The Use of Biomarkers in the Risk Stratification of Cystic Neoplasms

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KEYWORDS

• Pancreatic cysts • Biomarkers • Molecular diagnosis
• Intraductal papillary mucinous neoplasm (IPMN) • Mucinous neoplasm • Malignancy

KEY POINTS

- Distinguishing mucinous cysts from nonmucinous cysts is essential to diagnosing pancreatic cysts.
- A combination of DNA markers, amylase, and oncogene testing can be used to diagnose pancreatic cyst subtypes.
- Cyst fluid DNA markers and oncogenes may be used to stratify pancreatic cysts by their malignant potential.

BACKGROUND

Introduction

The frequent use of cross-sectional imaging has led to the identification of an increasing number of pancreatic cysts. The incidence of pancreatic cysts rises with age and is now estimated to be present in approximately 2% of adults.[1] Although a majority of these lesions are benign, 15% are cyst types known to be precursor lesions for invasive carcinoma, thus requiring further monitoring.[2] Given the high morbidity and mortality associated with pancreatic cancer, there is a significant interest in risk stratifying benign pancreatic cysts based on malignant potential. Currently, surgical resection is the only therapeutic intervention, and this is associated with considerable morbidity and mortality rates. This makes accurate biopsy or fluid sampling–based evaluation of these cysts essential.

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Although a majority of cysts identified in the pancreas are neoplastic, many of these lesions are not associated with a significant malignancy risk. These include predominantly serous cystadenomas (SCAs) and other benign pancreatic or peripancreatic cysts. There are also cysts that are identified in the pancreas adjacent to a solid mass or as a consequence of cystic degeneration of either adenocarcinomas or neuroendocrine tumors. Mucinous cysts, including mucinous cyst neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs), represent the majority of neoplastic premalignant cysts identified in the pancreas. A retrospective study of 851 individuals undergoing surgical resection of pancreatic cystic neoplasms over 33 years demonstrated that IPMNs are the most common subtype of cyst, followed by mucinous cystic neoplasms (MCNs), serous cystic neoplasms, and cystic neuroendocrine neoplasms.[3] Most diagnostic strategies approach pancreatic cysts by first attempting to recognize mucinous cysts and subsequently risk stratify suspected MCNs or IPMNs based on malignancy risk. In this article, this strategy is followed in presenting the utility of biomarkers.

In most studies of cystic biomarkers, a dichotomy is made between mucinous and nonmucinous cysts. Clinically, however, the distinction of greatest importance is between cysts with malignant potential, cysts without malignant potential, and malignancies. With this understanding, this article takes the approach of first discussing the role of biomarkers in distinguishing mucinous from nonmucinous cysts. Thereafter, the use of biomarkers for the risk stratification of cysts based on their malignant potential is discussed.

Nonmucinous Cysts

Of the nonmucinous cysts, SCAs are the most commonly encountered.[4] These cysts are typically found incidentally but may cause abdominal pain if large enough. Although not true cysts, pancreatic pseudocysts (PCs) are also common and often associated with pancreatitis.[4] Most importantly, SCAs and PCs have no malignant potential.[5] Non-neoplastic pancreatic cysts include a variety of rare cysts that do not frequently cause symptoms and pose no danger. They include true cysts (or benign epithelial cysts), retention cysts that may occur in the setting of ductal obstruction, and lymphoepithelial cysts. The lymphoepithelial cysts are lined by mature keratinized squamous epithelium surrounded by lymphoid tissue. Resection is rarely required.[6] Similarly, congenital cysts and squamoid cyst of ducts have virtually no malignant potential.[7]

Rare cystic tumors occurring as a result of degenerative/necrotic changes in solid tumors include cystic ductal adenocarcinomas, cystic endocrine neoplasia, and solid pseudopapillary tumor (SPT). SPTs are a rare but important cyst type because, despite variable degrees of aggressiveness, they are all considered malignant.[7] SPTs represent less than 10% of all pancreatic cysts and occur almost exclusively in young women. Identification is important because resection is usually curative.[8]

Mucinous Cysts

Mucinous cysts are further subdivided into MCNs, including mucinous cystadenomas and cystadenocarcinomas and intraductal papillary MCNs (IPMNs). MCNs and IPMNS harbor malignant potential and, therefore, require diagnosis and appropriate management.[9] Surgical removal of a premalignant MCN or IPMN confers a 5-year survival of nearly 100%. With the development of invasive carcinoma, however, survival drops to under 60%.[10]

Guideline-Based Management of Intraductal Papillary Mucinous Cystic Neoplasm

With the understanding that IPMNs are the cyst type with the most variable course, great efforts have been made to create guidelines based on clinical features for the