



Review

Diagnosis and management strategy for cystic neoplasm of the pancreas

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ABSTRACT

Objective: This article aimed to propose a management strategy for cystic neoplasm of the pancreas based on the available evidence in the medical literature.

Methods: A Medline search was undertaken to identify articles from 1988 to 2008 using the keywords 'pancreatic cyst', 'pancreatic neoplasms', and 'cystic neoplasm of pancreas'. Additional papers were identified by a manual search of the references from the key articles.

Comments: The optimal management of cystic neoplasms of pancreas remains controversial and should be individualized based on the balance between the risk and benefit. Multiple factors such as patient's comorbidity, performance status, life expectancy, and surgical risk, should be weighed against the malignant potential of the cyst.

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1. Introduction

Pancreatic cystic neoplasms are detected more frequently as a result of increasing use of cross-sectional imaging. Proper management of this heterogeneous group of tumors is important because of their high cure rate, as well as frequent confusion with the much commoner pancreatic pseudocyst. However, cystic neoplasms of the pancreas present a difficult diagnostic and treatment problem which stems from: (1) the inability to reliably diagnose the definitive type of cystic neoplasm of pancreas; (2) the inability to distinguish malignant from benign cystic lesions; and (3) the incomplete understanding of the natural history of cystic neoplasms of the pancreas.

With an increasing number of patients being identified with pancreatic cystic neoplasms, routine resection of all pancreatic cystic neoplasms is currently impractical. However, the criteria for a selective approach of management are also not well defined. The strategies for evaluating and managing patients with pancreatic cysts are still evolving. Therefore, a thorough understanding of the characteristics and behavior of each type of cystic neoplasm of the pancreas is important for the formulation of a proper management strategy. The goal of management is to identify pre-operatively those patients with pre-malignant or malignant disease who are appropriate candidates for pancreatic resection, and avoid the morbidity and mortality of major operations in asymptomatic patients with benign disease.

This article aimed to propose a management strategy for cystic neoplasms of the pancreas based on the available evidence in the

medical literature. A detailed discussion of each specific type of cystic neoplasm of the pancreas is beyond the scope of this article.

2. Methods

A Medline search was undertaken to identify articles from 1988 to 2008 using the keywords 'pancreatic cyst', 'pancreatic neoplasms', and 'cystic neoplasm of pancreas'. Additional papers were identified by a manual search of the references from the key articles.

3. Differential diagnosis of cystic lesions of the pancreas

Although the neoplastic nature of some pancreatic cysts has been recognized for more than a century, the nomenclature, classification and characterization of the various cystic neoplasms of the pancreas have become mature only in the last two decades. The most significant recent change in the diagnosis and treatment of cystic neoplasms of the pancreas is the recognition and description of the intraductal papillary mucinous neoplasm (IPMN) as a distinct pathological entity. In 1996, IPMN was classified by the World Health Organization (WHO) as distinct from other mucin-producing cystic neoplasms of the pancreas.

The differential diagnosis of pancreatic cysts and the histological varieties of cystic neoplasms of the pancreas are shown in Table 1. Inflammatory pancreatic cysts (i.e., pseudocysts) are by far the most common, accounting for approximately 75% of pancreatic cystic lesions.¹ A pancreatic pseudocyst is a localized collection of amylase-rich pancreatic secretions, necrotic debris and blood that, by definition, has no epithelial lining. The wall of a pseudocyst consists of fibrin, granulation tissue, and loose fibrotic tissue.

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Table 1
Differential diagnosis of cystic lesions of the pancreas

Congenital Infectious Inflammatory Neoplastic	Simple cyst
	Polycystic disease associated with: cystic fibrosis, Von Hippel–Landau disease, polycystic disease of the kidney and liver
	Enterogenous cyst
	Echinococcal cyst
	Pseudocyst
	Serous cystadenoma
	Mucinous cystic neoplasm
	Intraductal papillary mucinous neoplasm (IPMN)
	Solid pseudopapillary tumor
	Lymphoepithelial cyst
	Cystic variants of solid neoplasms
	Cystic ductal adenocarcinoma
	Cystic neuroendocrine tumor
	Cystic acinar cell carcinoma

Pseudocysts occur as a consequence of damage to the pancreatic parenchyma that results in necrosis and autodigestion of pancreatic tissue from the release and activation of pancreatic enzymes. It appears as a well-circumscribed, unilocular macrocyst on cross-sectional imaging.² A pseudocyst may be indistinguishable from a cystic neoplasm on imaging studies. The amylase level of pseudocyst fluid is almost always much higher than the fluid in cystic neoplasms. The differentiating features of the various cystic neoplasms of the pancreas are shown in Table 2.

3.1. Serous cystadenoma

Serous cystadenoma accounts for 32–39% of pancreatic cystic neoplasms.^{3,4} It is a benign neoplasm composed of uniform cuboidal glycogen-rich epithelial cells, presumably originating from the centroacinar cell/intercalated duct system and typically form innumerable small cysts containing serous fluid.⁵ The sponge-like gross appearance that gives this tumor the name microcystic is diagnostic of the entity. Oligocystic (unilocular) serous cystadenomas have been described, but they are unusual.^{6,7} The

fibrous stroma separating the cystic areas is relatively vascular and may calcify, giving rise to the characteristic sunburst, radial or stellate scar pattern on a computed tomography (CT) scan. When present, this finding is diagnostic. However, this typical feature is present in 13–18% of patients only.^{8–10} Confirming the diagnosis by CT can be more challenging in the case of oligocystic lesions, in which the macrocystic component can appear radiographically similar to that of inflammatory pseudocyst or mucinous cystic neoplasm. Almost all serous cystadenomas are benign, and the malignant potential of serous cystadenoma is extremely low.^{11–15} Serous cystadenomas are also associated with von Hippel–Landau syndrome (VHL), an autosomal dominant disorder characterized by hemangioblastomas of the central nervous system and retina, renal neoplasms and cysts, and pheochromocytomas.¹⁶

3.2. Mucinous cystic neoplasms

Mucinous cystic neoplasms account for 10–45% of pancreatic cystic neoplasms.^{3,17} It is a neoplasm composed of mucin-producing epithelial cells associated with an ovarian-type of stroma.^{5,18} These lesions may be unilocular or multilocular and may contain shaggy, papillary excrescences extending into the lumen of the cyst. The cystic spaces of this tumor are characteristically larger than that of serous cystadenoma. Calcification within the fibrous capsule of mucinous cystic neoplasms may present in a peripheral ‘eggshell’ pattern on plain X-ray or CT scan. Mucinous cystic neoplasms represent a spectrum of disease ranging from benign mucinous cystadenomas to very aggressive invasive mucinous cystadenocarcinomas. Carcinomatous foci may be patchy and difficult to discern macroscopically.

3.3. Intraductal papillary mucinous neoplasms (IPMN)

IPMN accounts for 21–33% of pancreatic cystic neoplasms.^{3,19} IPMN is an intraductal papillary mucin-producing neoplasm, arising in the main pancreatic duct or its major branches. The

Table 2
Characteristics of different cystic neoplasms of pancreas

	Serous cystadenomas	Mucinous cystic neoplasms	Intraductal papillary mucinous neoplasms	Solid and pseudopapillary tumors
Sex distribution	Female >> Male	Female >> Male	Male = Female	Almost exclusively in female
Age group at peak occurrence	6–7th decade	5–7th decade	6–8th decade	2–3rd decade
Location	Evenly distributed	Body/tail > Head	Head > body/tail	Evenly distributed
Typical imaging feature	Central scar or ‘sunburst’ calcification	Peripheral ‘eggshell’ calcification	A diffuse or segmental dilatation of any portion of the pancreatic ductal system; a lobulated multilocular cystic lesion located in the uncinate process and in contiguity with the dilated main pancreatic duct	Well-defined, low-attenuation mass with peripheral enhancement and complex cystic components with areas of necrosis and internal hemorrhage
Typical endoscopic feature	Nil	Nil	Mucin can be seen oozing from the ampulla of Vater	Nil
Gross appearance	Well-demarcated, somewhat bosselated masses, composed of innumerable small thin-walled cysts (<1 mm to 2 cm in diameter), imparting a sponge-like appearance on cross-section; oligocystic appearance less common	Macrocystic appearance with less than six cysts, each usually larger than 2 cm in diameter	Ectasia of the main pancreatic duct or branch ducts; ectatic branch ducts sometimes appear as a grapelike cluster of mucin-filled structures around the main pancreatic duct	Soft, tan to red masses with variable solid and cystic components with hemorrhagic changes
Communication with duct	No	No	Yes	No
Cyst content	Thin straw colored fluid	Thick, tenacious mucoid material	Mucoid	Necrotic/hemorrhagic
Epithelial lining	Glycogen-rich cuboidal epithelium	Mucin-producing, tall, columnar epithelium	Pseudostratified tall, columnar	Uniform cells with nuclear grooves
Stromal characteristics	Delicate and vascular to fibrous	‘Ovarian-type’	Fibrosis and atrophy	Some hyalinization
Malignant potential	Extremely low	High	Moderate	Low

papillary epithelial component, degree of mucin secretion, cystic dilatation, and invasiveness are variable. In addition, IPMN lacks the ovarian stroma, which is characteristic of a mucinous cystic neoplasm. IPMN is separated into various categories depending on the degree of cytoarchitectural atypia that is present: IPMN adenoma, IPMN borderline, IPMN with carcinoma in situ, and IPMN with invasive carcinoma. IPMN adenomas, IPMN borderline, IPMN with carcinoma in situ are considered as non-invasive IPMN. IPMN with invasive carcinoma is considered as invasive IPMN. A total of 25–48% of IPMN contain invasive carcinoma.^{19–25} IPMN is classified into those predominantly involving the main pancreatic duct (main duct type) and those predominantly involving the side branch of the ductal system (branch duct type) because they have different tumor biological behavior. Branch duct type IPMN is less often associated with invasive carcinoma than main duct type IPMN. However, the difference in the prognosis of the main duct type and the branch duct type is still a controversial issue. A number of retrospective studies have been performed to identify the clinicopathological features that can differentiate malignant IPMN from benign IPMN. There is still no consensus on this. Based on these studies, four features suggest malignant IPMN: (1) jaundice; (2) worsening or new onset of diabetes mellitus; (3) main duct type tumor; and (4) mural nodules.^{19–25}

3.4. Solid pseudopapillary tumor

Solid pseudopapillary tumors account for 5.5–12% of pancreatic cystic neoplasms.^{3,26} This typically occurs in young women. Morphologically, solid pseudopapillary tumors are typically large, encapsulated lesions, with solid and cystic areas and pseudopapillary patterns seen histologically. This tumor often presents as a large, multilobular mass composed of homogeneous, fleshy tissue separated by areas of hemorrhagic and necrotic cystic degeneration.^{26,27} Tumors are generally surrounded by a fibrous capsule and appear demarcated from the rest of the pancreas, although infiltration into surrounding tissues is not uncommon. Solid pseudopapillary tumor generally has a low malignant potential.^{28,29}

4. Diagnosis and investigation

A contrast-enhanced triphasic multidetector CT scan of the abdomen is fundamental to evaluate patients with a suspected pancreatic cystic lesion. CT scan is an excellent investigation for cystic lesions in the pancreas, not only for the initial detection of a lesion but also for the characterization of such lesions by visualization of the calcification of the cyst wall, septa, mural nodules, and features suggestive of pancreatitis.³⁰ The appearance of a pseudocyst is that of a low-attenuation, unilocular cyst with accompanying signs of acute or chronic pancreatitis. The presence of a central scar visualized on CT scan is highly diagnostic of serous cystadenomas. The uncommon finding of peripheral 'eggshell' calcification on CT scan is specific to a mucinous cystic neoplasm and is highly predictive of malignancy. Magnetic resonance imaging (MRI) is similar to the CT scan in its ability to show cystic lesions within the pancreas.³¹ MRI and magnetic resonance cholangiopancreatography (MRCP) has the added advantage of providing better characterization of the morphological features of a cyst and possibly of showing a communication between the cyst and the pancreatic duct in IPMN.^{32,33} Endoscopic retrograde cholangiopancreatography (ERCP) is a particularly useful adjunct to the diagnosis of cystic pancreatic lesions. The ductal abnormalities of chronic pancreatitis support an inflammatory origin of a pancreatic cyst. ERCP is considered as a standard for the diagnosis of IPMN also. A bulging papilla with mucin oozing out at the time of the procedure is pathognomonic of IPMN. However, this is seen only in about 20% of patients with IPMN.¹⁹ Endoscopic ultrasound (EUS)

can detect smaller tumors than those currently detectable by CT scan. However, EUS is confounded by the apparent subjectivity of its interpretation. The feature of serous cystadenoma in EUS often demonstrates as a honeycomb appearance or multiple tiny cysts. The classical features of IPMN in EUS include dilatation of the main pancreatic duct, hypoechoic thickening of the duct wall, mural nodules or papillary projections, and pancreatic atrophy. The technique also permits accurate placement of aspiration needles into a pancreatic cyst. Aspirated fluid has been evaluated by cytology and chemical measurements of amylase and tumor markers.^{34–36} Characterization of cyst fluid is best used to differentiate those with malignant potential mucinous cysts from serous cystic neoplasm and pseudocysts. However, a broad range of sensitivities and specificities and cutoff values have been reported for these markers, making interpretation very difficult. Cystic fluid of mucinous cystic neoplasms has been shown to be rich in carcinoembryonic antigen (CEA) and low in amylase, while cystic fluid of serous cystadenoma has been shown to be low in both CEA and amylase. In fact, not all cystic lesions of the pancreas require sampling. In many instances, the diagnosis based on clinical and radiological findings is straightforward. On other occasions, even though a precise diagnosis cannot be reached, the indication for surgery is definite, such as in cases of symptomatic cystic neoplasms of the pancreas. In asymptomatic patients, in patients with a high surgical risk, and in patients with diagnostic uncertainty, cyst fluid analysis helps to determine the optimal therapeutic strategy. However, the benefit of EUS and cyst aspiration must be balanced against the risk of bleeding, infection, pancreatitis and tumor cell spillage. A large prospective study (the Cooperative Pancreatic Cyst Study), after assessing a large number of cyst fluid tumor markers, concluded that CEA was most useful.³⁴ Receiver operator curve analysis of the tumor markers demonstrated that for cyst fluid CEA, the greatest area under the curve (0.79) for differentiating mucinous vs. non-mucinous cystic lesions was at an optimal cutoff of 192 ng/ml. The accuracy of CEA (88 of 111, 79%) was significantly greater than EUS morphology (57 of 112, 51%) or cytology (64 of 109, 59%). In the pooled analysis of 12 studies by van der Waaij et al., comprising data of 450 patients,³⁵ cysts with an amylase concentration <250 U/l were serous cystadenoma, mucinous cystadenoma, or mucinous cystadenocarcinoma (sensitivity 44%, specificity 98%), thus, virtually excluding pseudocyst. A CEA <5 ng/ml suggested a serous cystadenoma or pseudocyst (sensitivity 50%, specificity 95%). A CEA >800 ng/ml strongly suggested mucinous cystadenoma, or mucinous cystadenocarcinoma (sensitivity 48%, specificity 98%). A carbohydrate-associated antigen (CA) 19-9 <37 U/ml strongly suggested pseudocyst or serous cystadenoma (sensitivity 19%, specificity 98%). Cytological examination revealed malignant cells in 48% of mucinous cystadenocarcinoma ($n = 111$). The role of positron emission tomography (PET) has not been established. Some authors proposed that [¹⁸F]fluorodeoxyglucose (18-FDG) whole body PET imaging can identify cystic lesions of the pancreas, both malignant and pre-malignant. Sperti et al. reported a sensitivity and specificity of PET scan for detecting malignant pancreatic cystic lesions of 94%.³⁷ However, the corresponding figures reported by Mansour et al. were 57 and 85%, respectively.³⁸

5. Management strategy

The management strategy of a suspected pancreatic cystic neoplasm remains controversial and has not been universally accepted. This controversy arises because of the inability to diagnose a particular type of pancreatic cystic neoplasm accurately and the limited knowledge of the natural history, particularly small asymptomatic pancreatic cysts. The decision of whether to observe with regular surveillance or to operate on these small cystic

pancreatic lesions is difficult. Some authors advocated routine resection of all pancreatic cysts.^{39,40} These authors argue that because pre-operative differentiation between benign and malignant lesions is unreliable, and because the potential adverse consequences of non-resectional therapy are significant, all medically fit patients should undergo resection. Although this approach provides a guarantee to patients that no pre-malignant or malignant lesions be observed, it exposes patients with benign lesions to the risks of operation with unclear benefit. Some institutions are now reporting a selective approach to resection in patients who have small, incidentally discovered cysts of the pancreas.^{41–44} Factors analyzed as potential predictors of neoplasia included age, imaging features, cyst size, and symptoms.^{41–48} Selected asymptomatic patients with cystic lesions less than or equal to 3 cm in diameter and without a solid component may be followed radiographically, with a malignancy risk that approximates the risk of mortality from resection. The chance of malignancy was reported as 3–3.3% in a small number of studies.^{41,42} There are still no consensus on the selective criteria used.

The approach in a patient with a pancreatic cystic lesion begins with a detailed history to define prior pancreatitis or abdominal trauma. Pseudocysts are by far the most common cystic lesions. In most instances, pseudocysts can be distinguished from cystic neoplasms based on clinical history, biochemical investigations and cross-sectional imaging appearance, although patients with cystic neoplasms may also present with pancreatitis. Once a pancreatic pseudocyst has been excluded, attention should be paid to differentiate between the various types of cystic neoplasms. The most important diagnosis is to differentiate between mucinous and non-mucinous cystic lesions because of their different potential of malignancy. Currently, no single test can accurately make this distinction, and diagnosis depends on a combination of factors, including the clinical features, the biochemical and the imaging findings. Age, comorbidity, performance status, life expectancy and symptoms should be considered before pursuing an aggressive diagnostic workup or surgical management plan. The risk of surgery should be weighed against the symptoms and the risk of malignancy. The risk of surgery varies with the location of the lesion. Lesions in the tail or body of the pancreas can be treated with a distal pancreatectomy which is associated with much less morbidity and mortality than pancreaticoduodenectomy for lesions in the head of the pancreas. If serous cystadenoma cannot confidently be distinguished from mucinous cystic neoplasm or IPMN, resection is recommended for patients considered to be an acceptable surgical risk. When the diagnosis of serous cystadenoma is confidently determined based on clinical and radiographic evidence, only symptomatic tumors should be resected. If a decision is made not to carry out resection initially, serial imaging at a 6–12-month intervals, with resection for growth or the development of symptoms is recommended. In patients with a poor surgical risk, or in a moribund state, interval cross-sectional imaging is unnecessary.

Complete resection is generally considered curative for serous cystadenoma, mucinous cystic neoplasm and solid pseudopapillary tumor, and post-operative long-term monitoring is rarely necessary. Regular surveillance for disease recurrence is important after resection for IPMN as there is a risk of recurrence in both non-invasive and invasive IPMN, and repeat resection for an isolated recurrence in the pancreatic remnant gives good results. A regimen consisting of a yearly CT scan or MRI is most widely used for surveillance after resection of IPMN.¹⁹ However, the most effective method of surveillance, its frequency and the group of patients who would benefit most from monitoring remains unknown.

In conclusion, the balance between the risk and benefit for a patient is important in the management of cystic neoplasms of the pancreas. The threshold of surgery may be lower in those high

volume surgical centers for pancreatic surgery. A management strategy has been proposed based on the available evidence in the medical literature. However, the management of cystic neoplasm of the pancreas is still evolving.

Conflict of interest

We certify that we have no financial interests related to the material in this manuscript.

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