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Analysis of pancreatic cyst fluid

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Synopsis

Pancreatic cysts are extremely common, and are identified in between 2% to 13% on abdominal imaging studies. The majority of pancreatic cysts are pseudocysts, serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs) or intraductal papillary mucinous neoplasm (IPMNs). The management of pancreatic cysts depends on whether a cyst is benign, has malignant potential, or harbors high-grade dysplasia or invasive carcinoma. The diagnosis of pancreatic cysts, and assessment of risk of malignant transformation, incorporates a number of factors including clinical history, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound and fine needle aspiration of cyst fluid (EUS-FNA). This paper reviews the cyst fluid markers which are currently used, as well as promising markers under development.

Keywords

molecular markers; pancreatic cyst; cyst fluid; intraductal papillary mucinous neoplasm; serous cystadenoma; mucinous cysts

Introduction

Advances in cross-sectional imaging have resulted in the frequent detection of pancreatic cysts which are incidentally identified in between 2% to 13% cases.[1, 2] There are a large number of different types of pancreatic cysts (Table 1), with the most common pancreatic cysts encountered in clinical practice being pseudocysts, serous cystadenomas (SCAs), mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasm

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(IPMNs).[3] The management of pancreatic cysts is very much dependent on the type of pancreatic cyst (Figure 1).[4] Those with no, or very low malignant potential, such as pseudocysts and SCAs, require minimal or no follow up in the absence of symptoms related to the cyst.[5] Solid-pseudopapillary neoplasms (SPN) are low-grade malignant neoplasms, and surgically resection is recommended.[6] Invasive adenocarcinoma occurs in between 4% to 16% of surgically resected MCNs in modern studies.[7–9] Although some groups have recommended that asymptomatic MCNs may be followed[10], many surgeons favor resection based on the fact that these cysts have the potential for malignant transformation, surgery is curative, and if not undertaken patients require many years of surveillance.[11] The management of IPMNs depends on whether the main pancreatic duct is involved (main, or mixed-duct IPMN), which is associated with a higher risk of malignant transformation, with high-grade dysplasia or invasive adenocarcinoma identified in between 43 and 62% of patients who undergo surgical resection.[11] In contrast branch-duct type IPMNs, in which there is no main duct involvement, have a much lower risk of malignant transformation, and in the absence of symptoms, or concerning features, usually undergo surveillance.[11]

Thus, the key question from a clinical perspective is whether a cyst is benign, has malignant potential, or harbors high-grade dysplasia or invasive carcinoma, as this dictates whether patients can be discharged, undergo surveillance, or require surgical intervention respectively (Figure 1).[10, 11] The diagnosis of pancreatic cysts, and assessment of risk of malignant transformation, incorporates a number of factors including clinical history, computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS). EUS allows detailed visualization of the cyst (Figure 2a), and allows sampling of the cyst wall and fluid through EUS guided fine needle aspiration (EUS-FNA) (Figure 2). This is a relatively low risk procedure with the most common adverse events being pancreatitis (1.1%) and abdominal pain (0.34%).[12] The addition of EUS and EUS-FNA to either computer tomography (CT) or magnetic resonance imaging (MRI) has been shown to improve the overall accuracy for diagnosis of pancreatic cysts.[13] Most of this additional benefit is from aspiration of cyst fluid which can be sent for a range of tests including cytology, biochemical and molecular testing. This chapter will focus on the biochemical and molecular tests, while cyst fluid cytology is discussed in depth in Chapter 9.

BIOCHEMICAL TESTS FOR CYST FLUID

Carcinoembryonic antigen (CEA)

A) Identifying IPMNs and MCNs—CEA is currently considered the most accurate marker for differentiating mucinous, from non-mucinous cysts, that is IPMNs and MCNs from other cyst types. The role of CEA was established in the multicenter, prospective co-operative study in 2004, which found that the accuracy of cyst fluid CEA was superior to EUS, cytology or other tumor markers including CA 72-4, CA 125, CA 19-9, and CA 15-3, for identifying mucinous cysts.[14] However, since then several issues about CEA have arisen. The first is what is the optimal cutoff level to differentiate mucinous from non-mucinous cysts? The co-operative study identified the optimal level as 192 ng/mL, which was associated with 75% sensitivity, and 84% specificity for differentiating between mucinous

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and non-mucinous cysts, and this level is most commonly used in clinical practice and publications.[14] However, other groups have proposed alternative cutoffs. Using a higher cut off level of >800 ng/mL was shown in a meta-analysis to increase the specificity to 98%, although at the cost of lowering the sensitivity to 48%.[15] Similarly very low CEA levels of <5 ng/mL has a very high specificity of 95%, with 50% sensitivity, for non-mucinous cysts, such as serous cystadenomas and pseudocysts.[15]

The second issue is that although the initial studies were very promising, more recent data has suggested that cyst fluid CEA is imperfect at differentiating mucinous from non-mucinous cysts. The co-operative study found CEA had a high sensitivity and specificity (75% and 84% respectively), for identifying mucinous cysts.[14] In contrast, more recent studies have suggested a lower accuracy, with a large prospective study reporting a lower sensitivity and specificity of only 63% and 62% respectively.[16] These findings were confirmed in meta-analysis of 18 studies with 1438 patients, where CEA had 63% sensitivity and 88% specificity for identifying mucinous cysts.[17]

Finally, obtaining sufficient cyst fluid to assess CEA levels is often not possible, particularly in very small cysts, or if the fluid is very viscous. This issue was highlighted by a prospective European study in which CEA levels were obtained in only half of the cysts tested.[18]

B) CEA is not helpful in identifying cysts with high-grade dysplasia or invasive carcinoma—Some studies have suggested that a high cyst fluid CEA is associated with high-grade dysplasia or invasive cancer in IPMNs. However these studies were small, retrospective, and there was significant overlap between the CEA level in IPMNs with low-, or intermediate-grade dysplasia and those with high-grade dysplasia or invasive carcinoma. In contrast, much larger studies, including a prospective study and a meta-analysis, have found no association between CEA level and the presence of high-grade dysplasia or invasive carcinoma.[14, 19–21] Thus cyst fluid CEA level is not helpful in differentiating between benign and malignant pancreatic cysts.

Amylase

A) Excluding pseudocysts—Cyst fluid amylase level can be useful in excluding a pseudocyst from other types of pancreatic cysts. A large meta-analysis found a cyst fluid amylase level of < 250 IU/L had a very high specificity of 98% for excluding a pseudocysts.[15] In contrast, high cyst fluid amylase levels were found in numerous types of pancreatic cysts including SCAs, IPMNs and MCNs.

B) High amylase levels does not differentiate IPMNs from MCNs—One of the key questions is how to differentiate IPMNs from MCNs, as both have high cyst fluid CEA levels. On imaging, IPMNs communicate, or connect with the pancreatic duct, while MCNs have no communication. Theoretically, the communication between the main pancreatic duct and the cyst would cause IPMNs to have high cyst fluid amylase level, whereas MCNs should have a low amylase level. However, studies have shown that cyst fluid amylase level are similar in IPMNs and MCNs, and thus cannot be used to differentiate these two types of cysts.[22]

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Other markers

Several other tumor markers, including CA 72-4, CA 125, CA 19-9, and CA 15-3 have been evaluated. However, the diagnostic accuracy of these tumor makers has been found to be inferior to cyst fluid CEA in distinguishing mucinous from non-mucinous cysts in a number of studies.[14, 15] These markers are therefore not used in clinical practice.

ACCURACY OF CYST FLUID MARKERS CURRENTLY USED IN CLINICAL PRACTICE

As can be seen the currently available cyst fluid markers are imperfect at identifying cyst type, and cannot identify the presence of high-grade dysplasia or invasive carcinoma. This is highlighted by large surgical series, in which just over 20% of patients were found to have a benign cyst such as a SCA or a pseudocyst[23], while almost 80% of resected branch duct IPMNs have either low, or intermediate-grade dysplasia[24], and thus in retrospect, did not require surgical resection. Thus better markers are required.

MOLECULAR MARKERS

One of the problems with identifying mutations in pancreatic cysts is that the number of mutant alleles present is extremely low when compared with solid lesions, such as pancreatic ductal adenocarcinoma.[25] However recent advances in molecular genetics, in particular the development of techniques such as FastSeq sequencing, mean that mutant alleles present very low levels can be identified.[26] In the following section we discuss the potential of molecular markers in pancreatic cyst fluid. There are many other promising markers including mRNA and protein markers[27–30], and a review of these markers is available elsewhere.[31]

In 2011, the group at Johns Hopkins lead by Bert Vogelstein analyzed the entire coding region of the genome of SCA, SPN, MCNs and IPMNs using whole-exome sequencing.[25] There were two key findings: the first was that pancreatic cysts contained far fewer somatic mutations when compared with pancreatic ductal adenocarcinoma. The second was that each cyst type had a distinct mutational profile. SCAs contained a mutation in the von Hippel Lindau (*VHL*) gene. SPNs were found to have a single mutation in the *CTNNB1* gene. Both IPMNs and MCNs had mutations in *KRAS* or *RNF43*, while IPMNs were found to harbor a mutation in *GNAS,* which was not identified in any other cyst type. This preliminary study was performed in pancreatic tissue, and in a subsequent study the group was able to show that the same mutations were identifiable in pancreatic cyst fluid.[32] In a recent, multi-center study involving 130 patients all of whom had undergone surgical resection, the molecular marker panel was expanded to include a larger number of genetic mutations, as well as assessing loss of heterozygosity (LOH) and aneuploidy. This study confirmed not only the ability of the molecular markers to accurately identify cyst type (Table 2), but also to identify the presence of high-grade dysplasia or invasive carcinoma in IPMNs, which was associated with the presence of a mutation in *SMAD4*, *TP53*, LOH chromosome 17 (*RNF43* or *TP53* loci), or aneuploidy in chromosomes 5p, 8p, 13q, 18q. In addition, the group developed a novel concept of combining molecular markers with clinical features to further improve the diagnostic accuracy of these markers which increased the sensitivity and

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specificity further. One of the interesting results in this paper was the ability of the molecular markers to correctly identified low risk cysts. The markers correctly classified 56 of the 62 SCA, and IPMNs with low- or intermediate-grade dysplasia. Thus, use of the molecular markers could potentially decrease the number of unnecessary surgical resections by 90%. The use of molecular markers in pancreatic cysts has been assessed by other groups, who have also found very promising results.[33–35] These, and the results from studies described previously are encouraging, however larger studies, incorporating other cysts types, are required before these molecular markers can be recommended in clinical practice. These studies are currently ongoing, and the results are expected to be available in 2016.

Pancreatic juice

One of the limitations of assessing pancreatic cyst fluid is that it requires EUS-FNA. Potential limitations are that a biopsy is invasive, only a portion of a cyst is sampled, and in cases of multiple pancreatic cysts, sampling of all cysts may not be feasible. An alternative approach is to analyze molecular markers in pancreatic juice collected from the duodenum. This avoids the potential adverse events of direct sampling of pancreatic fluid using fine needle aspiration, and in addition pancreatic juice may contain alterations present in multiple cysts throughout the pancreas, rather than a single cyst. The results from preliminary studies are promising. Kanda et al examined secretin-stimulated pancreatic juice collected from the duodenum during upper endoscopy, and identified *GNAS* mutations in 66% of IPMNs, which is similar to that observed in EUS aspirated cyst fluid.[36] In a further development of this technique, the same authors examined the presence of *TP53* mutations, which is a known tumor suppressor gene that has been implicated in progression of IPMNs, in duodenal samples of pancreatic juice.[37] They found that *TP53* mutations were detected in pancreatic juice in almost 70% of patients with pancreatic ductal adenocarcinoma, pancreatic intraepithelial neoplasias-3 or high-grade IPMN, but was not identified in individuals with benign cysts, or lower grades of dysplasia. These studies suggest the potential of use of pancreatic juice for detecting mutations present in pancreatic cysts, and this technique may prove complementary to cyst fluid aspiration in the diagnostic work-up of pancreatic cysts.

Current clinical practice for the assessment of pancreatic cysts

In our practice, we perform EUS-FNA of pancreatic cysts when it will alter management. Cyst fluid is currently sent for CEA and cytology. We also obtain cyst fluid amylase in cases that there is clinical suspicion of a pseudocyst. We await further studies to validate the accuracy of the molecular markers, and to determine how to optimally combine them with the currently available tests. If these studies duplicate the results discussed above, it is likely that molecular markers will become part, and may replace many of the currently used cyst fluid tests.

Conclusion

Pancreatic cyst fluid analysis provides important information that can be used to improve the diagnosis of pancreatic cysts. The results of cyst fluid analysis should be used in combination with clinical history and imaging to help guide management decisions. New

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molecular makers have shown promise, and are likely to become incorporated into clinical care in the near future.

Abbreviations

CA	carbohydrate antigen
CEA	carcinoembryonic antigen
CT	computed tomography
EUS	endoscopic ultrasound
FNA	fine-needle aspiration
IPMN	intraductal papillary mucinous neoplasm
LOH	loss of heterozygosity
MCN	mucinous cystic neoplasm
MRI	magnetic resonance imaging
PCN	pancreatic cystic neoplasms
SCA	serous cystadenoma
SPN	solid-pseudopapillary neoplasm
VHL	von Hippel Lindau

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Key points

- Pancreatic cysts are common, and are incidentally identified in between 2% to 13% of individuals undergoing cross sectional imaging.
- Cyst fluid carcinoembryonic antigen (CEA) is currently considered the most accurate marker for differentiating mucinous (IPMNs and MCNs) from non-mucinous cysts, however recent studies suggest that its accuracy is approximately 65%.
- New molecular markers in cyst fluid have shown promise in differentiating SCAs, SPNs, MCNs and IPMNs, and identifying the presence of high-grade dysplasia or invasive adenocarcinoma.

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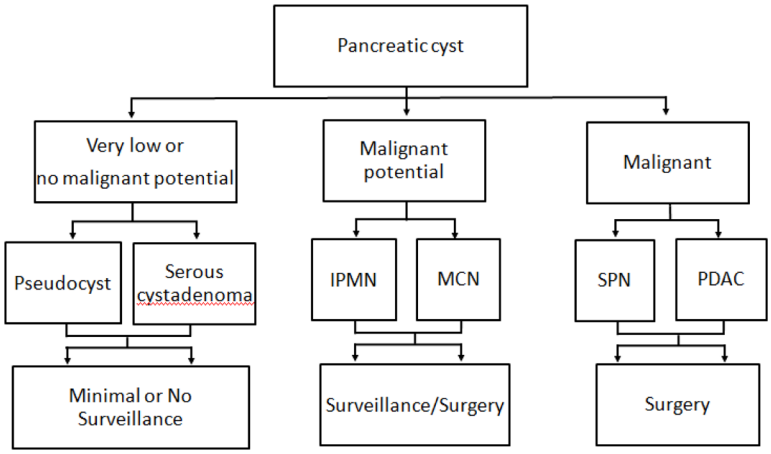

Figure 1.
Algorithm for the management of pancreatic cysts

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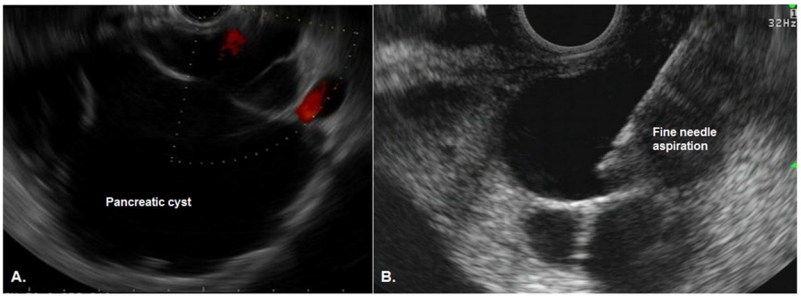

Figure 2.

Endoscopic ultrasound of a pancreatic cyst. A) EUS image of a pancreatic cyst with thin septations. B) EUS-guided fine needle aspiration. The needle (arrow) can be seen within the center of the cyst.

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Table 1

Classification of Pancreatic Cysts by Pathological Type

Epithelial Neoplasms									Nonepithelial Neoplasms	Secondary Neoplasms (Metastases to the Pancreas)^	Non-neoplastic Tumors of the Exocrine Pancreas
Exocrine Neoplasms					Endocrine Neoplasms	Epithelial Neoplasms with Multiple Directions of Differentiation	Epithelial Neoplasms of Uncertain Direction of Differentiation	Miscellaneous	Extragastrointestinal Stromal Tumor^		Congential cyst
Serous neoplasms Microcystic SCA Macrocystic SCA Solid SCA von-Hippel-Landau (VHL)-associated SCA Serous cystadenocarcinoma#	*Mucinous cystic neoplasms* MCN*	*Intraductal neoplasms* IPMN* Intraductal tubulopapillary neoplasm	*Invasive ductal adenocarcinoma* Invasive ductal adenocarcinoma^	*Acinar cell neoplasms* Acinar cell cystadenoma Acinar cell cystadenocarcinoma	Pancreatic neuroendocrine neoplasm^	Pancreatoblastoma^	Solid-pseudopapillary neoplasm	Teratoma^ Lymphoepithelial cyst Epidermoid cyst in intrapancreatic heterotopic spleen	Fibromatosis (Desmoid)^ Granular cell tumor^ Leiomyoma^ Lymphangioma Sarcoma^ Caverous hemangioma	Choriocarcinoma^	Duodenal Diverticulum Endometriotic Cyst^ Foregut Cyst Heterotopic Pancreas^ Autoimmune Pancreatitis^ Parampullary Duodenal Wall Cyst Hamartoma^

*these can be associated with low-, intermediate-, high-grade dysplasia, or an associated invasive carcinoma;

#these are extremly rare;

^with cystic degeneration. Table Adapted from Tumors of the Pancreas.

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Table 2

Identification of Cyst Type using Molecular Marker

Type of Cyst	Molecular Markers			
	Any of these	Any of these	Senstivity (95% CI)	Specificity (95% CI)
	Present	*Absent*		
SCA	*VHL* chr3 LOH	*KRAS* *GNAS* *RNF43* chr5p aneu chr8p aneu	100% (74–100%)	91% (84–95%)
SPN	*CTNNB1*	*KRAS* *GNAS* *RNF43* chr18 LOH	100% (69–100%)	100% (97–100%)
MCN	None	*CTNNB1* *GNAS* chr3 LOH chr1q aneu chr22q aneu	100% (74–100%)	75% (66–82%)
IPMN	*GNAS* *RNF43* chr9 LOH chr1q aneu chr8p aneu	None	76% (66–84%)	97% (85–99.9%)

MPD = main pancreatic duct. chr = Chromosome. CI=confidence intervals. aneu = aneuploidy.

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