Couvelard A, O'Toole D, Aubert A, *et al.* Clinical and morphological features of duodenal cystic dystrophy in heterotopic pancreas. Am J Gastroenterol. 2007 Apr; 102(4): 871–9.

28. Castell-Monsalve FJ, Sousa-Martin JM, Carranza-Carranza A. Groove pancreatitis: MRI and pathologic findings. Abdom Imaging. 2008; 33(3): 342–8.

29. Casetti L, Bassi C, Salvia R, Butturini G, Graziani R, Falconi M, *et al.* "Paraduodenal" pancreatitis: results of surgery on 58 consecutives patients from a single institution. World J Surg. 2009 Dec; 33(12): 2664–9.

30. Frulloni L, Gabbrielli A, Pezzilli R, Zerbi A, Cavestro GM, Marotta F, *et al.*

Chronic pancreatitis: report from a multicenter Italian survey (PanCroInfAISP) on 893 patients. Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver. 2009 Apr; 41(4): 311–7.

31. Ishigami K, Tajima T, Nishie A, Kakihara D, Fujita N, Asayama Y, *et al.* Differential diagnosis of groove pancreatic carcinomas *vs.* groove pancreatitis: usefulness of the portal venous phase. Eur J Radiol. 2010 Jun; 74(3): e95–100.

32. Kim JD, Han YS, Choi DL. Characteristic clinical and pathologic features for pre-operative diagnosed groove pancreatitis. J Korean Surg Soc. 2011 May; 80(5): 342–7.

33. Manzelli A, Petrou A, Lazzaro A, Brennan N, Soonawalla Z, Friend P. Groove pancreatitis. A mini-series report and review of the literature. JOP J Pancreas. 2011 May 6; 12(3): 230–3.

34. Levenick JM, Gordon SR, Sutton JE, Suriawinata A, Gardner TB. A comprehensive, case-based review of groove pancreatitis. Pancreas. 2009 Aug; 38(6): e169-175.

35. Kalb B, Martin DR, Sarmiento JM, Erickson SH, Gober D, Tapper EB, *et al.* Paraduodenal pancreatitis: clinical performance of MR imaging in distinguishing from carcinoma. Radiology. 2013 Nov; 269(2): 475–81.

36. Arvanitakis M, Rigaux J, Toussaint E, Eisendrath P, Bali MA, Matos C, *et al.* Endotherapy for paraduodenal pancreatitis: a large retrospective case series. Endoscopy. 2014 Jul; 46(7): 580–7.

37. Zaheer A, Haider M, Kawamoto S, Hruban RH, Fishman EK. Dual-phase CT findings of groove pancreatitis. Eur J Radiol. 2014 Aug; 83(8): 1337–43.

38. Arora A, Rajesh S, Mukund A, Patidar Y, Thapar S, Arora A, *et al.* Clinicoradiological appraisal of “paraduodenal pancreatitis”: Pancreatitis outside the pancreas! Indian J Radiol Imaging. 2015; 25(3): 303–14.

39. Oza VM, Skeans JM, Muscarella P, Walker JP, Sklaw BC, Cronley KM, *et al.* Groove Pancreatitis, a Masquerading Yet Distinct Clinicopathological Entity: Analysis of Risk Factors and Differentiation. Pancreas. 2015 Aug; 44(6): 901–8.

40. Lekkerkerker SJ, Nio CY, Issa Y, Fockens P, Verheij J, Busch OR, *et al.* Clinical outcomes and prevalence of cancer in patients with possible groove

pancreatitis. J Gastroenterol Hepatol. 2016 Nov; 31(11): 1895–900.

41. Boninsegna E, Negrelli R, Zamboni GA, Tedesco G, Manfredi R, Pozzi Mucelli R. Paraduodenal pancreatitis as a mimicker of pancreatic adenocarcinoma: MRI evaluation. Eur J Radiol. 2017 Oct; 95: 236–41.

42. Muraki T, Kim GE, Reid MD, Mittal P, Bedolla G, Memis B, *et al.* Paraduodenal Pancreatitis: Imaging and Pathologic Correlation of 47 Cases Elucidates Distinct Subtypes and the Factors Involved in its Etiopathogenesis. Am J Surg Pathol. 2017 Oct; 41(10): 1347–63.

43. Aguilera F, Tsamalaidze L, Raimondo M, Puri R, Asbun HJ, Stauffer JA. Pancreaticoduodenectomy and Outcomes for Groove Pancreatitis. Dig Surg. 2018; 35(6): 475–81.

44. Chantarojanasiri T, Isayama H, Nakai Y, Matsubara S, Yamamoto N, Takahara N, *et al.* Groove Pancreatitis: Endoscopic Treatment via the Minor Papilla and Duct of Santorini Morphology. Gut Liver. 2018 Mar 15; 12(2): 208–13.

45. Balduzzi A, Marchegiani G, Andrianello S, Romeo F, Amodio A, De Pretis N, *et al.* Pancreaticoduodenectomy for paraduodenal pancreatitis is associated with a higher incidence of diabetes but a similar quality of life and pain control when compared to medical treatment. Pancreatology. 2020 Mar; 20(2): 193–8.

46. Ooka K, Singh H, Warndorf MG, Saul M, Althouse AD, Dasyam AK, *et al.* Groove pancreatitis has a spectrum of severity and can be managed conservatively. Pancreatol Off J Int Assoc Pancreatol IAP Al. 2021 Jan; 21(1): 81–8.

47. Tarvainen T, Nykänen T, Parviainen H, Kuronen J, Kylänpää L, Sirén J, *et al.* Diagnosis, natural course and treatment outcomes of groove pancreatitis. HPB. 2021 Aug; 23(8): 1244–52.

48. Dhali A, Ray S, Ghosh R, Misra D, Dhali GK. Outcome of Whipple's procedure for groove pancreatitis: A retrospective cross-sectional study. Ann Med Surg 2012. 2022 Jul; 79: 104008.

49. Vujasinovic M, Pozzi Mucelli R, Grigoriadis A, Palmér I, Asplund E, Rutkowski W, *et al.* Paraduodenal pancreatitis - problem in the groove. Scand J Gastroenterol. 2022 Feb 9; 1–8.

50. Teo J, Suthananthan A, Pereira R, Bettington M, Slater K. Could it be groove pancreatitis? A frequently misdiagnosed condition with a surgical solution. ANZ J Surg. 2022 Sep; 92(9): 2167–73.

51. Değer KC, Köker İH, Destek S, Toprak H, Yapalak Y, Gönültaş C, *et al.* The clinical feature and outcome of groove pancreatitis in a cohort: A single center experience with review of the literature. Ulus Travma Ve Acil Cerrahi Derg Turk J Trauma Emerg Surg TJTES. 2022 Aug; 28(8): 1186–92.

52. Mathiew B, Moussu P, Mourani A, Passail G, Hervé M, Madani N. [Extensive duodenal stenosis related to parietal cystic dystrophy in heterotopic pancreas: efficacy of octreotide treatment]. Gastroenterol Clin Biol. 2000 Jan; 24(1): 128–30.

53. Basili E, Allemand I, Ville E, Laugier R. [Lanreotide acetate may cure cystic dystrophy in heterotopic pancreas of the duodenal wall]. Gastroenterol Clin Biol. 2001 Dec; 25(12): 1108–11.

54. Isayama H, Kawabe T, Komatsu Y, Sasahira N, Toda N, Tada M, *et al.* Successful treatment for groove pancreatitis by endoscopic drainage via the minor papilla. Gastrointest Endosc. 2005 Jan; 61(1): 175–8.

55. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug; 240(2): 205–13.

56. Kempeneers MA, Issa Y, Ali UA, Baron RD, Besselink MG, Büchler M, *et al.* International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis. Pancreatol Off J Int Assoc Pancreatol IAP Al. 2020 Mar; 20(2): 149–57.

Figures

Figure 1: 55-year old male followed for chronic calcifying pancreatitis and CDEP
A. MRI axial T2 image; B. MRI coronal T2 mage; C. Injected CT scan, coronal view in portal phase

Short white arrow: cyst contained within the duodenal wall with hemorrhagic infiltration

Long white arrow: microcysts in the head of the pancreas

White star: dilatation of the main pancreatic duct

Dotted white arrow: large calculus impacted in the main pancreatic duct

Figure 2: 49-year old male followed for calcifying chronic pancreatitis and CDEP
A. MRI axial T2 image; B. MRI axial T2 image; C. injected CT scan, axial view in portal phase

Short white arrow: microcyst contained within the thickened duodenal wall

Long white arrow: microcalcifications in the pancreatic head due to chronic calcifying pancreatitis

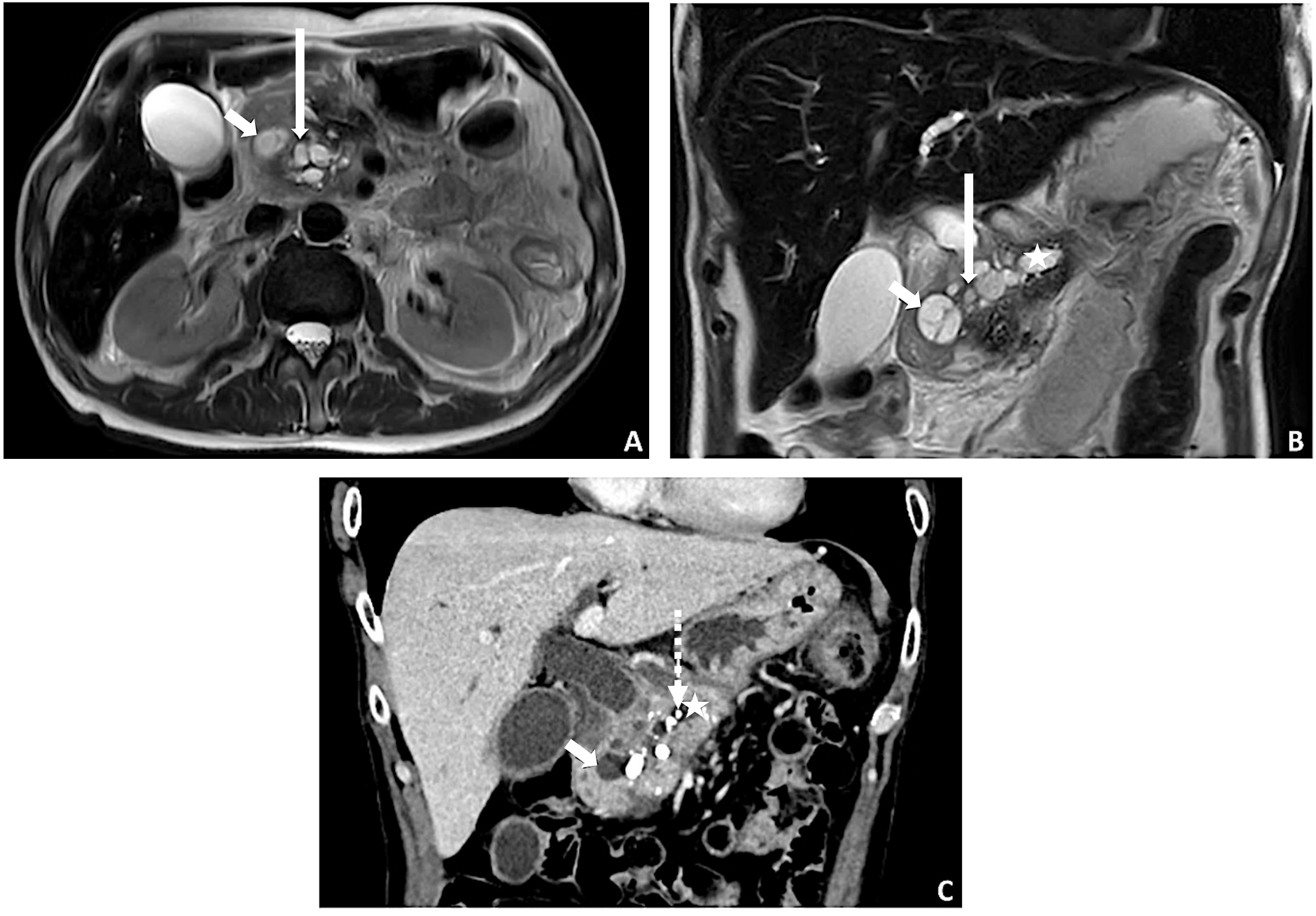
White star: dilatation of the main pancreatic duct

Figure 3: Schematic drawing of resection of the second portion of the duodenum with (A) pancreatic preservation
(B) reconstruction by duodeno-jejunal anastomosis, or
(C) by intestinal interposition
CPP (main pancreatic duct); CPB (common bile duct)

Figure 4: Proposed algorithm for management of symptomatic cystic dystrophy in ectopic pancreas (CDEP)

CPD (cephalic pancreato-duodenectomy); PPDR (pancreas preserving duodenal resection); MPD (main pancreatic duct); CBD (common bile duct)

Table 1: Summary of series with more than five patients followed for CDEP between 2006 and 2022


A
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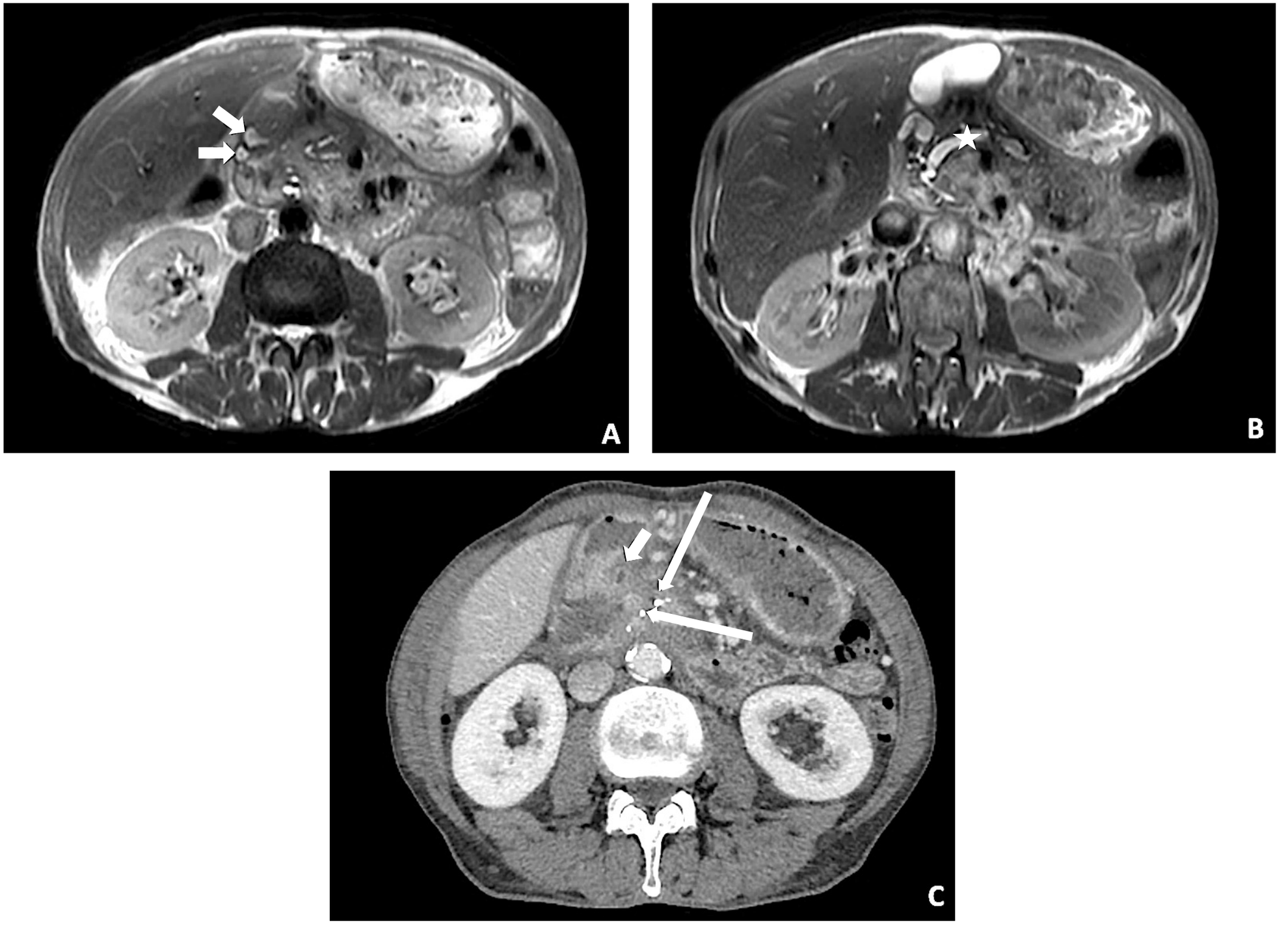
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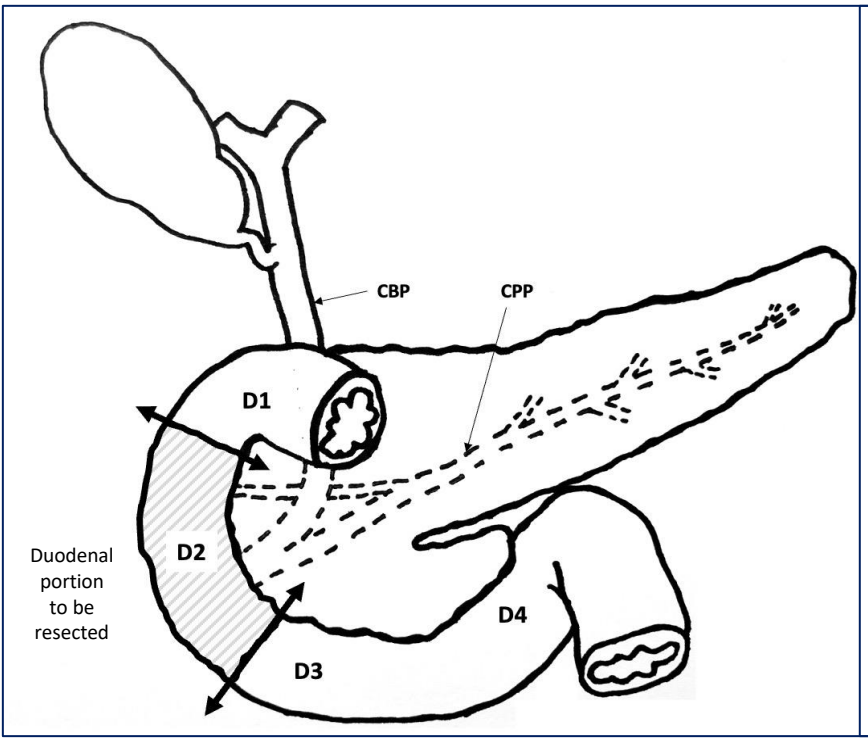
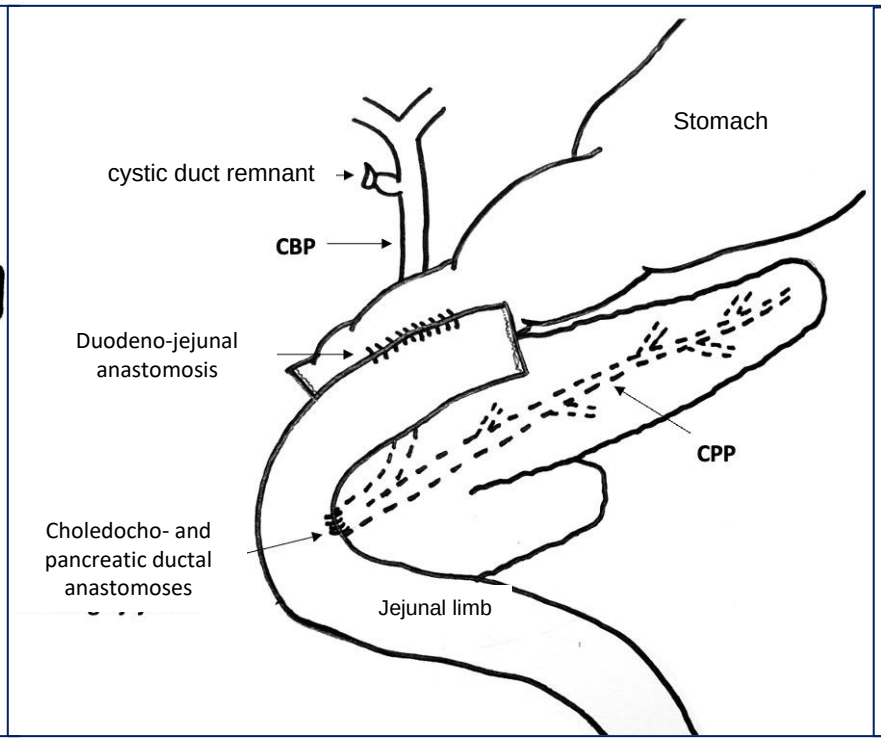
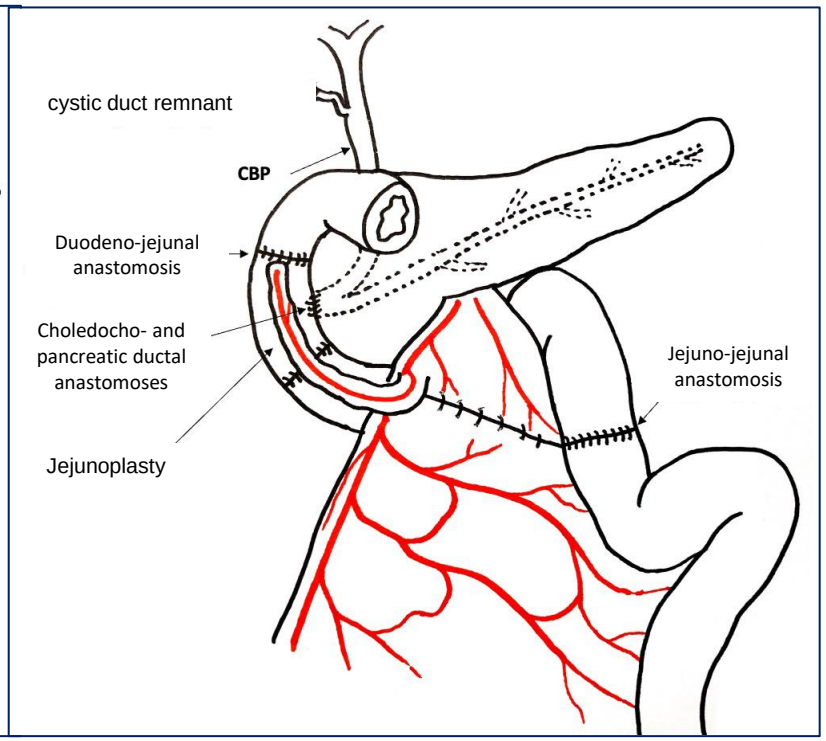
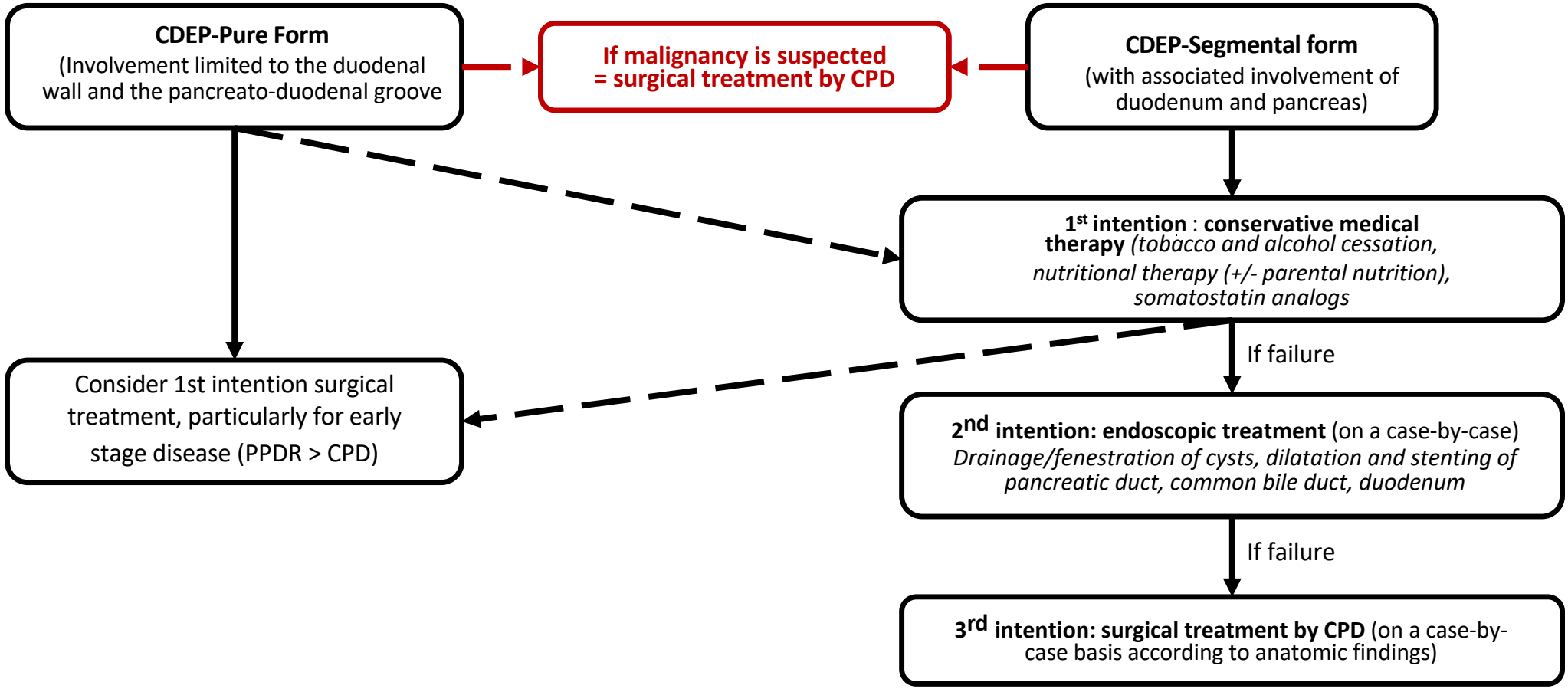

CBP
CPP
D1
D2
D3
D4
Duodenal portion to be resected


Stomach
cystic duct remnant
CBP
Duodeno-jejunal anastomosis
CPP
Choledocho- and pancreatic ductal anastomoses
Jejunal limb


cystic duct remnant
CBP
Duodeno-jejunal anastomosis
Choledocho- and pancreatic ductal anastomoses
Jejunoplasty
Jejuno-jejunal anastomosis


CDEP-Pure Form
(Involvement limited to the duodenal wall and the pancreato-duodenal groove
If malignancy is suspected = surgical treatment by CPD
CDEP-Segmental form
(with associated involvement of duodenum and pancreas)
1st intention : conservative medical therapy (tobacco and alcohol cessation, nutritional therapy (+/- parental nutrition), somatostatin analogs
If failure
Consider 1st intention surgical treatment, particularly for early stage disease (PPDR > CPD)
2nd intention: endoscopic treatment (on a case-by-case)
Drainage/fenestration of cysts, dilatation and stenting of pancreatic duct, common bile duct, duodenum
If failure
3rd intention: surgical treatment by CPD (on a case-by-case basis according to anatomic findings)

Year	Author	Country	Study type	n	Age*	Male sex	Exclusively surgical treatment	Exclusively endoscopic treatment	Folloe-up (years)**	Complete response after treatment
2006	Pessaux et al (23)	France	Retrospective	12	42	92%	100%	0%	5.3	92%
2006	Jouannaud et al (24)	France	Retrospective	23	45	87%	61%	9%	3.9	93%
2007	Rahman et al (25)	United Kingdom	Retrospective	11	48	91%	100%	0%	4.3	91%
2007	Tison et al (26)	France	Retrospective	9	48	89%	100%	0%	7.1	56%
2007	Rebours et al (27)	France	Retrospective	105	46	91%	28%	15%	1.3	73%
2008	Castell-Monsalve et al (28)	Germany	Retrospective	5	47	80%	60%	0%	2.1	-
2009	Casetti et al (29)	Italy	Prospective	58	45	93%	100%	0%	8	76%
2009	Frulloni et al (30)	Italy	Retrospective	55	-	91%	78%	29%	-	-
2010	Ishigami et al (31)	Japan	Retrospective	15	48	93%	40%	-	-	47%
2011	Kim et al (32)	Korea	Retrospective	6	50	83%	100%	0%	2.7	80%
2011	Manzelli et al (33)	United Kingdom	Retrospective	5	55	40%	100%	0%	1	100%
2012	Levenick et al (34)	United States	Retrospective	5	47	40%	100%	0%	2.6	100%
2013	Kalb et al (35)	United States	Retrospective	47	60	60%	100%	0%	-	-
2014	Arvanitakis et al (36)	Belgium	Retrospective	51	49	58%	76%	18%	4.5	71%
2014	Egorov et al (14)	Russia	Prospective	62	45	95%	84%	-	1.6	77%
2014	Zaheer et al (37)	United States	Retrospective	12	51	83%	100%	0%	0.8	17%
2015	Arora et al (38)	India	Retrospective	33	46	100%	3%	-	0.8	-
2015	Oza et al (39)	United States	Retrospective	13	52	85%	69%	31%	1	62%
2016	Lekkerkerker et al (40)	Holland	Retrospective	28	57	61%	29%	21%	3.8	62%
2017	De Preti et al (3)	Italy	Retrospective	120	41	97%	67%	-	10.4	81%
2017	Boninsegna et al (41)	Italy	Retrospective	28	51	93%	100%	0%	-	-
2017	Muraki et al (42)	United States	Retrospective	47	50	77%	100%	0%	-	-
2018	Aguilera et al (43)	United States	Retrospective	8	52	50%	100%	0%	1.5	50%
2018	Chantarojanasiri et al (44)	Japan	Retrospective	7	58	86%	0%	100%	8.1	71%
2018	Jun et al (20)	Korea	Retrospective	44	51	84%	70%	-	4.6	-
2020	Balduzzi et al (45)	Italy	Retrospective	75	58	85%	63%	15%	-	-
2021	Ooka et al (46)	United States	Retrospective	48	53	79%	15%	-	5	-
2021	Egorov et al (19)	Russia	Retrospective	84	48	95%	85%	9%	7.8	76%
2021	Tarvainen et al (47)	Finland	Retrospective	33	55	79%	12%	42%	5	75%
2022	Dhali et al (48)	India	Retrospective	9	43	100%	100%	0%	3.4	78%
2022	Vujasinovic et al (49)	Sweden	Retrospective	35	56	86%	14%	26%	-	34%
2022	Teo et al (50)	Australia	Retrospective	8	59	75%	100%	0%	3.5	64%
2022	Deger et al (51)	Turkey	Retrospective	25	55	80%	4%	40%	2.4	48%
-	TOTAL	-	-	1126	50.3 (± 5.1)	81 (±15.9)%	78 (34.5-100)%	13 (± 21.9)%	3.7 (1.6-5)	69.8(± 20.4)%

** Mean or médian according to the data from the studies, **After surgical or endoscopic treatment*