Analysis of Pancreatic Cyst Fluid

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KEYWORDS

• Molecular markers • Pancreatic cyst • Cyst fluid • Intraductal papillary mucinous neoplasm • Serous cystadenoma • Mucinous cysts

Key points

- Pancreatic cysts are common, and are incidentally identified in between 2% and 13% of individuals undergoing cross-sectional imaging.
- Cyst fluid carcinoembryonic antigen is currently considered the most accurate marker for differentiating mucinous (intraductal papillary mucinous neoplasms [IPMNs] and mucinous cystic neoplasms [MCNs]) from nonmucinous cysts; however, recent studies suggest that its accuracy is approximately 65%.
- New molecular markers in cyst fluid have shown promise in differentiating serous cystadenomas, solid-pseudopapillary neoplasms, MCNs, and IPMNs, and identifying the presence of high-grade dysplasia or invasive adenocarcinoma.

ABSTRACT

Pancreatic cysts are extremely common, and are identified in between 2% to 13% on abdominal imaging studies. Most pancreatic cysts are pseudocysts, serous cystic neoplasms, mucinous cystic neoplasms, or intraductal papillary mucinous neoplasms. 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 clinical history, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound, and fine-needle aspiration of cyst fluid. This article reviews the cyst fluid markers that are currently used, as well as promising markers under development.

OVERVIEW

Advances in cross-sectional imaging have resulted in the frequent detection of pancreatic cysts that are incidentally identified in between 2% and 13% of 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 (IPMNs).[3] The management of pancreatic cysts is very much dependent on the type of pancreatic cyst (**Fig. 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

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Abbreviations	
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 neoplasm
SCA	Serous cystadenoma
SPN	Solid-pseudopapillary neoplasm
VHL	Von Hippel Lindau

(SPNs) are low-grade malignant neoplasms, and surgical resection is recommended.[6] Invasive adenocarcinoma occurs in between 4% and 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 because 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 (see **Fig. 1**).[10,11] The diagnosis of pancreatic cysts, and assessment of risk of malignant transformation, incorporates a number of factors, including clinical history, CT, MRI, and endoscopic ultrasonography (EUS). EUS allows detailed visualization of the cyst (**Fig. 2**A), and sampling of the cyst wall and fluid through EUS-guided fine-needle aspiration (EUS-FNA) (see **Fig. 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 CT or 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 article focuses on the biochemical and molecular tests, whereas cyst fluid cytology is discussed in depth in the article (See Collins JA, Ali SZ, VandenBussche CJ: Pancreatic Cytopathology, in this issue).

BIOCHEMICAL TESTS FOR CYST FLUID

CARCINOEMBRYONIC ANTIGEN

Identifying Intraductal Papillary Mucinous Neoplasms and Mucin Producing Cysts

Carcinoembryonic antigen (CEA) is currently considered the most accurate marker for differentiating mucin producing from non mucin producing cysts; that is, IPMNs and MCNs from other cyst types. The role of CEA was established in the multicenter, prospective cooperative 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 mucin producing cysts.[14] However, since then, several issues with respect to CEA have arisen. The first is what is the optimal cutoff level to differentiate mucin producing from non-mucin producing cysts? The cooperative study identified the optimal level as 192 ng/mL, which was associated with 75% sensitivity, and 84% specificity for differentiating between mucin producing and non-mucin producing cysts, and this level is most commonly used in clinical practice and publications.[14] However, other groups have proposed alternative cutoffs. Using a higher cutoff level of greater than 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 less than 5 ng/mL have a very high specificity of 95%, with 50% sensitivity, for non-mucin producing cysts, such as serous cystadenomas and pseudocysts.[15]

The second issue is that although the initial studies were very promising, more recent data have suggested that cyst fluid CEA is imperfect at differentiating mucin producing from non-mucin producing cysts. The cooperative study found CEA had a high sensitivity and specificity (75% and 84%, respectively), for identifying mucin producing 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, in which CEA had 63% sensitivity and 88% specificity for identifying mucin producing cysts.[17]

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