Cyst Fluid Biomarkers for Intraductal Papillary Mucinous Neoplasms of the Pancreas: A Critical Review from the International Expert Meeting on Pancreatic Branch-Duct-Intraductal Papillary Mucinous Neoplasms

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Recognition of pancreatic cysts and intraductal papillary mucinous neoplasms of the pancreas (IPMN) has increased largely secondary to greater use of high-quality, cross-sectional abdominal imaging.[1,2] Although the general characteristics of IPMNs, radiographic diagnosis, cyst fluid composition, and their delineation from other pancreatic tumors have been well established, several issues regarding their growth and progression into malignancy remain poorly described. The degree of neoplastic transformation within IPMN is highly variable, from those with an entirely innocuous cell population typically resembling gastric epithelium and lacking any cytologic atypia, to those that have progressively increasing degrees of cytoarchitectural atypia. Though some patients with highly dysplastic and invasive IPMN may present with clinical symptoms or characteristic radiographic findings including jaundice, an associated pancreatic mass, or main pancreatic duct dilation; increasingly, IPMN are incidentally discovered. Once IPMN are radiographically diagnosed, there is currently no reliable way to determine the level of epithelial dysplasia or to predict the time frame of progression to high-grade dysplasia or cancer.[3-6] A biologic marker of IPMNs is urgently needed—one that can be easily obtained and tested without significant morbidity for the patient.

An evidence-based expert meeting on pancreatic branch-duct IPMNs (BD-IMPN) was held in Verona, Italy, and the authors reviewed the current role of existing technologies and molecular markers for predicting the biologic behavior of IPMNs. The status of endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration (FNA) cytology, cyst fluid biochemistry, mucins, cytokines, DNA, and microRNA profiles were critically reviewed by the group in order to identify the most promising clinically relevant biomarkers, and to target analyses for further development.

Endoscopic ultrasound

Endoscopic ultrasound (EUS) is a highly sensitive imaging modality for evaluation of pancreatic cystic lesions that was developed as a diagnostic modality, but rapidly gained a role in IPMN for morphologic assessment and for its interventional capabilities, namely, aspiration of cyst fluid and fine-needle aspiration (FNA). Diagnosis of IPMN based solely on EUS findings requires attention to cyst size, characteristics of the cyst wall, internal characteristics of the cyst, communication with the main pancreatic duct, and the existence of any background lesions. Using EUS morphologic parameters, the sensitivity, specificity, and accuracy to differentiate between benign and malignant, or potentially malignant, cystic lesions have been reported to be between 56% and 91%, 45% and 60%, and

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Abbreviations and Acronyms

BD = branch-duct
EUS = endoscopic ultrasound
FNA = fine-needle aspiration
IL = interleukin
IPMN = intraductal papillary mucinous neoplasm of the pancreas
MCN = mucinous cystic neoplasm
miRNA = micro-ribonucleic acid
MUCs = mucins
PDAC = pancreatic ductal adenocarcinoma

51% and 72%, respectively.[7,8] Although evaluation and the differential diagnosis of cystic lesions based solely on EUS morphology are feasible, inter-observer variability, operator dependency, and moderate diagnostic performance limit its accuracy without the addition of cyst fluid aspiration and FNA cytology, especially for determination of high-risk IPMN without overt malignant features.

Cyst fluid cytology analysis

Information gained from EUS morphology is enhanced in the context of additional clinical information, cross-sectional imaging, and cyst fluid analysis. Endoscopic ultrasound-FNA is a safe and accurate technique to obtain cytologic or histologic samples from pancreatic masses, and it can also be used to aspirate fluid from cystic lesions. Diagnostic accuracy has varied considerably among studies and may reflect differences in sampling methods, cytopathologist skill, and success in clinical pathologic correlation.[7] Cyst fluid cytology is an accurate test for diagnosing a malignant pancreatic cystic lesion,[9] but the sensitivity of cytology is often hampered by the low cellular content of the pancreatic cyst fluid. Additionally, distinguishing lesion cells from gastrointestinal contamination is often difficult, though crucial, to making an accurate interpretation.[10,11] The positive predictive value of EUS-FNA for invasive malignancy is very high, but its utility to determine the level of dysplasia in mucinous lesions remains to be improved.[5] The main issue is that in the absence of frank malignancy, distinguishing high- from low- or intermediate-grade dysplasia is difficult to determine from FNA cytology.

The neoplastic epithelial cells of serous cystic neoplasms are rarely identified on EUS-FNA specimens,[12] although a recent report identified vascular endothelial growth factor-A (VEGF-A) and VEGF receptor 2 to be overexpressed only in these cysts.[13] The cytologic features of IPMNs and mucinous cystic neoplasms (MCNs) are similar to each other, showing mucinous neoplastic epithelial cells. The MCNs may have large secretory epithelial cells with evidence of mucin secretion or atypia.[14] Unfortunately, the cellularity of the cyst fluid is seldom sufficient to distinguish IPMN from MCN.[10] Endoscopic ultrasound-FNA of pancreatic cystic lesions has a very low false positive rate, but a high false negative rate in the diagnosis of malignancy, mainly due to sampling error, occurring in up to 30% of cystic lesions vs 12% of solid lesions.[15] The combination of no high-risk stigmata, no worrisome features, and no high-grade atypia on cytology have comprised an EUS + EUS-FNA "triple test," which may provide a negative predictive value of 99% for conservative management.[16] The EUS-FNA cytology is a screening tool that contributes to the evaluation of pancreatic cysts and BD-IPMN. When positive for malignancy, it is critically useful; however, when negative, its utility in risk stratification and surgical decision making for IPMN is limited.[5] In this setting, additional analysis of the cyst fluid for markers of malignancy is far more useful.

Cyst fluid tumor markers

The fluid contents of cystic lesions of the pancreas are often analyzed for cytology,[17] but the low cellular content of cyst fluid has hampered the use of cytologic analysis. A variety of cyst fluid markers have been studied to help differentiate between the major types of cystic neoplasms (Table 1).[18] The presence of extracellular mucin in aspirated cyst fluid is moderately predictive of a mucinous neoplasm.[19] Furthermore, cyst fluid tumor markers such as carcinoembryonic antigen (CEA), CA 72-4, CA 125, CA 19-9, and CA 15-3 have been tested for their use in the diagnosis of pancreatic cystic neoplasms.[20] Of these, cyst fluid CEA concentration is reported to be the most accurate marker to differentiate mucinous from nonmucinous pancreatic cystic lesions, with an accuracy of 79% and sensitivity and specificity of 73% and 84%, respectively. The 2012 international consensus guidelines

Table 1. Cyst Fluid Glycoprotein and Amylase Expression in Intraductal Papillary Mucinous Neoplasms

Variable	Amylase, U/L	CEA, ng/mL	CA 72-4, U/mL	CA 19-9, U/mL	CA125, U/mL	CA 15-3, U/mL
Cut off	6,800	192	7	2,900	9	57
Sensitivity, %	66	73	80	68	83	19
Specificity, %	81	84	61	62	37	94
Accuracy, %	69	79	72	66	60	57