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# Current controversies in pancreatic cystic neoplasms

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ABSTRACT

Pancreatic cystic neoplasms are a growing clinical challenge. They are incidentally discovered with increased frequency. The evaluation and management have evolved over time with increasing need to establish the correct type of cystic neoplasm and understand the unique natural history of each subtype. This review highlights this evolving strategy and an approach to management where treatment is guided by symptoms and features worrisome for high-risk of developing an invasive neoplasm. A thoughtful approach should be taken for an asymptomatic patient where resection needs to show a clear advantage to prevent cancer.



It is a great honor and pleasure to be able to deliver the Scott Woods Memorial Lecture to the membership of the Midwest Surgical Association. Dr. Scott Warner Woods was a surgeon trained at Wayne State University in Detroit who spent his entire career in Ypsilanti, Michigan. As a solo practitioner with an academic curiosity, he was clinically very busy in the local community and Associate Clinical Professor of Surgery at Wayne State University. He was a very active member of the Midwest Surgical Association, being both its Treasurer for a decade, then President. It is because of Dr. Woods that the Midwest Surgical convenes its scientific meeting every other year at the Grand Hotel on Mackinac Island, Michigan. He was a valued clinician, and in that spirit I would like to deliver this presentation around a burgeoning clinical problem.

Pancreatic cystic neoplasms are a prevalent clinical dilemma which have been increasing in recognition. Pancreatic cysts are frequently encountered in the autopsy literature, and a provocative study published by De Jong in 2010 suggests that the advanced imaging currently in broad use will detect a significant number of cystic lesions in asymptomatic individuals.[1] He and his group reviewed Magnetic Resonance Imaging (MRI) studies in asymptomatic patients. It was noted that incidental cystic disease of the pancreas increases with age to such a degree that approximately 12% of patients between the ages of 70 and 80 will have an incidental cyst. This is problematic both from the standpoint of the number of patients that will need to be potentially investigated, and the increasing risk of morbidity and mortality in operating on patients in this age group. These population studies of cyst prevalence have translated into clinical reality. Gaujoux and colleagues have shown an increasing number of patients presenting for evaluation of pancreatic cysts, yet with an interesting correlation of associated decreasing cyst size.[2] This has been mirrored by our experience at the Cleveland Clinic where the average cyst size at presentation for evaluation is only 2.3 cm. This demonstrates the obvious clinical challenge of needing to evaluate and manage patients of small cysts which are inherently difficult to adequately characterize based on their size.[3] Historically, these seem to be much easier to evaluate and manage in past decades when they were clinically infrequently encountered. In the past, the first important feature to distinguish was whether a cyst represented a post inflammatory pseudocyst versus a true cystic neoplasm. This is still an important consideration and typically achieved by serial evaluation of imaging in the setting of pancreatitis. Since post-inflammatory acute pancreatic pseudocysts develop at a time interval after the initial onset of pancreatitis, review of the initial imaging should not demonstrate a well-defined cystic structure. The presence of a cystic structure consistent with a cystic neoplasm in the setting of pancreatitis may indicate that the cystic neoplasm is responsible for causing the pancreatitis. Historically again, cystic neoplasms were also easy to manage since any mucinous neoplasm was advised to be resected. This was an easier proposition to propose when cystic neoplasms presented at a larger size with more characteristic cross-sectional computed tomography (CT) imaging findings, were more likely to be symptomatic, and clearly appeared to be premalignant lesions.[4] This led to common admonishments in the surgical literature to be “aggressive” with all mucinous cystic

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neoplasms of the pancreas. Other considerations which led to a stance for an aggressive surgical approach were the potential costs of ongoing surveillance, presumed inevitability of surgery in older patients, and the radiographic challenge of determining when a given cystic neoplasm is progressing to a *nearly* invasive carcinoma. Unfortunately, the presumption in all of these surgical arguments in that surgery itself is innocuous, and can be applied equally well in both low- and high-volume referral centers. There are certainly arguments to be made which challenge this historical approach to management of cystic neoplasms. One challenge lies in the fact that nearly all of the data regarding pancreatic cystic neoplasms are retrospective surgical case-series which does not fully represent the entire population of patients with cystic disease. The natural history of pancreatic cystic neoplasms is now better understood given that longitudinal series have finally included nonoperative patients. There are factual data which concludes that the natural history of all mucinous lesions is not the same. The natural history in terms of developing carcinoma in a side-branch intraductal papillary mucinous neoplasm (SB-IPMN) versus a Mucinous Cystic Neoplasm are not equivalent and, therefore, understanding the exact type of mucinous cystic neoplasm is of critical importance. Thus the type of cystic neoplasm is vital, yet is it important to challenge further assumptions. In reference to mucinous cystic pancreatic neoplasms, verus serous cystic neoplasms it was assumed that no serous lesions would require resection since they are pathologically benign. Yet these lesions do increase in size, and the rate of growth of a serous lesion is likely the overriding determinant since they can be difficult to resect if they ultimately become symptomatic and prohibitively large.[5] Again, the subtype of cystic pancreatic clearly is important, but management approaches vary. As our understanding evolves it is important to maintain consistency to better evaluate outcomes. The hepatobiliary surgeons and gastroenterologists at the Cleveland Clinic have developed a consensus algorithm based primarily on symptoms. This was determined based on symptomatic patients with cystic pancreatic neoplasms having more ominous pathology,[4] and clearly you can help the patient alleviate their symptoms with resection. From our perspective the challenge, therefore, lies in evaluation and management of the asymptomatic patient. To minimize patient harm, the treatment should not be worse than the disease. Therefore, clearly the disease to prevent is invasive cancer, yet the expected mortality for cancer cannot be exceeded by the operative mortality or a preventive resection. In the current surgical era, we in the surgical community should hopefully not be publishing retrospective patient series where 80% of asymptomatic patients are operated for benign cystic lesions.[6] The frequency of resecting benign asymptomatic lesions will be diminished by a thoughtful management strategy, and minimizing patients fears regarding the development of pancreatic cancer. While high-risk lesions should clearly be resected, we should not play into the understandable patient fears for developing pancreatic cancer.

It is important to understand the current World Health Organization's (WHO) classification of pancreatic cystic neoplasms[7] (Table 1). The classification system includes serous microcystic adenoma, serous oligocystic adenoma, and serous cystadenocarcinoma. Serous cystadenocarcinoma are exceedingly rare and should be ignored from a practical perspective. The microcystic serous variety of cystadenoma is the classic variant characterized as nearly solid-appearing cystic lesions on computed tomography (CT) which typically includes a central scar (Fig. 1). There are various types of mucinous neoplasm. A mucinous cystic neoplasm (MCN) is a specific histologic type of mucinous lesion that includes ovarian stroma in the wall of the neoplasm. These typically occur in the body and tail of the pancreas, and are solitary (Fig. 2). Mucinous cystic neoplasms (MCNs) include a spectrum of mucosal dysplasia from adenomatous to noninvasive high-grade dysplasia and invasive carcinoma. It is important to designate these lesions as noninvasive or invasive pathology. In the past, the term “malignant” was used, but this is strongly discouraged since it is nonspecific, and the outcome of noninvasive forms is clearly different from the invasive variety. Intraductal papillary mucinous neoplasms (IPMNs) are a well-recognized form of mucinous lesions of the pancreas. They form a spectrum of disease from side-branch IPMN to main duct IPMN and mixed-type IPMN. The main duct forms pathonumonically extrude mucin from the ampulla when involving the distal duct, but in fact do not have to involve the entire length of the gland (Fig. 3). The side-branch form of IPMN is notable for a normal pancreatic duct and a cyst in communication with the duct. The communication of the cystic lesion distinguishes it from Mucinous Cystic Neoplasm and serous cyst neoplasms. Pseudocysts originate from a disruption of the pancreatic duct, but do not have neoplastic features of the cyst wall which are present in cystic neoplasms. Similar to Mucinous Cystic Neoplasm (MCN), pathologically IPMN's are graded by the degree of dysplasia which progress from low-grade dysplasia to borderline to high-grade dysplasia followed by invasive carcinoma. All IPMN lesions pathologically demonstrate at a minimum low-grade dysplasia. It is important to recognize that there are different ways to subtype IPMN. As previously stated, morphologic assessment can be done with division into main duct, side branch and mixed type. Intraductal papillary mucinous neoplasms can also be assessed pathologically by degree of dysplasia, and finally using the combination of proteomics and pathology specific subtypes can be determined that include gastric, intestinal, pancreaticobiliary and oncocytic. Survival based on dysplasia has been assessed and there is a clear survival advantage to all noninvasive dysplastic lesions.[8,9] Additionally, prognosis based on proteomics has been shown such that the gastric subtype is the most common and also most favorable. In terms of survival, the gastric subtype is followed by intestinal, oncogenic, and lastly and most ominously by pancreaticobiliary subtype.[9] It is often difficult to determine the pathological status prior to resection. Therefore, other harbingers of poor prognosis have been sought. One of these can include cyst size. The relationship between cyst size and invasive cancer is clearly best known for mucinous cystic neoplasm (MCN). Based on resectional data, at a mean size of 9 cm, approximately half of the patients with MCN will have invasive cancer.[10] It is important to realize that each type of cystic neoplasm is unique and, therefore, the size correlation with invasive cancer is not clearly known for side-branch IPMN. The natural history of main duct IPMN shows a cumulative invasive malignancy rate of approximately 40% and up to 70% of patients harboring invasive or high-grade dysplasia.[11,12] The mixed-type variety of IPMN also has a nearly identical ominous prognosis based on the main duct involvement. Side-branch type clearly has the most favorable prognosis with approximately 15% invasive cancer risk, based on resectional data.

The evaluation strategy for pancreatic cystic neoplasms centers around determining which subtype is the patient presenting with. Typically, three specific diagnostic tests are routinely utilized: MRI, endoscopic ultrasound (EUS) and fine needle cyst aspiration (FNA). Magnetic Resonance Imaging utilizes no radiation, is noninvasive or iodinated contrast agents, which has excellent resolution of cystic structures. It is valuable in assessing the involvement of the main pancreatic duct, delineating solid pancreatic masses or solid components within a cyst, multiple lesions, cyst communication with the main pancreatic duct and any nonpancreatic disease. Endoscopic ultrasound is an invasive procedure which typically requires general anesthesia that can also demonstrate mural nodules or solid components within the pancreas, duct communication, and intraluminal papillary projection and pathognomonic extrusion of