EDITORIAL

Pancreatic cyst surveillance: Threat or opportunity?

Singhi and colleagues[1] in their article, "American Gastrointestinal Association guidelines are inaccurate in detecting pancreatic cysts with advanced neoplasia: a clinicopathological study of 225 patients with supporting molecular data," have questioned the effectiveness of the recent AGA guidelines on the management of patients with pancreatic cystic malignancies.[1] Singhi et al have claimed that the AGA guidelines, when applied to their cohort of patients, missed 45% of intraductal papillary mucinous neoplasms [IPMNs]) with adenocarcinoma or high-grade dysplasia, whereas their pathway, based on EUS-guided FNA (EUS-FNA) and cyst fluid molecular analysis had a higher sensitivity (100%) and specificity (90%). How should clinicians interpret these findings, and what guidelines should be used in the complex management of pancreatic cystic malignancies?

The initial set of pancreatic cyst guidelines (by the American Society for Gastrointestinal Endoscopy in 2005) established preliminary practice recommendations for EUS-FNA, cyst fluid analysis, and risk analysis.[2] Cytology was well recognized as a highly specific diagnostic test, but the role of cyst fluid tumor markers was not clear.

In 2006, an international set of guidelines (Sendai) was established by the International Association of Pancreatology.[3] A management algorithm was developed that established intervention based on the size of the cyst and the presence of high-risk stigmata (mural nodules, dilated main duct, or positive cytologic results). If no high-risk stigmata were found in cysts >1 cm, a surveillance program was recommended based on the size of the cyst. If high-risk stigmata were recognized, then surgical resection was recommended. They recommended resection for all cysts with a diameter of >3 cm.

In 2007, the American College of Gastroenterology submitted a set of patient management guidelines.[4] There was a consensus to perform EUS-FNA in cysts >2 cm to differentiate between mucinous and nonmucinous cysts. Cyst fluid carcinoembryonic antigen was recognized as the best marker for this task, and cytology was advocated for the front-line detection of malignancy. Yearly cross-sectional imaging was recommended as a surveillance tool for mucinous cysts.

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The Sendai guidelines were recently updated with a meeting of the International Association of Pancreatology in Fukuoka in 2012.[5] Patients with a "worrisome feature" (cyst >3 cm, thickened/enhanced walls, main duct 5 to 9 mm, nonenhancing mural nodule, or abrupt change in caliber of pancreatic duct or distal pancreatic atrophy) were directed to EUS-FNA. Without "worrisome features," patient treatment was based on the size of the cyst. Cysts <1 cm were entered into a CT/magnetic resonance imaging (MRI) surveillance in 2 to 3 years. Cysts 1 to 2 cm were placed into a yearly surveillance program. Larger cysts were managed with EUS-FNA, and surgery was recommended for cysts >3 cm. If "high-risk stigmata" (nodule, duct dilation, or jaundice) on EUS were observed, surgical resection was recommended.

I submit that clinicians should carefully avoid enrollment of patients with serous cystadenomas by carefully reviewing the MRCP images with signs of a serous cystadenoma. If there is any doubt as to the diagnosis, EUS-FNA should be highly accurate for answering this simple question.

The validation of these guidelines has taken place through the use of retrospective studies. The cystic lesions were classified as high risk, worrisome, or low risk by the guidelines. In these studies, the sensitivity and specificity of the applied guidelines are compared with the actual surgical histologic results. In an initial American study at one institution, 154 patients who had undergone resection were evaluated according to the Sendai guidelines (and 6 modifications).[6] The classification of a cyst size ≥3 cm had an accuracy of 56% for predicting a malignancy. A later Asian study reviewed 114 patients with mucinous cysts and classified the cysts according to the Sendai and Fukuoka guidelines as high risk, worrisome, or low risk.[7] The number of high-risk features was associated with the likelihood of malignancy. The authors concluded that the Fukuoka guidelines were superior.[7] In a similar study of 177 patients who underwent surgical resection, the accuracy of the Sendai guidelines was 35.5% compared with 44.8% for the Fukuoka guidelines.[8]

The AGA commissioned an evidence-based review of the diagnosis and management of pancreatic cysts.[9] In their analysis of the literature, several important assumptions were made, and it is critical to be aware of these when the guidelines are used. They concluded that "although carcinoma in-situ is of undoubted major concern, there is a large body of evidence that this histologic lesion does not always progress to invasive adenocarcinoma." "Only studies that reported the presence or absence of invasive malignancy were evaluated. The diagnosis of carcinoma in situ or high-grade dysplasia was not considered to be an invasive malignancy in this analysis."

Based on the literature review, the AGA guidelines were used to answer 7 key questions.[10] Here are the key recommendations of the AGA (recommendation no. 1 was to discuss the surveillance program with the patient):

2. The AGA suggests that patients with pancreatic cysts <3 cm without a solid component or a dilated pancreatic duct undergo MRI for surveillance in 1 year and then every 2 years for a total of 5 years if there is no change in size or characteristics. (Conditional recommendation, very low-quality evidence).
3. The AGA suggests that pancreatic cysts with at least 2 high-risk features, such as size >3 cm, a dilated main pancreatic duct, or the presence of an associated solid component, should be examined with EUS-FNA. (Conditional recommendation, very low-quality evidence.)
4. The AGA suggests that patients without concerning EUS-FNA results should undergo MRI surveillance after 1 year and then every 2 years to ensure no change in risk of malignancy. (Conditional recommendation, very low-quality evidence.)
5. The AGA suggests that significant changes in the characteristics of the cyst, including the development of a solid component, increasing size of the pancreatic duct, and/or diameter >3 cm, are indications for EUS-FNA. (Conditional recommendation, very low-quality evidence.)
6. The AGA suggests against continued surveillance of pancreatic cysts if there has been no significant change in the characteristics of the cyst after 5 years of surveillance or if the patient is no longer a surgical candidate. (Conditional recommendation, very low-quality evidence.)
7. The AGA suggests that patients with both a solid component and a dilated pancreatic duct and/or concerning features on EUS and FNA should undergo surgery to reduce the risk of mortality from carcinoma. (Conditional recommendation, very low-quality evidence.)

Singhi and colleagues[1] used a clinical and molecular algorithm to guide patient treatment. A cohort of 225 patients was enrolled in a 17-month study. Diagnostic pathologic results were available for 41 (18%) patients; 13 (6%) patients harbored advanced neoplasia. Pancreatic cyst fluid from each case was assessed for molecular alterations in *KRAS*, *GNAS*, *VHL*, *TP53*, *PIK3CA,* and *PTEN*. In the cohort, the AGA guidelines identified advanced neoplasia with 62% sensitivity, 79% specificity, 57% positive predictive value, and 82% negative predictive value. Moreover, the AGA guidelines missed 45% of IPMNs with adenocarcinoma or high-grade dysplasia. For cases without confirmatory pathologic results, 27 of 184 (15%) patients with serous cystadenomas based on EUS findings, *VHL* alterations, or both would continue MRI surveillance. In comparison, a customized set of guidelines using molecular markers detected advanced neoplasia with 100% sensitivity and 90% specificity. The authors concluded that the AGA guidelines were inaccurate in detecting pancreatic cysts with advanced neoplasia. Further, because the AGA guidelines fail to exclude serous cystadenomas, the authors predicted that there will be inappropriate surveillance of low-risk cysts.

How do we reconcile these differences and provide a uniform approach to our patients presenting with a pancreatic cystic lesion? When should EUS-FNA be performed to identify high-risk IPMNs and differentiate them from nonmucinous lesions? In the Fukuoka guidelines, EUS-FNA, MRCP, or ERCP is performed on cysts >2 cm. In the AGA guidelines, EUS-FNA is performed when cysts are >3 cm and have a high-risk stigmata (associated mass or dilated duct).

I submit that clinicians should carefully avoid enrollment of patients with serous cystadenomas into a surveillance program by carefully reviewing the MRCP images for signs of microcystic morphology.[11] I don't agree with the AGA guidelines that EUS-FNA and cyst fluid analysis rarely provide a diagnosis.

More importantly, we need to decide whether the guidelines should be designed to detect early neoplasia (eg, high-grade dysplasia) or late (invasive) neoplasia. The AGA guidelines are designed for late neoplasia, whereas the Sendia-Fukuoka and Singhi guidelines are constructed for the detection of early neoplasia. It appears that "worrisome features" or early neoplasia in the elderly can be managed conservatively.[12] New imaging modalities, such as PET scanning, may improve the accuracy of imaging for the detection of neoplasia arising from IPMNs.[13]

The decision to risk a pancreatic resection must take into account a patient's age and health and the site of the cystic lesion. The threshold for the resection of a lesion in the tail should be substantially lower than for head lesions. Furthermore, perhaps early neoplasia (as defined by the Fukuoka guidelines) should be resected in the young. It is not clear to me that the finding of "late neoplasia" will have an impact on patient outcomes. If the AGA guidelines are implemented for economic reasons, clinicians and patients should be aware of the likely outcomes.

DISCLOSURE

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Abbreviations: AGA, American Gastrointestinal Association; IPMN, intraductal papillary mucinous neoplasms; HGD, high-grade dysplasia; MRI, magnetic resonance imaging.

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