Editorial

The value of cyst fluid analysis in the pre-operative evaluation of pancreatic cysts

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Like any clinical diagnostic test, analysis of pancreatic cyst fluid should add value in the decision making process of patient management. Pancreatic cysts are a complex group of benign, malignant and premalignant lesions with diverse clinical, radiological and pathological features (1). No longer are the vast majority of pancreatic cysts thought to be pseudocysts, inclusion cysts or benign neoplastic cysts that do not require follow-up. Our knowledge and understanding of neoplastic pancreatic cysts in general and mucinous pancreatic cysts in particular has grown exponentially since the recognition of intraductal papillary mucinous neoplasm (IPMN) as a distinct entity from mucinous cystic neoplasm (MCN) (2). Our realization that all neoplastic mucinous cysts have malignant potential has led to intensive evaluation of patients with both symptomatic and asymptomatic pancreatic cysts to determine the nature of the cyst, and thus the possible need for resection (3).

The current paradigm of pre-operative diagnosis uses clinical, radiological and pathological methods (4-7). One of the first questions to answer in this analysis is whether the cyst is serous or mucinous. Just a few years ago, this distinction alone was sufficient to determine the need for surgery (8). While serous cysts were resected primarily to relieve symptoms, all mucinous cysts, regardless of type, were resected due to the concern for malignant progression. What became clear from clinicopathological analysis of these resected mucinous neoplasms was that there were distinct types of mucinous cysts, distinguished by gender, age, location in the pancreas, association with the pancreatic ducts, pathological features, and likelihood of progression to cancer (3,9-12).

Most MCN are low-grade, non-invasive neoplasms that do not involve the main pancreatic duct. They are often large, multi-loculated, cysts and occur primarily in the body or tail of the pancreas of young to middle-aged women (12-14). The current recommendation is to resect all MCN regardless of whether there may be high-risk features because intervention at diagnosis avoids long-term, expensive, annual surveillance (15).

IPMNs, on the other hand, are a heterogeneous group of neoplastic cysts associated with the pancreatic ductal system that generally develop in the elderly. IPMNs are distinguished by main-duct versus branch-duct involvement, cyst lining epithelial cell type, and grade of dysplasia (9-12). Due to the typically older age at diagnosis, patients with IPMNs often have co-morbid conditions requiring careful consideration of the risk of surgical resection against the risk of malignancy. Studies have shown that most branch-duct IPMN are located in the pancreatic head or uncinate process and have a low risk of malignancy, not justifying the morbidity of a Whipple resection, especially in a high risk surgical candidate. Surgical management guidelines (aka Sendai Guidelines) have evolved from the numerous studies looking at the relative risk of malignancy associated with symptoms, cyst size, presence of a dilated main pancreatic duct as surrogate marker for main duct involvement, presence of a mural nodule, and cytological evidence of malignancy (15). The relative risk of malignancy is higher in main-duct IPMN in comparison to branch-duct IPMN, in part due to the higher risk of malignancy associated with the more common intestinal-type cyst lining of main-duct IPMN compared to the more common gastric-type cyst lining of branch-duct IPMN (9,11). So now, in addition to the challenge of

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distinguishing serous from mucinous cysts pre-operatively, there is the challenge of accurately subclassifying mucinous cysts and determining the risk of malignancy from pre-operative features.

One of the most helpful and accessible methods of distinguishing serous from mucinous cysts is the analysis of cyst fluid for carcinoembryonic antigen (CEA) and amylase (16,17). In this issue of The Journal of Gastrointestinal Oncology, Al-Rashdan, et al (18) show that cyst fluid analysis has limited value in pre-operative subclassification of the various mucinous cysts for surgical management. Their data do, however, validate the use of CEA in the distinction between non-mucinous and mucinous cysts. They show a median CEA value of 50 ng/ml in non-mucinous cysts and 206 ng/ml in mucinous cysts ($p<0.01$). This data is consistent with our findings that a CEA value greater than 192 ng/ml is an accurate marker of a mucinous cyst (16,17,19,20). In addition, they found no significant difference in the CEA levels between MCN and IPMN in general ($p=0.19$) or between MCN and branch-duct IPMN in particular ($p=0.64$). Their data also support the findings of others (21,22) who have not found amylase to be of use in differentiating MCN and branch-duct IPMNs. Although MCN are not connected to the pancreatic ducts that transport amylase-rich secretions, amylase levels in these cysts can be quite high, reaching levels greater than 100,000 U/L in their study. As Al Rashdan et al suggest, the images provided by EUS and other imaging modalities (CT/MRCP) are currently the best tests to distinguish MCN from branch-duct IPMN (5,23).

So what's the point? What is the value of pre-operative FNA and analysis of pancreatic cyst fluid? If all neoplastic mucinous cysts are pre-malignant and imaging can identify them accurately as suggested, why not just excise them all and save the patient from eventually developing pancreatic cancer? Pancreatic cysts are extremely common lesions. Approximately 2.6% of asymptomatic adults and over 8% of adults over 80 years of age undergoing abdominal imaging have a pancreatic cyst (24). Most incidental cysts are mucinous, but most of these are not malignant (9,15) Surgical resection of all pancreatic mucinous cysts is logistically impossible and certainly is not good patient care. Imaging may be very helpful for differentiating mucinous cysts, but nearly 20% of serous cystadenomas are macrocystic with few septations, mimicking a mucinous cyst, while IPMNs can cause pancreatitis and simulate the appearance of a pseudocyst (25). In addition, imaging is not at all helpful in differentiating low-grade from high-grade dysplastic or even malignant mucinous cysts (26).

The detection of a malignant mucinous cyst is the second challenge for cyst fluid analysis. In the data from Al-Rashdan's study there is no correlation between CEA or amylase levels with histological grade of the mucinous cysts, in part due to the low numbers among the various grades of histologically confirmed neoplasms. Although early studies of pancreatic cyst fluid analysis suggested that CEA levels correlated with malignancy (16) subsequent studies have not shown this to be true (17,19,20). In our recent study of pancreatic cyst fluid from over 750 patients, CEA of $\geq$110 ng/ml was the most accurate test for the diagnosis of a mucinous cyst, with an accuracy of 86% compared to EUS (48%) and cytology (58%), but cytology was the most accurate test for detecting malignancy, with an accuracy of 75% compared to EUS (66%) and CEA (62%) (17). Although often paucicellular and non-diagnostic, cyst fluids may contain cells that are suspicious for or diagnostic of malignancy (27-29). Cytological analysis of the cyst fluid may also provide diagnostic evidence of a cyst type that contradicts the clinical impression of a mucinous cyst, such as a lymphoepithelial cyst or cystic neuroendocrine tumor (30,31). The contribution of cytology is not discussed in Al Rashdan's study, although cytological analysis is outlined in their Table 2. Cytology identified 3 "positive" cyst fluids, but it is not known whether these interpretations were true positive or false positive results. Interestingly, a positive cytology with high grade dysplasia (HGD) on histology would have been considered a false positive outcome, given that only invasive cancer was considered malignant in their study (as per the 2010 WHO classification (32).

Surgical resection of a mucinous cyst with HGD is really the ideal outcome. Once invasive cancer arises in a mucinous cyst, the prognosis for the patient decreases significantly (9,10,12). The specificity of cytology for detecting malignancy at the threshold of "positive" for malignancy is extremely high. This high specificity comes at the price of sensitivity however (28). Cytological detection of high grade dysplasia is the optimal detection point for providing early intervention, either surgically or with cyst ablation therapy (28,33). Distinguishing intermediate grade dysplasia (e.g. moderate dysplasia (12) or borderline malignancy (34)) from high grade dysplasia (e.g. carcinoma in-situ (12)) is not only a challenge for histological analysis, but is especially a challenge for cytological analysis (35). The heterogeneity of the cyst lining typical of most mucinous cysts may cause the cells in the cyst fluid to under-estimate the final histological grade (27), and cellular degeneration coupled with a lack of standardized criteria and pathologist's experience with these types of specimens contributes to the poor performance of cytological analysis in many cases (personal experience). That being said, the recognition of high-grade dysplasia on cytological analysis is a powerful finding for early detection of cancer (28,33), and if you don'

t look, you won't find it.

Aside from CEA, amylase and cytological analysis, the future is looking to pancreatic cyst fluids as a rich source of DNA for molecular analysis. There is an explosion of research in this area which is beyond the scope of this editorial. In brief and to the best of our knowledge, no established molecular test is specific for the detection of malignancy. A KRAS mutation supports a mucinous etiology, but is inaccurate in distinguishing IPMN from MCN or in determining malignancy (36,37). The very recent report of GNAS mutation analysis shows promise in distinguishing mucinous from serous cysts and IPMN from MCN, but, again, is not a mutation that correlates with histological grade (38).

While further development of more specific markers of cyst type and biological behavior is awaited, imaging and cyst fluid analysis, including CEA, amylase and cytology, currently offer the best means of accurately assessing pancreatic cysts preoperatively. If cyst fluid analysis does not support a mucinous etiology on the one hand, or high grade dysplasia in a mucinous cyst on the other, conservative patient management is a viable alternative in asymptomatic patients without high risk imaging features, especially in an unsuitable surgical candidate.

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