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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.

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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

Table 1
Computed tomography image of microcystic serous cystadenoma. Although often asymptomatic, these lesions can grow quite large, with this image showing the pancreatic lesion at the level of the iliac crest.

Serous microcystic adenoma
Serous oligocystic adenoma
Serous cystadenocarcinoma
Mucinous cystadenoma (Mucinous Cystic Neoplasm)
Mucinous cystic tumor-borderline
Mucious Cystadenocarcinoma
Noninvasive
Invasive
Intraductal papillary mucinous adenoma
Intraductal papillary mucinous neoplasm-borderline
Intraductal papillary mucinous carcinoma
Noninvasive
Invasive

mucin from the minor and major papilla (Fig. 4). Endoscopic ultrasound also affords the ability for the third component, fine needle aspiration. Fine needle aspiration of cyst fluid is somewhat controversial since there is a theoretical risk for tumor seeding, although this appears to be clinically insignificant when performed during EUS. Fine needle aspiration is valuable in determining at least three laboratory outcomes providing the cyst is greater than 1.7 cm.[13] The three factors that we evaluate cyst fluid for, in descending order, are cyst cytology, cyst fluid CEA level, and amylase content. The cytology of cyst fluid can also aid in determining presence of mucin by PAS staining (14). Cyst fluid for CEA level greater than 192 ng/DL indicates a mucinous-type cyst, of any mucinous variety but the value is not indicative of malignant potential. Cyst amylase content can independently help establish communication of the cyst with the main pancreatic duct. All of these factors in unison can help distinguish what subtype of cyst is present, and this is assessed in consort with the cross-sectional imaging and endoscopic ultrasound findings. Cyst fluid may also be valuable in determining certain mucoproteins, mRNA or DNA levels. Molecular profiling may be of some value in the future, but study of these variables are limited, particularly by cyst fluid volume in small cysts. The combination of various variables in cyst fluid are felt to be diagnostic and representative of mucinous types of cysts (15). Once the cyst has been characterized into his various subtypes, then a decision must be made regarding observation versus resection. Our bias is that this should be primarily based on symptoms followed by cyst type, followed by cyst cytopathology during the patient's initial evaluation. Cyst types that require resection are main duct or mixed-type IPMN as well as mucinous cystic neoplasm. These are based on malignant potential such that resection in an asymptomatic individuals is warranted. Mucinous Cystic Neoplasms (MCNs) are gratifying to diagnose and treat since they occur in healthy young women and typically will require a laparoscopic distal pancreatectomy with typically good surgical outcome. Lacking these specific features and worrisome imaging findings that include mural nodule or thickened cyst walls, the challenge remains for the balance of asymptomatic patients. We proposed and performed an early natural history study at the Cleveland Clinic regarding management of asymptomatic pancreatic cystic neoplasms.[3] This natural history study segregated patients by symptoms, worrisome imaging findings and mucinous lesions by aspiration. Of note, the majority of patients were not resected highlighting the relative poor value of resectional series in understanding the totality of diseases. A total of 221 patients were managed by this algorithm. Thirty-two percent of them were symptomatic and were operated. The remaining 68% were asymptomatic and were evaluated by cyst aspiration. Half of these operated by aspiration included discovery of mucinous lesions which were resected. In the resection cohort, the majority of lesions were mucinous types of lesions as opposed to other surgical series. More importantly, of the 100 patients that were followed for greater than a year, 4% were operated and none of them were found to have a high-grade or invasive carcinoma. This was one of the early studies which suggested that a selective approach to resection of pancreatic neoplasms can be safely performed. The challenge remains as to what criteria should be utilized for resection in the asymptomatic individual. The initial Sendai criteria only focused on size.[12] Clearly, it would be advantageous to be able to base management on size alone as it would make decision making very straight-forward, but data have been lacking to support that premise other than for patients with Mucinous Cystic Neoplasm. Using size as the sole determinant will likely overtreat some patients with large lesions who harbor low-grade dysplasia, and small lesions at high risk. Small lesions with noninvasive and invasive disease less than 3 cm were shown by Schmitt et al. to be present in



Fig. 1. Computed tomography image of microcystic serous cystadenoma although asymptomatic these lesions can grow quite large with this image showing this pancreatic lesion at the Iliac crest.

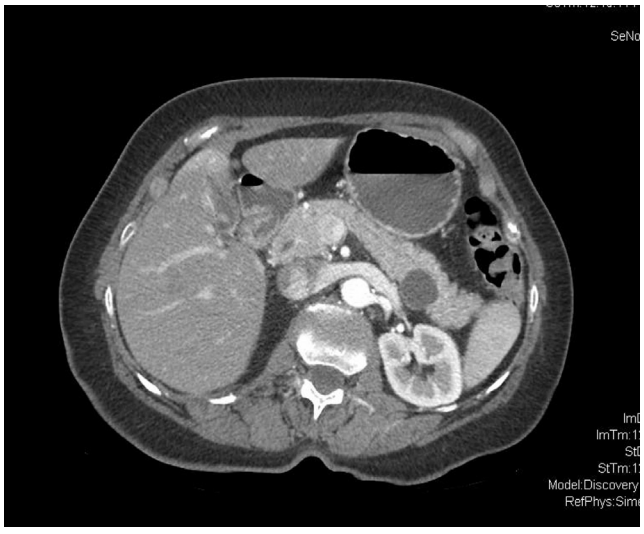


Fig. 2. Computed tomography image of a solitary cystic lesion in the tail of the pancreas. Aspiration suggested and resection confirmed a mucinous cystic neoplasm (MCN) with ovarian stroma.



Fig. 3. Specimen photograph of total pancreatectomy specimen with the duct opened to show the dilated main pancreatic duct with papillary projections.

cystic neoplasms of less than 30 mm (16). Fortunately, close inspection of these data do suggest that they were symptomatic lesions, further supporting the rationale to base treatment principally on symptoms. Since our algorithm dealt specifically with symptoms and not size, we surveyed our outcomes as if we had managed the patients by size alone. In this follow-up study of our natural history study, we demonstrated that no management option reliably prevents progression of disease (14). This study looked at over 300 patients with less than 3 cm of cyst, and 150 greater than 3 cm. In the patients greater than 3 cm, 58% were not operated principally because they were found to be nonmucinous. Of the 19 mucinous lesions in this category who refused operation, three did progress. Of the patients less than or equal to 3 cm in size, 84% were not resected which included 50 mucinous lesions, two of which progressed, and 243 nonmucinous or indeterminant lesions, in each group there were two failures. These data in aggregate suggests that there is no one definitive tool to prevent progression of disease to carcinoma, but in aggregate we concluded that had we used size alone, 20% would have been managed inappropriately either with unnecessary operation for benign lesions greater than 3 cm or missed high-grade mucinous lesions or carcinomas less than 3 cm



Fig. 4. Endoscopic image of the ampulla of Vater showing extrusion of mucin from the pancreatic and common bile duct from papillary mucinous neoplasms involving both ducts.

(14). Some of these considerations have been acknowledged in the most recent Sendai criteria: (17). Size is not the principal initiating differentiating feature, but rather the symptoms of jaundice, solid enhancing component within a cyst or main duct pancreatic diameter greater than 9 mm. All of these would warrant resection. Other worrisome features that likely would warrant resection include thickened or enhancing cyst wall, main duct dilatation between 5 and 9 mm, nonenhancing mural nodule or abrupt change in caliber of the pancreatic duct. Lacking any of these features, the algorithm does again resort to size. Unfortunately, this bias in the algorithm is toward surgery: cysts between 2 and 3 cm are advised to have endoscopic ultrasound at three to six month intervals. This surveillance regimen is daunting and will heighten the sense of worry in patients and likely lead to additional possibly unwarranted resections. The latest Sendai criteria also are confusing regarding aspiration analysis of cyst fluid. This is considered investigational in Japan where many of the consensus members are from, and it also unclear what to do with the worrisome imaging if there are conflicting results with endoscopic ultrasound. Overall, the revised guidelines are valuable, but a surgeon still needs to take a thoughtful approach. The outcome of a thoughtful approach has been demonstrated by the series from Memorial Sloan-Kettering,[2] where patients undergoing surveillance demonstrated that 1% of patients developed carcinoma during surveillance, and the operative mortality was also 1%. This equation of operative mortality equaling cancer risk is likely appropriate in asymptomatic patients, although it negates all surgical morbidity. It is possible that we are still resecting too many patients during surveillance since the vast majority of patients undergoing resection during surveillance have low-grade dysplasia (18). Since low-grade dysplasia is present in all IPMN patients by definition since they are neoplastic, resecting low-grade lesions likely has no benefit in prevention of cancer, but clearly is associated with operative surgical morbidity and mortality. There is clearly concern about development of cancer during surveillance of side-branch IPMN. Side-branch IPMN dominates the subtype of cystic neoplasms in the pancreas currently. These lesions are often multiple and deciding which lesion is at the greatest risk to develop cancer is problematic. There are interesting data from Japan which does not correlate the site of the side-branch IPMN with the site of invasive carcinoma which developed during surveillance in a small number of patients (19). These data indicate that if the cystic lesion had been resected, the invasive ductal carcinoma which subsequently developed in another segment of the pancreas would not have been avoided. While the changes of IPMN are likely a harbinger for increased risk of carcinoma of the typical ductal variety, it is difficult to assess when and where this risk may occur in the pancreas. The development of high-risk lesions or invasive carcinoma have occurred during our surveillance period. Typically, in side-branch IPMN this has occurred with either increase in size of the lesion or development of mixed type IPMN. These changes in our experience have developed in asymptomatic individuals. There are reassuring data in side-branch IPMN that asymptomatic side-branch disease at 60 months is associated with zero risk of malignancy, but should a side-branch IPMN become symptomatic, the risk of developing a malignancy at 60 months is 37% (19). Our initial interest in cystic pancreatic disease started two decades ago when we reviewed our surgical series of cystic neoplasms.[4] This series was typical for a high number of resections of benign lesions, and high number of malignant lesions in symptomatic patients. This spurred us to investigate these patients and ultimately develop a nonoperative natural history study. Facilitated by data acquisition across several surgical specialists interested in pancreatic disease and by harnessing the capabilities of the electronic medical record has allowed us to prospectively collect data on the presence of

symptoms and morphologic cyst features in a large number of patients. Structured reporting allows us to assess the presence or absence of symptoms which is not truly available in a retrospective process. We have subsequently surveyed a total of 1345 patients from 1997 through 2016. A total of 252 (18%) were resected based on our management algorithm. The mean cyst size at the time of initial evaluation was 2.3 cm, and at the time of last follow-up was 2.46 cm. Of the 252 patients that were surgically treated, 123 (49%) were symptomatic, and the remaining half asymptomatic. The pathology of the resected patients included Side-branch IPMN predominated in 32% with only three having an invasive cancer. Despite our low rate of resection, our invasive cancer rate overall was very low at 3.5% of patients initially resected.

Pancreatic cystic neoplasms remain a difficult patient cohort to manage due to increasing detection and predominance of asymptomatic patients. The evaluation strategy should be aimed at determining which specific type of cystic neoplasm the patient harbors, and based on that type of cystic neoplasm one should be able to reasonably determine management. Resection of Mucinous Cystic Neoplasm (MCN) main and mixed-type IPMN are warranted in all surgically acceptable risk patients given the likelihood of eventually developing invasive carcinoma. A minority of patients with side-branch IPMN require resection, and this should be based on symptoms and the development of worrisome features. Surveillance of these patients is currently warranted to see if they develop harbingers of aggressive disease which include cyst growth and development of main duct involvement. Lacking these developments, continued surveillance is warranted, although the length of this surveillance is unknown. A thoughtful approach to surgical resection in these patients is advised, and the development of shared management practices amongst a group of clinically active surgeons will help solve the current future mysteries of this disease.

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