Review paper

An updated review of pancreatic cystic lesions

Zaktualizowany przegląd zmian torbielowatych w trzustce

Pradhyumna Muralidharan[1], Jeffrey Pradeep Raj[2], Pavani Nathala[3]

[1]Medical Intensive Care Unit, St. Johns Medical College, Bengaluru, India
[2]Department of Clinical Pharmacology, Seth G.S Medical College & King Edward Memorial Hospital, Mumbai, India
[3]Division of Infectious Diseases, University of Louisville, KY, USA

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Abstract

A pancreatic cystic lesion (PCL) is a collection of fluid in the pancreas, which is often diagnosed incidentally during abdominal imaging, and often poses a diagnostic and therapeutic challenge. PCLs not only have diverse histological and imaging appearances but also differ in clinical presentation, biologic behaviour, growth pattern, and risk of malignancy. Apart from their diagnosis, the management of PCL is also multifactorial, which takes into consideration risk of malignancy, cost of cyst analysis, cyst surveillance, anatomic location of the cyst, the patient's age, and overall health status. Although guidelines exist for surgical and conservative management, each case needs to be tailored to malignant risk, surgical risk, and life expectancy in mind. This would thereby reduce both the monetary and non-monetary burden on patients. In this review, we aim to provide insight into the various recent advances in the diagnosis and management of PCL.

Streszczenie

Zmiana torbielowata w trzustce (PCL) to zbiornik płynu, który często jest diagnozowany przypadkowo podczas obrazowania jamy brzusznej. Nierzadko stanowi on wyzwanie diagnostyczne i terapeutyczne. Zmiany torbielowate różnią się między sobą wynikami badań histologicznych i obrazowych, a także obrazem klinicznym, cechami biologicznymi, wzorcem wzrostu i ryzykiem nowotworu. Postępowanie w PCL jest wieloczynnikowe, uwzględnia ryzyko złośliwości, koszty analizy torbieli, kontrolę nad torbielą, jej lokalizację anatomiczną, wiek i ogólny stan zdrowia pacjenta. Chociaż istnieją wytyczne dotyczące postępowania chirurgicznego i zachowawczego, każdy przypadek musi być rozpatrywany indywidualnie z uwzględnieniem ryzyka złośliwości, ryzyka chirurgicznego i średniej długości życia. W ten sposób zmniejszyłoby się obciążenie pacjentów – zarówno finansowe, jak i innego rodzaju. Autorzy przedstawiają najnowsze informacje dotyczące postępów w diagnostyce i leczeniu PCL.

Introduction

A pancreatic cystic lesion (PCL) is a collection of fluid in the pancreas, which often presents a therapeutic and diagnostic challenge. Pancreatic cystic lesions are broadly classified as non-neoplastic and neoplastic cystic lesions. Neoplastic lesions are further broadly subcategorised into mucin-producing and non-mucin-producing [1]. The majority of cystic pancreatic lesions are incidental findings in patients undergoing abdominal imaging performed for unrelated reasons. The prevalence of such incidental lesions is approximately 2.5%, and their frequency increases with age to as much as 10% in those aged ≥ 70 years [2]. A non-malignant pseudocyst is the most common cystic lesion and is noted in individuals with a history of pancreatitis. In high-risk populations with a family history of pancreatic cancer or a hereditary predisposition to malignancy, non-pseudocyst cystic lesions may be identified in as many as one-third of patients [3]. Cystic pancreatic lesions have diverse histological and imaging appearances, and they also differ in clinical presentation, growth pattern, and risk of malignancy [3]. Patients with pancreatic cysts have an increased risk of pancreatic malignancy compared with the general population (relative risk: 22.5, 95% CI: 11.0–45.3) and the risk increases with the size of the cyst [3, 4]. The classic example of a non-mucin-

producing cystic neoplasm is a serous cystadenoma. Papillary cystic neoplasms (e.g. solid pseudopapillary tumours) and cystic pancreatic neuroendocrine tumours are additional examples. Thus, the management decision for a pancreatic cyst, whether to perform conservative or surgical resection, takes into consideration the risk of malignancy, the cost of cyst analysis, cyst surveillance, the anatomical location of the cyst, the patient's age, and overall health status [1]. A recent review suggests that the mortality rate from pancreatic resection for pancreatic cyst is 2.1% with a morbidity rate of 30%, which highlights the importance of appropriate management decisions and tailored therapy, despite the guidelines [5]. In this current review, we aim to provide an insight into the pathogenesis, clinical features, and management of various cystic pancreatic neoplasms (Table 1). The first step in evaluating a cyst is to perform magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) to further evaluate the cyst if not already done. A dedicated pancreatic protocol computed tomography (CT) scan is an alternative for patients who are unable to undergo MRI/MRCP. The use of MRI and CT helps to identify the pancreatic cyst with an accuracy of 40–90% for MRI and 40–81% for CT [6]. Endoscopic ultrasound (EUS) has also been recommended as a part of the imaging modality because it helps to identify pancreatic cystic neoplasms (PCN) with features that should be considered for surgical resection, but it cannot explain the exact type of PCN. Contrast-enhanced EUS (CH-EUS) helps in evaluating the mural nodule, vascularity, or septations, which helps to see any malignant transformation. EUS-fine needle aspiration (FNA) improves the diagnostic accuracy and helps to differentiate mucinous from non-mucinous PCN, as well as malignant from benign PCN.

Epidemiology

The incidence of pancreatic cysts in the US is estimated to be between 3% and 15% [7]. Another large study from the US that reviewed around 25,000 records of radiological, surgical, and pathological reports revealed the incidence rate of pancreatic cystic lesions to be 1.2%. Of the 49 cysts resected in this study, half were asymptomatic lesions. Twenty-nine percent of the resected cysts were classified as benign, 51% as premalignant, and 20% as malignant [8, 9]. Pancreatic cysts are detected in approximately 2.4% of patients who undergo abdominal imaging with multidetector-row CT or MRI for unrelated reasons [10]. Pancreatic cystic neoplasms account for more than 50% of pancreatic cysts, even in patients with a history of pancreatitis [8, 11]. In another case series involving 212 patients, 37% had asymptomatic lesions. Of these incidental pancreatic cystic lesions, 42% were premalignant, and 17% harboured in-situ or invasive cancer [12]. These data demonstrate that a significant percentage of neoplastic cysts are discovered incidentally [13].

Intraductal papillary mucinous neoplasm (IPMN)

Intraductal papillary mucinous neoplasms are cystic lesions (typically ≥ 1.0 cm) lined by intraductal dysplastic epithelium, which secrete excessive mucin, causing cystic dilation of the pancreatic ducts (PDs) [14]. IPMN on the basis of involvement of the PDs are classified as main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), or mixed variant IPMN involving both the main PD and its side branches [14]. IPMN also have various histological subtypes, such as: gastric, intestinal, pancreatobiliary, and oncocytic. BD-IPMN are usually of the gastric type, which is MUC5AC positive, is low grade, and only a small proportion turn into carcinoma. Main duct IPMNs usually have intestinal-type epithelium and a large and complex invasive property [15]. Progression to cancer can occur in all morphologic variants of IPMN. The survival rates are worse if progression occurs from invasive adenocarcinoma originating in gastric-type IPMNs, when compared to other types of IPMNs. Intestinal-type histology is found more frequently in MD-IPMN and is associated with intermediate to high risk of dysplasia and is therefore thought to cause more aggressive disease than gastric-type histology [16, 17]. The oncocytic type has papillae with oncocytic cells and is MUC6 positive [18, 19]. The oncocytic type is large and has a less invasive property, and it gets a clinical diagnosis of cystadenocarcinoma but has a good prognosis. The pancreatobiliary type is the least common, and it is also referred to by some as a high-grade version of the gastric type. The risk of progression of IPMN does not decrease even after resection, so investigations such as CT, MRCP/EUS, physical examination, and blood tests for tumour markers and glycohaemoglobin twice a year in patients with IPMN, even if they have undergone resection, are recommended [20]. All types of IPMN have a risk of developing PDAC more with BD-IPMN than with MD-IPMN [21].

IPMNs usually occur in the seventh decade of life and occur more frequently in males, with the highest male-to-female ratio of 3 : 1 seen in the Asian population [13, 22]. Although the true incidence of IPMNs is unknown, they are reported to be the most common PCN. IPMNs account for approximately 1% to 3% of pancreatic exocrine neoplasms and 20% to 50% of all PCNs [23, 24]. The site of occurrence of main duct IPMN is often the pancreatic head (> 50% of the time), whereas BD-IPMN is often multifocal, with 21–41% of those with BD-IPMNs having a multifocal disease, with > 2 cysts of various sizes throughout the pancreas [23]. BD-IPMNs are usually asymptomatic when

Table 1. Brief overview of different types of pancreatic cystic lesions

Parameter	Serous cystic tumour	Mucinous neoplasm	Main-duct intraductal papillary mucinous neoplasm	Branch-duct intraductal papillary mucinous neoplasm	Solid pseudopapillary neoplasm
Age at presentation	Usually 5th–6th decade	Peak incidence in 5th decade	Usually in the 7th decade of life	Usually in the 7th decade of life	3rd to 4th decade of life
Gender distribution	More common in women	Common in women > 95%	Male-to-female ratio of 3 : 1	More common in males	More common in women
Typical clinical presentation	Incidental, may present as abdominal pain or mass abdomen	Incidental or abdominal pain or malignancy related	Non-specific, abdominal pain, malaise, nausea/vomiting, and weight loss	Non-specific, abdominal pain, malaise, nausea/ vomiting, and weight loss	Abdominal discomfort, increased abdominal girth, poor appetite and nausea
Typical imaging characteristics	Central fibrous scar with calcification is pathognomonic (30% cases)	15% cases peripheral egg shell calcification on CT	Dilated main pancreatic duct ± parenchymal atrophy	Dilated pancreatic duct branch or duct branches	On CT, well-circumscribed, encapsulated masses with varying areas of soft tissue and necrotic foci
Typical aspirate characteristic	Typically thin and clear but may be bloody	Drop sign is an optical important clue, and consists of a drop of viscous mucous, which is hanging from the tip of the needle	Clear viscous fluid (positive "string sign")	Clear viscous fluid (positive "string sign")	Bloody
Cytology findings	Classically reveals glycogen-rich cuboidal cells	Columnar, mucin-producing epithelium with an underlying ovarian-type stroma	Columnar cells with variable atypia Stains positive for mucin; yield < 50%	Columnar cells with variable atypia Stains positive for mucin; yield < 50%	Characteristic branching papillae with myxoid stroma High yield from solid component
Typical CEA levels	Levels < 5 ng/ml	CEA level ≥ 480 ng/ml combined with viscosity > 1.6 accurately predict MCN	Elevated CEA > 192 ng/ml	Elevated CEA > 192 ng/ml	CEA levels are low
DNA analysis	No mutation generally seen, commonly associated with Von Hippel Lindau syndrome	K-ras mutation specific (> 90%)	66% contained a GNAS mutation, 81% KRAS	66% contained a GNAS mutation, 81% KRAS	CTNNB1 mutation specific
Malignant potential	Negligible	Premalignant or malignant	Malignant	Malignant	Low potential malignancy
Treatment	Surgical resection if lesion > 4 cm, postoperative surveillance unnecessary	Distal pancreatectomy in young individuals	Resection and post-resection surveillance	Resection or close monitoring	Resection, with favourable prognosis

small with no calcification and no common capsule. A cross-sectional study by Capurso *et al*., involving 390 patients, demonstrated that history of diabetes (especially with prior insulin use), chronic pancreatitis, and family history of pancreatic adenocarcinoma might increase the risk of IPMN development [25]. BD-IPMNs are more inactive, with a mean frequency of malignancy and invasive carcinoma around 25% and 18%, respectively, compared with 61% and 43% in MD-IPMN [23].

Symptomatic patients present with nonspecific symptoms such as abdominal pain, malaise, nausea/vomiting, and weight loss, whereas those with invasive carcinoma present with weight loss, diabetes mellitus, and/or painless jaundice [26, 27]. Laboratory investigation involves analysis of cyst fluid and estimation of carcinoembryonic antigen (CEA)/CA – 19 [28, 29]. IPMNs have clear, viscous fluid on physical examination (indicated by positive "string sign") and an elevated CEA > 192 ng/ml (CEA has a sensitivity of 73%, specificity of 84%, and accuracy of 79% in differentiating mucinous from non-mucinous pancreatic cystic lesions). Serum CA 19-9 and CEA do not help in differentiating between benign and malignant mucinous cysts of the pancreas [30]. A study by Wu *et al*. involving DNA analysis of IPMNs revealed that 66% contained a GNAS mutation, 81% KRAS, and 51% both GNAS and KRAS [30]. Imaging techniques such as EUS are increasingly used to differentiate the types of IPMNs and in treatments such as intracystic injection of ethanol or ethanol/paclitaxel for cyst ablation [31]. EUS is used for the detection of mural nodules and invasive nature, as well as for detecting malignant characteristics. EUS-guided needle aspiration can be useful for obtaining the fluid CEA, amylase levels, and cytology of the cyst [32]. In centres with high expertise a combination of EUS-FNA and cytological interpretation helps to identify small BD-IPMNs [32, 33]. In a recent investigation it was shown that preoperative FNA-EUS is not associated with gastric or peritoneal cancer seeding. According to one meta-analysis, EUS-FNA accurately diagnosed IPMNs 72% of the time [34, 35].

The Sendai Guidelines from 2006, expanded in 2012 (now called the Fukuoka Guidelines), for the management of IPMN stated that surgical resection is the recommended modality for MD-IPMN when the pancreatic duct (PD) diameter is > 10 mm [36]. These guidelines also recommend resection of suspected BD-IPMN with cyst size > 3 cm or cyst size < 3 cm and the presence of mural nodules, dilation of the main PD > 6 mm, thick irregular wall, thick septa, and solid nodules identified on imaging [37]. A recent meta-analysis by Yamao *et al*. showed that the Sendai Consensus Guidelines had a low PPV (11–52%) but a high NPV (90–100%) for predicting malignancy in BD-IPMN [38]. Because the management of BD- IPMN is challenging, due to its less aggressive progression, imaging follow-up through CT/MRI is necessitated based on the size of the lesion. BD-IPMN smaller than 1 cm are evaluated annually, those measuring 1–2 cm are evaluated every 6–12 months, and those measuring 2–3 cm are imaged at intervals of 3–6 months [37]. The absolute criteria for surgical resection of BD-IPMN include jaundice, cytology positive for high-grade dysplasia or cancer, and the presence of contrast-enhanced mural nodule > 5 mm or solid mass. The relative indications for surgical resection include growth rate of 0.5 mm/year, increased serum CEA 19-9 level, main pancreatic ductdiameter between 5 mm and 9.9 mm, cyst diameter > 40 mm, symptoms such as new onset diabetes, mural nodule < 5 mm. Patients with IPMN and with no indication for surgery should undergo a 6-month follow-up in the first year, and then yearly follow-up is required. Patients undergoing partial pancreatectomy for IPMN require lifelong follow-up. Several studies have shown increased risk of malignancy ranging from 12–47% if the cyst size in IPMN is over 30 mm [39]. With regards to the prognosis, for patients with resected non-invasive IPMN, the 5-year survival rate is 90% to 95%. Whereas, for patients with IPMNs with an associated invasive carcinoma, the 5-year survival rates are reported to be between 36% and 60% [27]. Postoperatively patients need yearly follow-up evaluations of benign IPMNs and imaging follow-up in addition to measurement of serum markers (CEA and CA19-9) after resection of invasive IPMN, according to the International Association of Pancreatology [37, 40, 41]. 5 Extrapancreatic neoplasm is common in 20–30% of patients with IPMN; these include neoplasm of GIT, skin, breast, renal cell, thyroid, and prostate malignancies [42]. HGD, positive margins of the resected tissue, and family history are predictors for its recurrence. With respect to family history, He *et al*. found that patients with a family history of pancreatic cancer develop recurrence after resection of non-invasive IPMN (23% vs. 7%, $p < 0.05$), and family history was the pre-operative predictor of recurrence [43].

Serous cystic tumours (SCN)

Serous cystic neoplasm is benign, and no deaths are recorded due to dissemination/malignant behaviour of SCN; specific mortality due to SCN is nearly zero [44, 45]. They are cystic tumours that are histologically composed of cuboidal, glycogen-rich epithelial cells. They are filled with serous fluid and are classified according to the degree of dysplasia, as either serous cystadenoma (SCA) or serous cystadenocarcinoma (SCAC) [46–48]. SCN is more common in women, and patients are usually diagnosed during the fifth or sixth decade of life [49]. They account for approximately 16% of resected pancreatic cystic tumours and are most common in the body or tail of the pancreas but can involve the entire organ [50, 51].

Up to 90% of patients with von Hippel-Lindau syndrome have been reported to develop SCN [50]. Serous cystadenomas can be divided into microcystic, honeycomb, and oligocystic/macrocystic forms [52].

On CT a central fibrous scar with calcification can be seen in up to 30% of these lesions and is pathognomonic for SCNs [53, 54]. Microcyst is seen in 70% cases; they appear solid or show macrocavities, and can be confused as mucinous cystic neoplasm (MCN) on CT. They appear as multiple cysts (> 6) and each measuring < 2 cm in diameter [50]. The honeycomb pattern is seen in 20% of patients and shows multiple small cysts that appear as solid masses on CT and maintain high signal intensity on T2-weighted MRI [50]. The oligocystic (macrocystic) pattern is the least common (< 10%) and can be difficult to distinguish from MCN based on MRI or CT [55]. The absence of communication on imaging with the pancreatic duct helps in the differentiation of MCN and SCN from IPMN [56]. Needle-based confocal laser endomicroscopy (nCLE) is an emerging imaging technique performed during EUS-FNA and provides real-time images of the internal structure of the pancreatic cyst [57–59]. In the CONTACT study by Napoléon *et al*., a superficial vascular network pattern was used to identify SCA with a sensitivity of 69%, a specificity of 100%, positive predictive value of 100%, negative predictive value of 82%, and accuracy of 87%. CEA levels are low in patients with SCA [60, 61]. In a study of 450 patients, van der Waaij *et al*. revealed that CEA levels below 5 ng/ml suggested an SCA or pseudocyst (PC) with 50% sensitivity and 95% specificity [62]. The size of 60% of SCNs is stable, and the remaining 40% increase in size, but the growth is slow and new onset of symptoms are rare [63].

Management in the form of surgical resection is indicated only if the lesion is > 4 cm in size, the patient is symptomatic, and if there is uncertainty with regard to the nature of the cyst [60, 64, 65]. Follow-up imaging in a non-resected patient is controversial with regards to the length of time; some studies support follow-up for up to 2 years [66]. In patients who have had a surgical resection, postoperative surveillance is unnecessary, unless histology showed SCAC [66].

Mucinous cystic neoplasm (MCN)

Mucinous cystic neoplasms are premalignant or malignant cysts forming epithelial tumours of the pancreas, which are histologically composed of columnar, mucin-producing epithelium with an underlying ovarian-type stroma, which is a unique finding, and some authors consider it as a prerequisite for diagnosis [67]. MCN are more common in women (> 95%) and are usually located in the distal pancreas (> 95%), with a peak incidence in the fifth decade [68–71]. They can arise from the neck, body, or tail of the pancreas [23]. The World Health Organisation has classified MCN into three stages: benign (adenomatous), low-grade malignant (borderline), and malignant (carcinoma *in situ* and invasive) [72].

Imaging techniques such as CT reveal the presence of septae, which are better visualised on T1-weighted images with intravenous gadolinium administration. The cysts have high signal intensity on T2-weighted images, and in 15% of cases, peripheral eggshell calcifications may be found on CT, which indicates an increased likelihood of invasive cystadenocarcinoma [73–75]. Cyst fluid analysis with CEA level ≥ 480 ng/ml combined with viscosity > 1.6 has also been shown to predict mucinous cysts accurately. Higher levels of CEA (i.e. > 800 ng/ml) have revealed 98% specificity, 48% sensitivity, and 79% accuracy in differentiating mucinous cystadenoma (MCA) or mucinous cystadenocarcinoma (MCAC) from SCA or PC (pseudocyst) [61]. In addition, estimation of amylase levels is also diagnostic; cyst fluid amylase levels < 250 U/l have been shown to have a sensitivity of 44% and specificity of 98% in the diagnosis of SCA, MCA, or MCAC and can be used to exclude PC [61].

Management in an elderly patient is through observation, in case the lesion is < 3 cm and mural nodules are absent. If the size is over 40 mm, then surgical resection is mandatory. Surgical resection is also required if MCN is symptomatic or if there is a mural nodule, irrespective of the size [76]. However, the size of MCN needs to be monitored; some evidence suggests that there is rapid growth of the MCN during pregnancy and that the chances of rupture also increase [77]. Hence, during pregnancy monitoring must be done. If the size is between 30 mm and 40 mm, other comorbidities such as age, patient preference, and surgical risk should be taken into consideration. When the size is less than 40 mm, then MRI and EUS should be done either individually or using a combination of both [78]. In invasive carcinoma distal pancreatectomy with lymph node dissection and splenectomy is recommended if imaging shows high-grade dysplasia. In low risk cases, malignancy can be treated with distal pancreatectomy with splenic preservation with or without preservation of splenic vessels or PSP. A PSP can be considered if there are chances of long-term development of diabetes. However, early morbidity and longer hospitalisation are major drawbacks [79]. Distal pancreatectomy is indicated in young individuals, considering the risk of progression to malignancy [37]. Studies have reported a 5-year survival of 94.7–100% in patients with non-invasive MCN and 57–62.5% in those with invasive MCN [80]. In patients with invasive carcinoma, disease recurrence ranges from 37% to 83% at 5 years. In the presence of an invasive lesion, repeat CT or MRI every 6 months to check for local recurrence and distant metastases is mandated [81].

Solid pseudopapillary neoplasm (SPN)

Solid pseudopapillary neoplasms are low potential malignant tumours, which are uncommon and account for less than 4% of the resected pancreatic cystic lesions [82]. SPNs without histological criteria of malignant behaviours, such as angioinvasion, perineural invasion, or infiltration of the surrounding parenchyma, may metastasise. Therefore, all SPNs are classified as low-grade malignant neoplasms [82]. SPNs metastasise to the liver or peritoneum in 10–15% of cases [83]. SPNs are rare; hence, most studies are retrospective, making comparison difficult [84]. SPNs are genetically characterised by the activation of beta-catenin and its target genes in the WNT signalling pathway [85]. They occur more commonly in women and generally present during the third and fourth decades of life [86, 87]. SPNs can occur throughout the pancreas but usually occur in the pancreatic body or tail [88, 89]. Macroscopically, SPNs appear as large, well-demarcated, solitary, mixed solid, and cystic heterogeneous masses. It is thought that these tumours begin as solid masses with poorly supported small vessels; therefore, cells distant to these vessels undergo swelling and degenerative change resulting in a pseudopapillary pattern and cystic spaces [90]. The cytological analysis includes branching papillae with myxoid stroma surrounded by monomorphic neoplastic cells [91]. The neoplastic cells are similar to neuroendocrine tumour cells. Thus, it is important to perform appropriate immunostains (vimentin, CD10, and β-catenin) to differentiate this neoplasm [90, 92]. Clinical presentation is generally nonspecific with symptoms like abdominal discomfort, increased abdominal girth, poor appetite, and nausea, which commonly occur from tumour compression of adjacent organs [48].

On CT, SPNs appear as well-circumscribed, encapsulated masses with varying areas of soft tissue and necrotic foci. The capsule is usually thick and enhancing. Peripheral calcification has been reported in 30% of patients, but no septations are visualised [93]. On MRI, the neoplasm is seen as a well-defined lesion with a mix of high and low signal intensity on T1- and T2-weighted images, which reflects the complex nature of the mass. Areas filled with blood products demonstrate high signal intensity on T1-weighted images [94]. On EUS, SPNs are usually well-defined, hypoechoic masses. They may be solid, mixed solid and cystic, or cystic [95]. Internal calcifications can be seen in some patients. The reported diagnostic accuracy of EUS-FNA for SPN based on cytology and immunohistochemistry is 65% [90]. The cyst fluid CEA is low, reflecting the presence of non-mucinous epithelium [29].

Management of SPNs is mainly surgical, taking into consideration the malignant potential (in 10–15% of individuals) of the lesion [96]. Surgeries such as distal pancreatectomy, central pancreatectomy, local resection, enucleation, and pancreaticoduodenectomy are performed depending on the site of the tumour [97]. Common metastatic sites include the liver, IVC wall, and spleen [98]. Despite its malignant potential, SPN does have a favourable prognosis, with a 5-year survival rate of around 95% after surgical resection [97]. Postoperative surveillance should be continued for at least 5 years, considering that the mean recurrence period is 4 years. Elderly patients, male patients, and those with aneuploidy DNA content have a poor prognosis and increased mortality [97, 99].

Summary

The detection of PCL is on the rise due to increased use of imaging techniques. The preliminary approach to a PCL begins with performing good-quality MRI imaging of the pancreas to identify malignant and mucinous cysts [100]. EUS-FNA has emerged as the modality of choice to evaluate further and sample PCL [101]. Although the AGA guidelines recommend utilisation of EUS in the presence of three high-risk factors, it would be reasonable to perform EUS even in the presence of one risk factor, considering the malignant potential [102]. EUS can further aid in diagnosis with direct visualisation using Spyglass technology and needle confocal laser endomicroscopy [103]. It would be ideal if the cyst biology could be accurately predicted via molecular analysis of aspirated cyst fluid [104]. Cytology is useful if malignancy is detected, with its high positive predictive value and 90% specificity. In addition, increased expression of IL-1β, IL-5, and IL-8 has also been linked to high-grade dysplasia or malignancy [104]. Elevated cyst fluid vascular endothelial growth factor-A (VEGF-A) > 8500 pg/ml has 100% sensitivity and 97% specificity for SCA [105]. A recent study stated that a composite of clinical and molecular markers improved sensitivity and specificity for MCN and IPMN to 90–94% and 84–97%, respectively [106]. Consensus guidelines for surgical management do exist, but considering the morbidity involved in the surgery, risk stratification methods are essential. Considering the guidelines as mentioned above and various diagnostic techniques, each case needs to be tailored considering the malignant risk, surgical risk, and life expectancy. This would thereby help in optimising therapy and avoid unnecessary burden both in terms of monetary and non-monetary forms to the patient. Broadening the dimensions of research is essential in controversial areas of management of cystic neoplasms of the pancreas.

Conflict of interest

The authors declare no conflict of interest.

References

1. Stark A, Donahue TR, Reber HA, Hines OJ. Pancreatic cyst disease. JAMA 2016; 315: 1882-1893.
2. Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, Johnson PT, Fishman EK, Hruban RH. Prevalence of unsuspected pancreatic cysts on MDCT. Am J Roentgenol 2008; 191: 802-807.
3. Matsubara S, Tada M, Akahane M, Yagioka H, Kogure H, Sasaki T, Arizumi T, Togawa O, Nakai Y, Sasahira N, Hirano K, Tsujino T, Isayama H, Toda N, Kawabe T, Ohtomo K, Omata M. Incidental pancreatic cysts found by magnetic resonance imaging and their relationship with pancreatic cancer. Pancreas 2012; 41: 1241-1246.
4. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol 2019; 10: 10-27.
5. Scheiman JM, Hwang JH, Moayyedi P. American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015; 148: 824-848.e822.
6. Jang DK, Song BJ, Ryu JK, Chung KH, Lee BS, Park JK, Lee SH, Kim YT, Lee JY. Preoperative diagnosis of pancreatic cystic lesions. Pancreas 2015; 44: 1329-1333.
7. Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, Topazian M, Takahashi N, Fletcher J, Petersen G, Klein AP, Axilbund J, Griffin C, Syngal S, Saltzman JR, Mortele KJ, Lee J, Tamm E, Vikram R, Bhosale P, Margolis D, Farrell J, Goggins M; American Cancer of the Pancreas Screening (CAPS) Consortium. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. Gastroenterology 2012; 142: 796-804; quiz e714-795.
8. Spinelli KS, Fromwiller TE, Daniel RA, Kiely JM, Nakeeb A, Komorowski RA, Wilson SD, Pitt HA. Cystic pancreatic neoplasms. Ann Surg 2004; 239: 651-659.
9. Rawla P, Bandaru SS, Vellipuram AR. Review of infectious etiology of acute pancreatitis. Gastroenterol Res 2017; 10: 153-158.
10. de Jong K, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CH, van Heel E, Klass G, Fockens P, Bruno MJ. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol 2010; 8: 806-811.
11. Tada M, Kawabe T, Arizumi M, Togawa O, Matsubara S, Yamamoto N, Nakai Y, Sasahira N, Hirano K, Tsujino T, Tateishi K, Isayama H, Toda N, Yoshida H, Omata M. Pancreatic cancer in patients with pancreatic cystic lesions: a prospective study in 197 patients. Clin Gastroenterol Hepatol 2006; 4: 1265-1270.
12. Fernández-del Castillo C, Targarona J, Thayer SP, Rattner DW, Brugge WR, Warshaw AL. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. Arch Surg 2003; 138: 427-433.
13. Crippa S, Fernández-Del Castillo C, Salvia R, Finkelstein D, Bassi C, Domínguez I, Muzikansky A, Thayer SP, Falconi M, Mino-Kenudson M, Capelli P, Lauwers GY, Partelli S, Pederzoli P, Warshaw AL. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. Clin Gastroenterol Hepatol 2010; 8: 213-219.e214.
14. Sakorafas GH, Sarr MG. Cystic neoplasms of the pancreas: what a clinician should know. Cancer Treat Rev 2005; 31: 507-535.
15. Patra KC, Bardeesy N, Mizukami Y. Diversity of precursor lesions for pancreatic cancer: the genetics and biology of intraductal papillary mucinous neoplasm. Clin Transl Gastroenterol 2017; 8: e86.
16. Mino-Kenudson M, Fernandez-del Castillo C, Baba Y, Valsangkar NP, Liss AS, Hsu M, Correa-Gallego C, Ingkakul T, Perez Johnston R, Turner BG, Androutsopoulos V, Deshpande V, McGrath D, Sahani DV, Brugge WR, Ogino S, Pitman MB, Warshaw AL, Thayer SP. Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. Gut 2011; 60: 1712-1720.
17. Tan MC, Basturk O, Brannon AR, Bhanot U, Scott SN, Bouvier N, LaFemina J, Jarnagin WR, Berger MF, Klimstra D, Allen PJ. GNAS and KRAS mutations define separate progression pathways in intraductal papillary mucinous neoplasm-associated carcinoma. J Am Coll Surg 2015; 220: 845-854.e841.
18. Basturk O, Khayyata S, Klimstra DS, Hruban RH, Zamboni G, Coban I, Adsay NV. Preferential expression of MUC6 in oncocytic and pancreatobiliary types of intraductal papillary neoplasms highlights a pyloropancreatic pathway, distinct from the intestinal pathway, in pancreatic carcinogenesis. Am J Surg Pathol 2010; 34: 364-370.
19. Adsay NV, Adair CF, Heffess CS, Klimstra DS. Intraductal oncocytic papillary neoplasms of the pancreas. Am J Surg Pathol 1996; 20: 980-994.
20. Ohtsuka T, Tanaka M. Postoperative surveillance of branch duct IPMN. In: Intraductal Papillary Mucinous Neoplasm of the Pancreas. Springer, Japan 2013; 189-199.
21. Tamura K, Ohtsuka T, Ideno N, Aso T, Shindo K, Aishima S, Ohuchida K, Takahata S, Ushijima Y, Ito T, Oda Y, Mizumoto K, Tanaka M. Treatment strategy for main duct intraductal papillary mucinous neoplasms of the pancreas based on the assessment of recurrence in the remnant pancreas after resection. Ann Surg 2014; 259: 360-368.
22. Ingkakul T, Warshaw AL, Fernandez-Del Castillo C. Epidemiology of intraductal papillary mucinous neoplasms of the pancreas: sex differences between 3 geographic regions. Pancreas 2011; 40: 779-780.
23. Farrell JJ, Fernández-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. Gastroenterology 2013; 144: 1303-1315.
24. Laurent L, Vullierme M-P, Rebours V, Maire F, Hentic O, Francoz C, Durand F, Ruszniewski P, Lévy P. Estimation of the prevalence of intraductal papillary mucinous neoplasm of the pancreas in the French population through patients waiting for liver transplantation. United Eur Gastroenterol J 2016; 5: 499-503.
25. Capurso G, Boccia S, Salvia R, Del Chiaro M, Frulloni L, Arcidiacono PG, Zerbi A, Manta R, Fabbri C, Ventrucci M, Tarantino I, Piciucchi M, Carnuccio A, Boggi U, Leoncini E, Costamagna G, Delle Fave G, Pezzilli R, Bassi C, Larghi A; Italian Association for Study of Pancreas (AISP); Intraductal Papillary Mucinous Neoplasm (IPMN) Study Group. Risk factors for intraductal papillary mucinous neoplasm (IPMN) of the pancreas: a multicentre case-control study. Am J Gastroenterol 2013; 108: 1003-1009.
26. Sperti C, Pasquali C, Guolo P, Polverosi R, Liessi G, Pedrazzoli S. Serum tumor markers and cyst fluid analysis are useful for the diagnosis of pancreatic cystic tumors. Cancer 1996; 78: 237-243.

27. Salvia R, Fernández-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, Pederzoli P, Warshaw AL. Main-duct intraductal papillary mucinous neoplasms of the pancreas. Ann Surg 2004; 239: 678-687.
28. Rawla P, Sunkara T, Raj JP. Role of biologics and biosimilars in inflammatory bowel disease: current trends and future perspectives. J Inflamm Res 2018; 11: 215-226.
29. Brugge WR, Lauwers GY, Sahani D, Fernandez-del Castillo C, Warshaw AL. Cystic neoplasms of the pancreas. N Engl J Med 2004; 351: 1218-1226.
30. Wu J, Matthaei H, Maitra A, Dal Molin M, Wood LD, Eshleman JR, Goggins M, Canto MI, Schulick RD, Edil BH, Wolfgang CL, Klein AP, Diaz LA Jr, Allen PJ, Schmidt CM, Kinzler KW, Papadopoulos N, Hruban RH, Vogelstein B. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med 2011; 3: 92ra66-92ra66.
31. Pitman MB, Genevay M, Yaeger K, Chebib I, Turner BG, Mino-Kenudson M, Brugge WR. High-grade atypical epithelial cells in pancreatic mucinous cysts are a more accurate predictor of malignancy than "positive" cytology. Cancer Cytopathol 2010; 118: 434-440.
32. Genevay M, Mino-Kenudson M, Yaeger K, Konstantinidis IT, Ferrone CR, Thayer S, Castillo CF, Sahani D, Bounds B, Forcione D, Brugge WR, Pitman MB. Cytology adds value to imaging studies for risk assessment of malignancy in pancreatic mucinous cysts. Ann Surg 2011; 254: 977-983.
33. Tanaka M, Fernández-del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, Salvia R, Shimizu Y, Tada M, Wolfgang CL. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017; 17: 738-753.
34. Yoon WJ, Daglilar ES, Fernández-del Castillo C, Mino-Kenudson M, Pitman MB, Brugge WR. Peritoneal seeding in intraductal papillary mucinous neoplasm of the pancreas patients who underwent endoscopic ultrasound-guided fine-needle aspiration: The PIPE Study. Endoscopy 2014; 46: 382-387.
35. Thosani N, Thosani S, Qiao W, Fleming JB, Bhutani MS, Guha S. Role of EUS-FNA-based cytology in the diagnosis of mucinous pancreatic cystic lesions: a systematic review and meta-analysis. Dig Dis Sci 2010; 55: 2756-2766.
36. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, Yamaguchi K, Yamao K, Matsuno S; International Association of Pancreatology. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006; 6: 17-32.
37. Tanaka M, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, Kimura W, Levy P, Pitman MB, Schmidt CM, Shimizu M, Wolfgang CL, Yamaguchi K, Yamao K; International Association of Pancreatology. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012; 12: 183-197.
38. Yamao K, Yanagisawa A, Takahashi K, Kimura W, Doi R, Fukushima N, Ohike N, Shimizu M, Hatori T, Nobukawa B, Hifumi M, Kobayashi Y, Tobita K, Tanno S, Sugiyama M, Miyasaka Y, Nakagohri T, Yamaguchi T, Hanada K, Abe H, Tada M, Fujita N, Tanaka M. Clinicopathological features and prognosis of mucinous cystic neoplasm with ovarian-type stroma. Pancreas 2011; 40: 67-71.
39. Masica DL, Dal Molin M, Wolfgang CL, Tomita T, Ostovaneh MR, Blackford A, Moran RA, Law JK, Barkley T, Goggins M, Irene Canto M, Pittman M, Eshleman JR, Ali SZ, Fishman EK, Kamel IR, Raman SP, Zaheer A, Ahuja N, Makary MA, Weiss MJ, Hirose K, Cameron JL, Rezaee N, He J, Joon Ahn Y, Wu W, Wang Y, Springer S, Diaz LL Jr, Papadopoulos N, Hruban RH, Kinzler KW, Vogelstein B, Karchin R, Lennon AM. A novel approach for selecting combination clinical markers of pathology applied to a large retrospective cohort of surgically resected pancreatic cysts. J Am Med Inform Assoc 2016; 24: 145-152.
40. Maker AV. ASO Author reflections: improving identification of intraductal papillary mucinous neoplasm patients at risk – current status and the role of IPMN molecular biomarkers. Ann Surg Oncol 2018; 25 (Suppl 3): 818-819.
41. Nguyen AH, Toste PA, Farrell JJ, Clerkin BM, Williams J, Muthusamy VR, Watson RR, Tomlinson JS, Hines OJ, Reber HA, Donahue TR. Current recommendations for surveillance and surgery of intraductal papillary mucinous neoplasms may overlook some patients with cancer. J Gastrointest Surg 2014; 19: 258-265.
42. Larghi A, Panic N, Capurso G, Leoncini E, Arzani D, Salvia R, Del Chiaro M, Frulloni L, Arcidiacono PG, Zerbi A, Manta R, Fabbri C, Ventrucci M, Tarantino I, Piciucchi M, Carnuccio A, Boggi U, Costamagna G, Delle Fave G, Pezzilli R, Bassi C, Bulajic M, Ricciardi W, Boccia S. Prevalence and risk factors of extrapancreatic malignancies in a large cohort of patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Ann Oncol 2013; 24: 1907-1911.
43. He J, Cameron JL, Ahuja N, Makary MA, Hirose K, Choti MA, Schulick RD, Hruban RH, Pawlik TM, Wolfgang CL. Is it necessary to follow patients after resection of a benign pancreatic intraductal papillary mucinous neoplasm? J Am Coll Surg 2013; 216: 657-665.
44. Jais B, Rebours V, Malleo G, Salvia R, Fontana M, Maggino L, Bassi C, Manfredi R, Moran R, Lennon AM, Zaheer A, Wolfgang C, Hruban R, Marchegiani G, Fernández Del Castillo C, Brugge W, Ha Y, Kim MH, Oh D, Hirai I, Kimura W, Jang JY, Kim SW, Jung W, Kang H, Song SY, Kang CM, Lee WJ, Crippa S, Falconi M, Gomatos I, Neoptolemos J, Milanetto AC, Sperti C, Ricci C, Casadei R, Bissolati M, Balzano G, Frigerio I, Girelli R, Delhaye M, Bernier B, Wang H, Jang KT, Song DH, Huggett MT, Oppong KW, Pererva L, Kopchak KV, Del Chiaro M, Segersvard R, Lee LS, Conwell D, Osvaldt A, Campos V, Aguero Garcete G, Napoleon B, Matsumoto I, Shinzeki M, Bolado F, Fernandez JM, Keane MG, Pereira SP, Acuna IA, Vaquero EC, Angiolini MR, Zerbi A, Tang J, Leong RW, Faccinetto A, Morana G, Petrone MC, Arcidiacono PG, Moon JH, Choi HJ, Gill RS, Pavey D, Ouaïssi M, Sastre B, Spandre M, De Angelis CG, Rios-Vives MA, Concepcion-Martin M, Ikeura T, Okazaki K, Frulloni L, Messina O, Lévy P. Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas). Gut 2016; 65: 305-312.
45. Reid MD, Choi HJ, Memis B, Krasinskas AM, Jang KT, Akkas G, Maithel SK, Sarmiento JM, Kooby DA, Basturk O,

Adsay V. Serous neoplasms of the pancreas. Am J Surg Pathol 2015; 39: 1597-1610.
46. Charville GW, Kao CS. Serous neoplasms of the pancreas: a comprehensive review. Arch Pathol Labor Med 2018; 142: 1134-1140.
47. Rawla P, Raj JP. Doxycycline-induced acute pancreatitis: a rare adverse event. Gastroenterol Res 2017; 10: 244-246.
48. Papadopoulos N, Hruban RH. Molecular mechanisms of cystic neoplasia. In: The Pancreas. John Wiley & Sons, Ltd 2018; 580-588.
49. Yoon WJ, Lee JK, Lee KH, Ryu JK, Kim YT, Yoon YB. Cystic neoplasms of the exocrine pancreas. Pancreas 2008; 37: 254-258.
50. Yoon WJ, Brugge WR. Pancreatic cystic neoplasms: diagnosis and management. Gastroenterol Clin North Am 2012; 41: 103-118.
51. Tseng JF, Warshaw AL, Sahani DV. Lauwers GY, Rattner DW, Castillo CF. Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment. Ann Surg
52. Sakorafas GH, Smyrniotis V, Reid-Lombardo KM, Sarr MG. Primary pancreatic cystic neoplasms revisited. part i: serous cystic neoplasms. Surg Oncol 2011; 20: e84-e92.
53. Procacci C, Graziani R, Bicego E, Bergamo-Andreis IA, Guarise A, Valdo M, Bogina G, Solarino U, Pistolesi GF. Serous cystadenoma of the pancreas: report of 30 cases with emphasis on the imaging findings. J Comput Assist Tomogr 1997; 21: 373-382.
54. Huh J, Byun JH, Hong SM, Kim KW, Kim JH, Lee SS, Kim HJ, Lee MG. Malignant pancreatic serous cystic neoplasms: systematic review with a new case. BMC Gastroenterology 2016; 16: 97-97.
55. Cohen-Scali F, Vilgrain V, Brancatelli G, Hammel P, Vullierme MP, Sauvanet A, Menu Y. Discrimination of unilocular macrocystic serous cystadenoma from pancreatic pseudocyst and mucinous cystadenoma with CT: initial observations. Radiology 2003; 228: 727-733.
56. Brugge WR. Diagnosis and management of cystic lesions of the pancreas. J Gastroint Oncol 2015; 6: 375-388.
57. Giovannini M. Needle-based confocal laser endomicroscopy. Endosc Ultrasound 2015; 4: 284.
58. Lévy P, Rebours V. The role of endoscopic ultrasound in the diagnosis of cystic lesions of the pancreas. Visc Med 2018; 34: 192-196.
59. Rawla P, Vellipuram AR, Bandaru SS, Raj JP. Splenic infarct and pulmonary embolism as a rare manifestation of cytomegalovirus infection. Case Rep Hematol 2017; 2017: 1-3.
60. Napoléon B, Lemaistre A-I, Pujol B, Caillol F, Lucidarme D, Bourdariat R, Morellon-Mialhe B, Fumex F, Lefort C, Lepilliez V, Palazzo L, Monges G, Filoche B, Giovannini M. A novel approach to the diagnosis of pancreatic serous cystadenoma: needle-based confocal laser endomicroscopy. Endoscopy 2014; 47: 26-32.
61. Carr RA, Yip-Schneider MT, Dolejs S, Hancock BA, Wu H, Radovich M, Schmidt CM. Pancreatic cyst fluid vascular endothelial growth factor a and carcinoembryonic antigen: a highly accurate test for the diagnosis of serous cystic neoplasm. J Am Coll Surg 2017; 225: 93-100.
62. van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc 2005; 62: 383-389.
63. Pelaez-Luna MC, Moctezuma-Velazquez C, Hernandez-Calleros J, Uscanga-Dominguez LF. Serous cystadenomas follow a benign and asymptomatic course and do not present a significant size change during follow-up. Rev Invest Clin 2015; 67: 344-349.
64. European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018; 67: 789-804.
65. Gomatos IP, Halloran C, Ghaneh P, Raraty M, Polydoros F, Campbell F, Evans J, Sutton R, Garry J, Whelan P, Neoptolemos JP. Management and outcome of 64 patients with pancreatic serous cystic neoplasms. Dig Surg 2016; 33: 203-212.
66. Malleo G, Bassi C, Rossini R, Manfredi R, Butturini G, Massignani M, Paini M, Pederzoli P, Salvia R. Growth pattern of serous cystic neoplasms of the pancreas: observational study with long-term magnetic resonance surveillance and recommendations for treatment. Gut 2011; 61: 746-751.
67. Valsangkar NP, Morales-Oyarvide V, Thayer SP, Ferrone CR, Wargo JA, Warshaw AL, Fernández-del Castillo C. 851 resected cystic tumors of the pancreas: a 33-year experience at the Massachusetts General Hospital. Surgery 2012; 152: S4-S12.
68. Le Baleur Y, Couvelard A, Vullierme MP, Sauvanet A, Hammel P, Rebours V, Maire F, Hentic O, Aubert A, Ruszniewski P, Lévy P. Mucinous cystic neoplasms of the pancreas: definition of preoperative imaging criteria for high-risk lesions. Pancreatology 2011; 11: 495-499.
69. Crippa S, Salvia R, Warshaw AL, Domínguez I, Bassi C, Falconi M, Thayer SP, Zamboni G, Lauwers GY, Mino-Kenudson M, Capelli P, Pederzoli P, Castillo CF. Mucinous cystic neoplasm of the pancreas is not an aggressive entity. Ann Surg 2008; 247: 571-579.
70. Rawla P, Sunkara T, Thandra KC, Gaduputi V. Hypertriglyceridemia-induced pancreatitis: updated review of current treatment and preventive strategies. Clin J Gastroenterol 2018; 11: 441-448.
71. Hackert T, Michalski CW, Büchler MW. Mucinous cystic neoplasms of the pancreas: a surgical diseasemucinous cystic neoplasms of the pancreas research. JAMA Surg 2017; 152: 26-26.
72. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology 2004; 126: 1330-1336.
73. Buetow PC, Rao P, Thompson LD. From the Archives of the AFIP. Mucinous cystic neoplasms of the pancreas: radiologic-pathologic correlation. RadioGraphics 1998; 18: 433-449.
74. Wilentz RE, Albores-Saavedra J, Zahurak M, Talamini MA, Yeo CJ, Cameron JL, Hruban RH. Pathologic examination accurately predicts prognosis in mucinous cystic neoplasms of the pancreas. Am J Surg Pathol 1999; 23: 1320.
75. Curry CA, Eng J, Horton KM, Urban B, Siegelman S, Kuszyk BS, Fishman EK. CT of primary cystic pancreatic neoplasms. Am J Roentgenol 2000; 175: 99-103.
76. Nilsson LN, Keane MG, Shamali A, Millastre Bocos J, Marijinissen van Zanten M, Antila A, Verdejo Gil C, Del Chiaro M, Laukkarinen J. Nature and management of pancreatic mucinous cystic neoplasm (MCN): a systema-

tic review of the literature. Pancreatology 2016; 16: 1028-1036.
77. Naganuma S, Honda K, Noriki S, Kimura S, Murakami M, Koneri K, Katayama K, Yamaguchi A, Itoh H. Ruptured mucinous cystic neoplasm with an associated invasive carcinoma of pancreatic head in a pregnant woman: report of a case and review of literature. Pathol Int 2010; 61: 28-33.
78. Arshad HMS, Bharmal S, Duman DG, Liangpunsakul S, Turner BG. Advanced endoscopic ultrasound management techniques for preneoplastic pancreatic cystic lesions. J Investig Med 2017; 65: 7.
79. Faitot F, Gaujoux S, Barbier L, Novaes M, Dokmak S, Aussilhou B, Couvelard A, Rebours V, Ruszniewski P, Belghiti J, Sauvanet A. Reappraisal of pancreatic enucleations: a single-center experience of 126 procedures. Surgery 2015; 158: 201-210.
80. Robinson SM, Scott J, Oppong KW, White SA. What to do for the incidental pancreatic cystic lesion? Surg Oncol 2014; 23: 117-125.
81. Sahani DV, Kambadakone A, Macari M, Takahashi N, Chari S, Fernandez-del Castillo C. Diagnosis and management of cystic pancreatic lesions. AJR Am J Roentgenol 2013; 200: 343-354.
82. Ng KH, Tan PH, Thng CH, Ooi LL. Solid pseudopapillary tumour of the pancreas. ANZ J Surg 2003; 73: 410-415.
83. Amato E, Mafficini A, Hirabayashi K, Lawlor RT, Fassan M, Vicentini C, Barbi S, Delfino P, Sikora K, Rusev B, Simbolo M, Esposito I, Antonello D, Pea A, Sereni E, Ballotta M, Maggino L, Marchegiani G, Ohike N, Wood LD, Salvia R, Klöppel G, Zamboni G, Scarpa A, Corbo V. Molecular alterations associated with metastases of solid pseudopapillary neoplasms of the pancreas. J Pathol 2019; 247: 123-134.
84. Lee HS, Kim HK, Shin BK, Choi JH, Choi YJ, Kim HY. A rare case of recurrent metastatic solid pseudopapillary neoplasm of the pancreas. J Pathol Transl Med 2017; 51: 87-91.
85. Abraham SC, Klimstra DS, Wilentz RE, Yeo CJ, Conlon K, Brennan M, Cameron JL, Wu TT, Hruban RH. Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol 2002; 160: 1361-1369.
86. Reddy S, Cameron JL, Scudiere J, Hruban RH, Fishman EK, Ahuja N, Pawlik TM, Edil BH, Schulick RD, Wolfgang CL. Surgical management of solid-pseudopapillary neoplasms of the pancreas (Franz or Hamoudi tumors): a large single-institutional series. J Am Coll Surg 2009; 208: 950-957.
87. Casillas J, Levi JU, Ruiz-Cordero R, et al. Solid pseudopapillary tumor of the pancreas. In: Casillas J, Levi JU, Quiroz AO, Ruiz-Cordero R, Garcia-Buitrago MT, Slleman D (eds). Multidisciplinary Teaching Atlas of the Pancreas. Springer, Berlin Heidelberg 2016; 329-362.
88. Butte JM, Brennan MF, Gönen M, Tang LH, D'Angelica MI, Fong Y, Dematteo RP, Jarnagin WR, Allen PJ. Solid pseudopapillary tumors of the pancreas. clinical features, surgical outcomes, and long-term survival in 45 consecutive patients from a single center. J Gastrointest Surg 2010; 15: 350-357.
89. Rawla P, Sunkara T, Thandra KC, Gaduputi V. Efficacy and safety of budesonide in the treatment of eosinophilic esophagitis: updated systematic review and meta-analysis of randomized and non-randomized studies. Drugs R D 2018; 18: 259-269.
90. Jani N, Dewitt J, Eloubeidi M, Varadarajulu S, Appalaneni V, Hoffman B, Brugge W, Lee K, Khalid A, McGrath K. Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas: a multicenter experience. Endoscopy 2007; 40: 200-203.
91. Pettinato G, Carlos Manivel J, Ravetto C, Terracciano LM, Gould EW, di Tuoro A, Jaszcz W, Albores-Saavedra J. Papillary cystic tumor of the pancreas: a clinicopathologic study of 20 cases with cytologic, immunohistochemical, ultrastructural, and flow cytometric observations, and a review of the literature. Am J Clin Pathol 1992; 98: 478-488.
92. Yang F, Yu X, Bao Y, Du Z, Jin C, Fu D. Prognostic value of Ki-67 in solid pseudopapillary tumor of the pancreas: Huashan experience and systematic review of the literature. Surgery 2016; 159: 1023-1031.
93. Buetow PC, Buck JL, Pantongrag-Brown L, Beck KG, Ros PR, Adair CF. Solid and papillary epithelial neoplasm of the pancreas: imaging-pathologic correlation on 56 cases. Radiology 1996; 199: 707-711.
94. Rajtar KZ, Sznajder K, Milto KM. Diagnostic imaging of a solid pseudopapillary tumour of the pancreas in a 20-year-old woman – a case study. Gastroenterol Rev 2016; 11: 214-217.
95. Ortega Espinosa CR, de la Mora Levy JG, Alonso-Larraga JO, del Monte JS, Ramirez-Solis ME, Hernandez-Guerro A. The role of endoscopic ultrasound–guided fine-needle aspiration in solid-pseudopapillary tumor of the pancreas. Pancreatology 2017; 17: S33.
96. Yu P, Cheng X, Du YL, Yang L, Xu Z, Yin W, Zhong Z, Wang X, Xu H, Hu C. Solid pseudopapillary neoplasms of the pancreas: a 19-year multicenter experience in China. J Gastrointest Surg 2015; 19: 1433-1440.
97. Law JK, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, Ali SZ, Fishman EK, Kamel I, Canto MI, Dal Molin M, Moran RA, Khashab MA, Ahuja N, Goggins M, Hruban RH, Wolfgang CL, Lennon AM. A systematic review of solid-pseudopapillary neoplasms. Pancreas 2014; 43: 331-337.
98. Tang LH, Aydin H, Brennan MF, Klimstra DS. Clinically aggressive solid pseudopapillary tumors of the pancreas. Am J Surg Pathol 2005; 29: 512-519.
99. Al-Habbaa A, Rawla P, Morra ME, Abotaha AA, Sakr EE, Abdo Shehata MA, Shahin KM, Abdel Mageed S, Huy NT. Valvular involvement in granulomatosis with polyangiitis: case report and systematic review of literature. Echocardiography 2018; 35: 1456-1463.
100. Kalb B, Sarmiento JM, Kooby DA, Volkan Adsay N, Martin DR. MR imaging of cystic lesions of the pancreas. RadioGraphics 2009; 29: 1749-1765.
101. Lu X, Zhang S, Ma C, Lv Y, Zou X. The diagnostic value of EUS in pancreatic cystic neoplasms compared with CT and MRI. Endosc Ultrasound 2015; 4: 324-329.
102. Lee A, Kadiyala V, Lee L. Evaluation of AGA and Fukuoka guidelines for EUS and surgical resection of incidental pancreatic cysts. Endosc Int Open 2017; 05: E116-E122.
103. Kawaguchi Y, Mine T. Endoscopic approach to the diagnosis of pancreatic cystic tumor. World J Gastrointest Oncol 2016; 8: 159-164.

104. Maker AV, Katabi N, Qin LX, Klimstra DS, Schattner M, Brennan MF, Jarnagin WR, Allen PJ. Cyst fluid interleukin-1beta (IL1beta) levels predict the risk of carcinoma in intraductal papillary mucinous neoplasms of the pancreas. Clin Cancer Res 2011; 17: 1502-1508.
105. Reid MD, Choi H, Balci S, Akkas G, Adsay V. Serous cystic neoplasms of the pancreas: clinicopathologic and molecular characteristics. Semin Diagn Pathol 2014; 31: 475-483.
106. Springer S, Wang Y, Dal Molin M, Masica DL, Jiao Y, Kinde I, Blackford A, Raman SP, Wolfgang CL, Tomita T, Niknafs N, Douville C, Ptak J, Dobbyn L, Allen PJ, Klimstra DS, Schattner MA, Schmidt CM, Yip-Schneider M, Cummings OW, Brand RE, Zeh HJ, Singhi AD, Scarpa A, Salvia R, Malleo G, Zamboni G, Falconi M, Jang JY, Kim SW, Kwon W, Hong SM, Song KB, Kim SC, Swan N, Murphy J, Geoghegan J, Brugge W, Fernandez-Del Castillo C, Mino-Kenudson M, Schulick R, Edil BH, Adsay V, Paulino J, van Hooft J, Yachida S, Nara S, Hiraoka N, Yamao K, Hijioka S, van der Merwe S, Goggins M, Canto MI, Ahuja N, Hirose K, Makary M, Weiss MJ, Cameron J, Pittman M, Eshleman JR, Diaz LA Jr, Papadopoulos N, Kinzler KW, Karchin R, Hruban RH, Vogelstein B, Lennon AM. A combination of molecular markers and clinical features improve the classification of pancreatic cysts. Gastroenterology 2015; 149: 1501-1510.

Address for correspondence:

Jeffrey Pradeep Raj MD
Department of Clinical Pharmacology
Seth GS Medical College & King Edward Memorial Hospital
Mumbai, India
E-mail: jpraj.m07@gmail.com