Predictive Value of Pancreatic Cyst Fluid Carcinoembryonic Antigen (CEA) for Malignancy in Pancreatic Cystic Lesions: A Narrative Review

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Abstract
Pancreatic cystic lesions are increasingly detected owing to advances in abdominal imaging. Although most pancreatic cysts are benign, some have premalignant or malignant potential, making accurate cyst characterization and risk stratification clinically important. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) enables pancreatic cyst fluid analysis and provides additional diagnostic information beyond imaging findings. Carcinoembryonic antigen (CEA) is the most widely used pancreatic cyst fluid biomarker for differentiating mucinous from non-mucinous cystic lesions. However, variations in diagnostic cutoff values and its limited ability to distinguish benign from malignant lesions restrict its use as an independent predictor of malignancy. This narrative review summarizes the current evidence regarding the diagnostic and predictive value of pancreatic cyst fluid CEA and discusses its role in pancreatic cyst characterization, malignant risk assessment, and integration with clinical, imaging, and cytological findings.

Keywords: Pancreatic cystic lesions; Pancreatic cyst fluid; Carcinoembryonic antigen; CEA; Pancreatic malignancy; Mucinous cysts; Biomarkers.
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Introduction

Pancreatic cystic lesions are increasingly detected owing to advances in radiological imaging. Although many pancreatic cysts are asymptomatic and benign, some have premalignant or malignant potential, making accurate characterization and prediction of malignant risk clinically important **(1)**.

Endoscopic ultrasound (EUS) provides high-resolution imaging of pancreatic cystic lesions; however, morphological features alone may not reliably distinguish malignant from non-malignant lesions. Therefore, EUS-guided fine-needle aspiration (EUS-FNA) with pancreatic cyst fluid analysis has become an important tool for improving diagnostic accuracy **(2,3)**.

Carcinoembryonic antigen (CEA) is one of the most widely used pancreatic cyst fluid tumor markers for differentiating mucinous from non-mucinous pancreatic cystic lesions. Elevated cyst fluid CEA levels are commonly associated with mucinous cysts; however, diagnostic accuracy and proposed cutoff values vary among studies and laboratories **(4)**.

Although pancreatic cyst fluid CEA is useful for identifying mucinous lesions, its ability to differentiate benign from malignant cysts and independently predict malignant transformation remains limited. Therefore, CEA levels should be interpreted in

conjunction with clinical findings, imaging characteristics, EUS morphology, cytology, and other cyst fluid analyses.

This review aims to summarize the current evidence regarding the diagnostic and predictive value of pancreatic cyst fluid CEA, evaluate its role in differentiating pancreatic cystic lesions, and discuss its potential utility in predicting pancreatic cyst malignancy.

Anatomy and Function of the Pancreas

Anatomy of the Pancreas

The pancreas is an elongated glandular organ with both endocrine and exocrine functions. It is located mainly in the retroperitoneum and extends transversely across the posterior abdominal wall at approximately the level of the first and second lumbar vertebrae. The head of the pancreas lies within the C-shaped curve of the duodenum, whereas the tail extends toward the splenic hilum **(5)**.

Anatomically, the pancreas is divided into five regions: the head, uncinate process, neck, body, and tail. The head represents the widest portion of the gland and is closely related to the duodenum. The uncinate process arises from the posteromedial aspect of the pancreatic head and extends posterior to the superior mesenteric vessels. The pancreatic body extends across the midline, whereas the tail represents the most mobile portion of the gland and usually reaches the splenic hilum **(6)**.

The pancreatic parenchyma has a lobular structure and consists predominantly of exocrine tissue together with scattered endocrine islets. The pancreatic duct begins in the tail and extends throughout the gland before draining into the duodenum. This ductal system plays an important role in transporting pancreatic secretions and may also be involved in the development of several pancreatic cystic lesions, particularly intraductal papillary mucinous neoplasms **(7)**.

Exocrine and Endocrine Functions

The pancreas consists of two major functional components: the exocrine pancreas and the endocrine islets. The exocrine component represents most of the pancreatic tissue and is composed primarily of acinar and ductal cells. Acinar cells produce digestive enzymes, including amylase, lipase, and proteolytic enzymes, whereas ductal cells secrete water and bicarbonate. These secretions are transported through the pancreatic ducts into the duodenum, where they contribute to nutrient digestion and absorption **(8)**.

The endocrine component consists of the islets of Langerhans, which contain different hormone-producing cells. Beta cells produce insulin, alpha cells secrete glucagon, delta cells produce somatostatin, and pancreatic polypeptide cells regulate pancreatic secretory activity. Together, these hormones contribute to glucose homeostasis and the regulation of metabolic functions **(9)**.

Pancreatic Cystic Lesions

Overview and Epidemiology

Pancreatic cystic neoplasms comprise a heterogeneous group of lesions that are frequently diagnosed incidentally. More than 70% of incidentally discovered pancreatic cystic neoplasms are asymptomatic. However, some lesions have premalignant or malignant potential and may progress to invasive pancreatic malignancy, creating an important clinical challenge **(15)**.

The detection of pancreatic cystic lesions has increased because of the widespread use and improved sensitivity of abdominal imaging techniques. Pancreatic cysts are frequently identified during computed tomography or magnetic resonance imaging performed for unrelated medical conditions. Their reported prevalence ranges from approximately 2% to 20% among patients undergoing abdominal imaging **(16)**.

Pancreatic cysts may be classified as neoplastic or non-neoplastic. Neoplastic cysts include intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, solid pseudopapillary neoplasms, and cystic pancreatic neuroendocrine tumors. Non-neoplastic lesions include pseudocysts, simple cysts, lymphoepithelial cysts, and other non-neoplastic cysts. Accurate identification of cyst type is important because malignant potential and clinical management differ substantially among these lesions **(17)**.

Classification of Pancreatic Cystic Lesions

More than 20 types of epithelial and non-epithelial pancreatic cysts have been described. However, most pancreatic cysts belong to a limited number of common histological categories. Pseudocysts and serous cystic neoplasms are generally considered benign, whereas intraductal papillary mucinous neoplasms and mucinous cystic neoplasms represent the major premalignant pancreatic cystic lesions **(18)**. IPMNs and MCNs account for a substantial proportion of incidentally detected pancreatic cystic neoplasms. Solid pseudopapillary neoplasms and cystic pancreatic neuroendocrine tumors are less common but have variable malignant potential **(19)**.

1. Pancreatic Pseudocysts

Pancreatic pseudocysts generally develop following acute or chronic pancreatitis. They commonly appear as unilocular cystic lesions and may contain internal debris. Pseudocysts may communicate with the pancreatic duct; however, this communication is not always clearly demonstrated by imaging **(20)**.

The diagnosis of a pseudocyst should be made cautiously in patients without a previous history of pancreatitis. A pancreatic cyst detected during an

initial episode of pancreatitis may represent the cause rather than the consequence of pancreatic inflammation and should not automatically be classified as a pseudocyst **(20)**.

2. Serous Cystic Neoplasms

Serous cystic neoplasms are generally benign and slow-growing lesions that occur more commonly in women during the fifth to seventh decades of life. They typically demonstrate a microcystic or honeycomb appearance but may also appear as macrocystic, unilocular, or predominantly solid lesions **(21)**.

A central fibrous scar may represent a characteristic imaging feature of serous cystic neoplasms, although it is observed in only a proportion of cases. The absence of characteristic morphological features may make differentiation from other pancreatic cystic lesions difficult and may require additional evaluation using EUS and pancreatic cyst fluid analysis **(21)**.

3. Mucinous Cystic Neoplasms

Mucinous cystic neoplasms predominantly occur in women during the fourth to sixth decades of life. They are commonly located in the body or tail of the pancreas and are usually solitary, thick-walled, and unilocular or oligolocular lesions **(21)**.

A characteristic histological feature of MCNs is the presence of ovarian-type stroma. Unlike IPMNs, MCNs generally do not communicate with the main pancreatic duct. Peripheral or eggshell calcification may also be observed and can support the diagnosis **(21)**.

MCNs have premalignant potential and may progress to high-grade dysplasia or invasive carcinoma. Earlier studies reported relatively high rates of advanced neoplasia. However, when characteristic ovarian-type stroma is histologically confirmed, invasive malignancy is detected in approximately 5–15% of cases **(22)**.

4. Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasms are among the most common mucinous pancreatic cystic lesions. They originate from pancreatic ductal epithelial cells and may occur throughout the pancreas. IPMNs are frequently multifocal and are associated with increased mucin production and variable degrees of pancreatic duct dilatation **(23)**.

According to the pattern of pancreatic duct involvement, IPMNs are divided into main-duct, branch-duct, and mixed-type lesions. Main-duct IPMNs are characterized by segmental or diffuse dilatation of the main pancreatic duct. Branch-duct IPMNs originate from the side branches and may appear as clusters resembling a bunch of grapes. Mixed-type IPMNs demonstrate features involving both the main pancreatic duct and its branches **(23)**.

The risk of malignant transformation varies according to the anatomical and histological subtype. The reported risk ranges from approximately 1–38% among branch-duct IPMNs and from 33–85% among main-duct or mixed-type IPMNs. However, estimates derived from surgical populations may overestimate the actual risk among unselected patients **(24)**.

5. Solid Pseudopapillary and Cystic Neuroendocrine Neoplasms

Solid pseudopapillary neoplasms are uncommon pancreatic tumors that occur predominantly in young women. These tumors may contain both solid and cystic components and generally demonstrate favorable outcomes following complete surgical resection. Nevertheless, a proportion of lesions may demonstrate locally aggressive or metastatic behavior **(25)**.

Cystic pancreatic neuroendocrine neoplasms arise from pancreatic endocrine cells and commonly develop secondary cystic degeneration. They may demonstrate thick enhancing walls and variable malignant potential **(26)**.

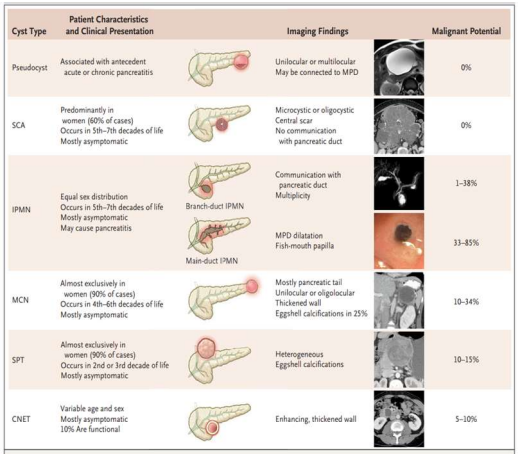

Figure 1. Common Types of Pancreatic Cysts and Their Characteristics (20).

Endoscopic Ultrasound in the Evaluation of Pancreatic Cystic Lesions

Overview of Endoscopic Ultrasound

Endoscopic ultrasound combines endoscopy with high-frequency ultrasonography and allows detailed visualization of structures located near the gastrointestinal tract. The close proximity of the ultrasound probe to the pancreas provides high-resolution images and allows accurate assessment of pancreatic lesions and surrounding structures **(10)**.

EUS provides real-time imaging and enables detailed evaluation of lesion morphology, internal architecture, adjacent vessels, and surrounding tissues. It can also guide fine-needle aspiration and fine-needle biopsy for

the collection of fluid or tissue samples from pancreatic lesions **(11)**.

Role of EUS in Pancreatic Cystic Lesions

Pancreatic cystic lesions represent an increasingly common diagnostic challenge. EUS provides detailed information regarding cyst size, shape, wall thickness, internal septations, mural nodules, communication with the pancreatic duct, and other morphological characteristics. It also allows assessment of tissue stiffness using elastography and vascular enhancement using contrast-enhanced EUS **(12)**.

One of the major advantages of EUS is its ability to perform EUS-guided fine-needle aspiration. Cyst fluid obtained through EUS-FNA can be examined using biochemical markers, cytology, tumor markers, and molecular analyses. Therefore, EUS-FNA provides information that cannot be obtained using imaging alone **(13)**.

Despite the high image resolution provided by EUS, morphological findings alone cannot accurately identify all pancreatic cyst types or reliably distinguish benign from malignant lesions. Therefore, combining EUS findings with pancreatic cyst fluid analysis may improve diagnostic accuracy and support more accurate risk assessment **(14)**.

Assessment of Malignant Risk

The initial evaluation of pancreatic cystic lesions includes assessment of clinical manifestations, radiological characteristics, laboratory investigations, and cyst fluid findings. The primary objective is to identify lesions associated with high-grade dysplasia or invasive malignancy while avoiding unnecessary intervention in patients with low-risk lesions.

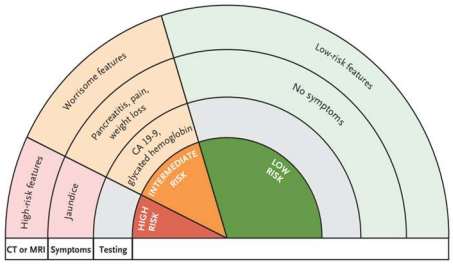

Figure 2. Approach to the Assessment of Cancer Risk in Patients with Pancreatic Cysts (20).

High-risk stigmata include obstructive jaundice associated with a pancreatic cystic lesion, main pancreatic duct dilatation greater than 10 mm, and the presence of an enhancing solid component or mural nodule measuring at least 5 mm. These characteristics demonstrate a relatively high positive predictive value for advanced neoplasia **(27)**.

Worrisome features include a cyst diameter greater than 3 cm, main pancreatic duct dilatation between 5 and 10 mm, an enhancing mural nodule smaller than 5 mm, thickened or enhancing cyst walls, lymphadenopathy, distal pancreatic atrophy, changes in pancreatic duct caliber, and rapid cyst growth. These characteristics are associated with an increased risk of advanced neoplasia but demonstrate a lower predictive value than high-risk stigmata **(28)**.

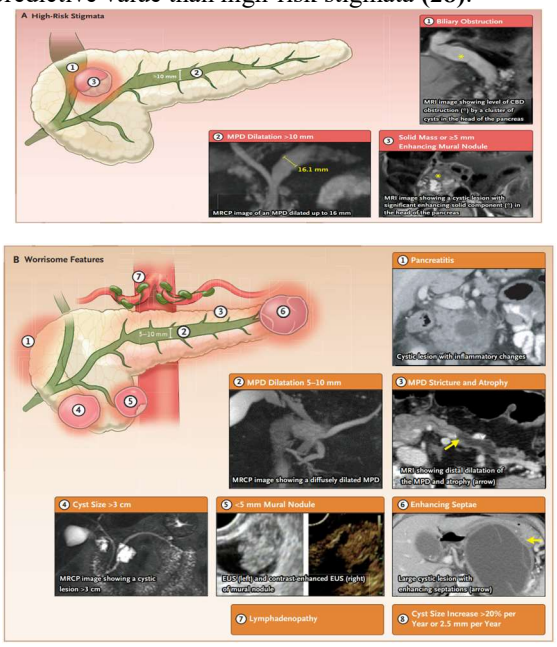

Figure 3. Characteristic High-Risk Stigmata and Worrisome Features on Imaging Studies (20).

Imaging Evaluation

Imaging is primarily used to characterize pancreatic cyst type and identify features associated with high-grade dysplasia or pancreatic malignancy. CT, MRI, and magnetic resonance cholangiopancreatography are frequently used during the initial evaluation **(29)**.

CT may demonstrate cyst morphology, calcification, enhancing solid components, and anatomical relationships. MRI and MRCP provide improved characterization of internal cyst morphology and are particularly useful for identifying communication between pancreatic cystic lesions and the pancreatic duct **(29)**.

Despite advances in imaging techniques, CT and MRI remain limited in accurately classifying all pancreatic cyst types. Furthermore, morphological findings may overlap between benign, premalignant, and malignant lesions. Therefore, EUS-FNA and cyst fluid analysis are frequently used when imaging findings are inconclusive or when risk features are present **(29)**.

Pancreatic Cyst Fluid Analysis

EUS-guided aspiration allows pancreatic cyst fluid to be evaluated using cytological, biochemical, immunological, and molecular methods. Cyst fluid analysis may improve cyst classification when morphological findings are inconclusive. However, no

single currently available test provides perfect differentiation between benign, premalignant, and malignant pancreatic cystic lesions **(30)**.

Commonly evaluated cyst fluid markers include carcinoembryonic antigen, glucose, amylase, cytological features, and molecular alterations. Although several markers assist in identifying mucinous lesions, accurate prediction of high-grade dysplasia and invasive malignancy remains challenging.

Cytological Examination

Morphological characteristics observed during EUS cannot reliably classify all pancreatic cystic lesions. EUS-FNA cytology may improve diagnostic accuracy, particularly when malignant epithelial cells are identified. However, the sensitivity and negative predictive value of cytology remain limited because pancreatic cyst fluid often contains few diagnostic cells **(31)**.

Previous analyses reported moderate sensitivity and relatively high specificity for cytological identification of mucinous cystic lesions. The sensitivity of cytology for distinguishing benign from malignant IPMN also remains limited **(29)**.

Low cellularity represents an important limitation. In one prospective analysis, adequate cellular material was obtained from only approximately one-third of pancreatic cyst fluid samples **(32)**.

Pancreatic Cyst Fluid Carcinoembryonic Antigen

Biological and Diagnostic Role of CEA

Carcinoembryonic antigen is a glycoprotein involved in cellular adhesion and is expressed by several epithelial tumors. Measurement of CEA in pancreatic cyst fluid has become an important component of the diagnostic evaluation of pancreatic cystic lesions. **(2,33)**

Pancreatic cyst fluid CEA is mainly used to differentiate mucinous from non-mucinous cysts. Elevated levels are frequently associated with IPMNs and MCNs, whereas lower levels are generally observed in serous cystic neoplasms and other non-mucinous lesions **(33)**.

The diagnostic role of cyst fluid CEA is therefore primarily related to identification of mucinous epithelial differentiation rather than direct assessment of malignant transformation. **(2,29,30)**

CEA in Differentiating Mucinous and Non-Mucinous Cysts

Mucinous pancreatic cystic lesions are clinically important because they have the potential to progress to high-grade dysplasia and invasive carcinoma. Accurate identification of mucinous lesions is therefore essential for appropriate surveillance and management.

Pancreatic cyst fluid CEA is one of the most widely used biomarkers for differentiating mucinous from non-mucinous lesions. Elevated CEA levels support the diagnosis of IPMN or MCN but should not be interpreted independently because overlap may occur among different pancreatic cyst types **(2,33)**.

Although CEA improves the identification of mucinous lesions, its diagnostic performance may vary according to patient characteristics, cyst type, laboratory technique, and the cutoff value used. **(2,30)**

Diagnostic Cutoff Values of Pancreatic Cyst Fluid CEA

A pancreatic cyst fluid CEA cutoff value of approximately 192 ng/mL is commonly used to support the diagnosis of a mucinous pancreatic cystic lesion. At this threshold, CEA generally demonstrates moderate sensitivity and relatively high specificity **(29)**.

However, no single cutoff value provides perfect diagnostic performance. Higher cutoff values may increase specificity but reduce sensitivity, whereas lower cutoff values may increase sensitivity at the expense of specificity. **(34)**

Very high CEA concentrations may strongly support mucinous differentiation, whereas very low levels may favor a non-mucinous lesion. Nevertheless, intermediate values may be difficult to interpret and should be evaluated in combination with imaging findings, cyst morphology, cytology, and other laboratory parameters **(35)**.

Differences in assay techniques and laboratory methods may also affect measured CEA concentrations and contribute to variation among published cutoff values.**(36)**

Role of CEA in Predicting Pancreatic Cyst Malignancy

The potential role of pancreatic cyst fluid CEA in predicting malignancy remains controversial. Although elevated CEA levels indicate mucinous differentiation, they do not reliably distinguish benign mucinous lesions from lesions containing high-grade dysplasia or invasive carcinoma **(2)**.

CEA levels may be markedly elevated in some non-malignant mucinous cysts, whereas malignant lesions may occasionally demonstrate only moderate or low concentrations. Consequently, the degree of CEA elevation does not consistently reflect the severity of dysplasia or the presence of invasive malignancy.

The diagnostic value of CEA therefore differs from its predictive value. CEA may assist in identifying a cyst type associated with malignant potential but should not be considered an independent marker of malignant transformation.

The relationship between increasing CEA concentrations and malignant progression has not been consistently demonstrated across studies. Variations in cyst type, pathological classification, sample size,

laboratory assays, and diagnostic thresholds may contribute to inconsistent findings.

Accordingly, pancreatic cyst fluid CEA should be considered one component of a comprehensive risk assessment rather than a standalone predictor of malignancy. **(29,30)**

Integration of CEA with Other Diagnostic Modalities

Interpretation of pancreatic cyst fluid CEA should be integrated with patient history, clinical manifestations, cyst morphology, imaging findings, EUS characteristics, and cytological assessment.

Imaging findings such as cyst size, mural nodules, wall enhancement, main pancreatic duct dilatation, and rapid growth provide information regarding malignant risk that cannot be obtained from CEA measurement alone **(27–29)**.

EUS enables detailed evaluation of cyst morphology and allows targeted fluid sampling. Cytological identification of malignant epithelial cells provides strong evidence of malignancy but is limited by low sensitivity and low cellularity **(31,32)**.

Combining CEA with imaging and cytology may improve overall diagnostic assessment by integrating information regarding cyst type, epithelial characteristics, and malignant risk.

Molecular analysis and other emerging cyst fluid biomarkers may also provide complementary information. However, additional studies are required to determine the optimal combination of diagnostic tests and establish standardized clinical algorithms.

Other pancreatic cyst markers Markers

The cyst fluid contains glycoproteins like CEA, CA 19-9, CA 125, CA 15-3, CA 72-4, which are secreted from the epithelial lining. Various studies have tried to distinguish mucinous and non-mucinous lesions by measuring the levels of these tumor markers after aspiration. It is important to ascertain the size of the lesion as smaller lesions will yield lower fluid volumes. An estimate of the cyst fluid volume can be made from the cyst size using the formula $V = 4/3\ \pi r^3$, where r represents the cyst radius **(37).**

Current Evidence Gaps and Future Directions

Despite the widespread use of pancreatic cyst fluid CEA, its ability to predict malignant transformation remains uncertain. CEA is primarily useful for differentiating mucinous from non-mucinous pancreatic cysts; however, it cannot reliably distinguish benign mucinous lesions from those containing high-grade dysplasia or invasive malignancy.

Variability in cyst fluid sampling techniques, laboratory assays, study populations, pathological classifications, and proposed cutoff values contributes to inconsistent diagnostic performance. Furthermore, overlap in CEA levels among different pancreatic cystic lesions limits its reliability as a standalone predictor.

Most available studies have focused on the diagnostic role of CEA in identifying mucinous lesions rather than its independent ability to predict malignant progression. Therefore, additional prospective studies are required to clarify the relationship between cyst fluid CEA concentrations and the degree of dysplasia. Future multicenter studies should standardize cyst fluid collection methods, CEA measurement techniques, and diagnostic cutoff values. Additional research should determine whether combining CEA with imaging characteristics, EUS morphology, cytology, molecular markers, and other cyst fluid parameters improves the prediction of pancreatic cyst malignancy.

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