Molecular Diagnostics in the Evaluation of Pancreatic Cysts

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KEYWORDS

• Pancreas • Pancreatic ductal adenocarcinoma • Intraductal papillary mucinous neoplasm • Mucinous cystic neoplasm • Serous cystadenoma • Solid-pseudopapillary neoplasm • Genetics • Diagnostics

Key points

- Due to the increased use and improvements in abdominal imaging, incidental pancreatic cysts are becoming frequently encountered.
- Although many cysts, such as serous cystadenomas (SCAs) and non-neoplastic cysts have a benign clinical course, others, such as intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN), represent precursor lesions to invasive pancreatic ductal adenocarcinoma (PDAC).
- Despite a multidisciplinary approach, preoperatively distinguishing pancreatic cysts from one another can be challenging and, if incorrect, can pose a significant health risk to the patient. The application of molecular techniques has emerged as a promising adjunct to the evaluation of pancreatic cysts.
- DNA obtained from preoperative endoscopic ultrasound fine-needle aspiration can be analyzed for genetic abnormalities that are specific for cyst type and likelihood of progression to high-grade dysplasia and/or PDAC.
- Mutations in *KRAS*, *GNAS*, and/or *RNF43* are highly specific for IPMNs and MCNs. Moreover, IPMNs and MCNs with high-grade dysplasia and/or PDAC often harbor alterations in *TP53*, *PIK3CA*, and/or *PTEN*. In contrast, *VHL* mutations and/or deletions are present in SCAs. Non-neoplastic cysts are devoid of any alterations in the aforementioned genes.

ABSTRACT

Within the past few decades, there has been a dramatic increase in the detection of incidental pancreatic cysts. It is reported a pancreatic cyst is identified in up to 2.6% of abdominal scans. Many of these cysts, including serous cystadenomas and pseudocysts, are benign and can be monitored clinically. In contrast, mucinous cysts, which include intraductal papillary mucinous neoplasms and mucinous cystic neoplasms, have the potential to progress to pancreatic adenocarcinoma. In this review, we discuss the current management guidelines for pancreatic cysts, their underlying genetics, and the integration of molecular testing in cyst classification and prognostication.

OVERVIEW

With the rapid utilization and ongoing advancements in cross-sectional abdominal imaging, the detection of pancreatic cysts has become increasingly frequent. It is estimated that more than 2% of the general population in the United States harbors a pancreatic cyst.[1,2] Many of these cysts, including serous cystadenomas (SCA) and pseudocysts, are benign and can be monitored clinically. In contrast, mucinous cysts, which include intraductal papillary mucinous neoplasms (IPMNs)

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and mucinous cystic neoplasms (MCNs), have the potential to progress to pancreatic adenocarcinoma (PDAC).[3–6]

Currently, a multidisciplinary approach is recommended for the assessment of pancreatic cysts. This includes clinical and radiographic evaluation, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), cytology, cyst fluid analysis (eg, viscosity), and tumor markers (eg, carcinoembryonic antigen [CEA]). Despite a combination of methodologies, the distinction between mucinous cysts from other pancreatic cysts and those that will progress to PDAC can be challenging. Recently, the application of molecular techniques has emerged as a promising adjunct to the evaluation of pancreatic cysts.[7–10] Although the cellular content of pancreatic cyst aspirates is often suboptimal, DNA from lysed or exfoliated epithelial cells shed into the fluid from the cyst lining can be analyzed for genetic abnormalities. Moreover, whole-exome sequencing of the most common pancreatic cysts has identified distinct mutational profiles for each cyst type as well as genetic alterations that coincide with the development of PDAC. Within this review, we discuss the current management guidelines for pancreatic cysts, their underlying genetics, and the integration of molecular testing within this field.

PANCREATIC CANCER AND PANCREATIC CYSTS

In the United States, PDAC is the fourth leading cause of cancer deaths in both men and women. In 2015, an estimated 48,960 individuals were diagnosed with PDAC, and approximately 40,560 died from this deadly disease. Although surgical resection offers the only possibility of cure, more than 85% of patients present with inoperable disease at the time of diagnosis. Therefore, chemotherapy and radiation are the mainstay of treatment in most patients. Despite aggressive combined modality treatment approaches, the 5-year survival of PDAC is a dismal 6% and has remained unchanged for the past 40 years.

Fundamentally, PDAC is a genetic disease and arises from noninvasive intraductal precursor lesions that accumulate genetic alterations. Among these precursor lesions are microscopic pancreatic intraepithelial neoplasia (PanIN), and macroscopic mucinous pancreatic cysts that include IPMNs and MCNs. Although PanINs are too small to identify radiographically, mucinous cysts are often found by routine imaging and represent ideal lesions for early detection strategies. However, most IPMNs and MCNs are indolent, with a minority undergoing malignant transformation. In addition, as surgical intervention remains the preferred treatment option for mucinous cysts, patients must consider the operative mortality and morbidity of these procedures, which range from 2% to 4% and 40% to 50%, respectively. Consequently, treatment guidelines by the International Association of Pancreatology and American Gastroenterological Association (AGA) were established.

SENDAI AND FUKUOKA GUIDELINES

During the 11th Congress of the International Association of Pancreatology held in Sendai, Japan, in 2004, a multidisciplinary group of physicians held a consensus meeting on the management of IPMNs and MCNs. Published in 2006, the “Sendai” guidelines recommended that patients with main duct or mixed main and branch duct IPMN should undergo surgical resection assuming good surgical candidacy and reasonable life expectancy. Similarly, it was recommended that all MCNs should be resected. However, for branch duct IPMNs, the Sendai guidelines advocated serial imaging yearly for mucinous cysts smaller than 1 cm, twice a year for cysts between 1 and 2 cm, 2 to 4 times a year for cysts between 2 and 3 cm, and surgical resection for cysts larger than 3 cm (**Fig. 1**).[11] Further, surgical resection was recommended for any cyst with at least 1 of the following: associated clinical symptoms, the presence of a mural nodule, a dilated pancreatic duct ($\geq$6 mm), and/or “positive cytology.” Subsequently, several studies found the Sendai guidelines were highly sensitive for mucinous cysts harboring advanced neoplasia (high-grade dysplasia and PDAC) but suffered from low specificity. In a review of 147 patients, Pelaez-Luna and colleagues[12] reported a sensitivity of 100%, but a specificity of 23% in detecting advanced neoplasia. Similarly, Tang and colleagues[13] found implementation of the consensus guidelines within their cohort of 204 patients would have 100% sensitivity, but 31% specificity.

In retrospect, both cyst size and nonspecific patient symptoms are considered poor predictors of advanced neoplasia. Although a mucinous cyst 3 cm or larger is more likely to have advanced neoplasia, smaller cysts also can have significant malignant potential. Buscaglia and colleagues[14] published a cyst size of larger than 1.5 cm as the optimal cutoff as a predictor of advanced neoplasia. In comparison, Gomez and colleagues[15] proposed a cyst size of larger than 2.5 cm. Moreover, many benign, nonmucinous cysts can be quite large. Clinical symptoms as a