American Gastroenterological Association guidelines are inaccurate in detecting pancreatic cysts with advanced neoplasia: a clinicopathologic study of 225 patients with supporting molecular data

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Background and Aims: The American Gastroenterological Association (AGA) recently reported evidence-based guidelines for the management of asymptomatic neoplastic pancreatic cysts. These guidelines advocate a higher threshold for surgical resection than prior guidelines and imaging surveillance for a considerable number of patients with pancreatic cysts. The aims of this study were to assess the accuracy of the AGA guidelines in detecting advanced neoplasia and present an alternative approach to pancreatic cysts.

Methods: The study population consisted of 225 patients who underwent EUS-guided FNA for pancreatic cysts between January 2014 and May 2015. For each patient, clinical findings, EUS features, cytopathology results, carcinoembryonic antigen analysis, and molecular testing of pancreatic cyst fluid were reviewed. Molecular testing included the assessment of hotspot mutations and deletions for *KRAS*, *GNAS*, *VHL*, *TP53*, *PIK3CA,* and *PTEN*.

Results: Diagnostic pathology results were available for 41 patients (18%), with 13 (6%) harboring advanced neoplasia. Among these cases, 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 intraductal papillary mucinous neoplasms with adenocarcinoma or high-grade dysplasia. For cases without confirmatory pathology, 27 of 184 patients (15%) with serous cystadenomas (SCAs) based on EUS findings and/or *VHL* alterations would continue magnetic resonance imaging (MRI) surveillance. In comparison, a novel algorithmic pathway using molecular testing of pancreatic cyst fluid detected advanced neoplasias with 100% sensitivity, 90% specificity, 79% positive predictive value, and 100% negative predictive value.

Conclusions: The AGA guidelines were inaccurate in detecting pancreatic cysts with advanced neoplasia. Furthermore, because the AGA guidelines manage all neoplastic cysts similarly, patients with SCAs will continue to undergo unnecessary MRI surveillance. The results of an alternative approach with integrative molecular testing are encouraging but require further validation. (Gastrointest Endosc 2016;83:1107-17.)

The appropriate management of patients with pancreatic cysts has been a subject of debate for over 3 decades. Pancreatic cysts encompass a wide variety of lesions that include congenital, inflammatory, and neoplastic cysts. Among the most common cysts, pseudocysts and serous cystadenomas (SCAs) have a benign clinical course,

Abbreviations: AGA, American Gastroenterological Association; CEA, carcinoembryonic antigen; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; MRI, magnetic resonance imaging; PanNET, pancreatic neuroendocrine tumor; SCA, serous cystadenoma.

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whereas intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) represent precursor lesions to invasive adenocarcinoma. Historically, the inability to preoperatively subtype a pancreatic cyst and predict its biologic behavior led many investigators to recommend all cystic lesions of the pancreas be surgically resected.[1-3] Given the increase in incidental pancreatic cysts because of widespread use of cross-sectional radiology and the development of imaging parameters for malignancy, a paradigm shift occurred to a more selective approach in treatment.

In 2006 the International Association of Pancreatology published consensus guidelines for the management of IPMNs and MCNs.[4] These "Sendai guidelines" proposed imaging surveillance for cysts < 3 cm and surgical resection for cysts ≥ 3 cm or any cysts with associated clinical symptoms, high-risk features (dilated main pancreatic duct and/or mural nodule), or malignant cytopathology.[4] Because of the reported poor specificity for cysts with advanced neoplasia, these guidelines were revised in 2012 and are commonly referred to as the "Fukuoka guidelines."[5,6] In the second iteration, an emphasis on high-risk features and clinical symptoms was favored over adherence to cyst size. Subsequent studies demonstrated increased specificity for advanced neoplasia but at a loss in sensitivity.[7] There are difficulties in applying the Sendai and Fukuoka guidelines because they address IPMNs and MCNs only and are not informative for cystic lesions that cannot be assigned to these categories.

Recently, the American Gastroenterological Association (AGA) presented their own guidelines, but these guidelines were labeled as evidence-based rather than consensus-based and were accompanied by an extensive technical review of the literature.[8,9] The AGA guidelines are a significant departure from those outlined by the Sendai and Fukuoka guidelines. One of the most controversial aspects of the AGA guidelines is a higher threshold for surgical intervention that requires at least 2 high-risk features or positive cytopathology. Further, these guidelines pertain to the management of asymptomatic neoplastic pancreatic cysts rather than IPMNs and MCNs alone and, consequently, advocate imaging surveillance for a much larger population of patients with pancreatic cysts. Many investigators have expressed concern over whether adopting the AGA guidelines will result in inaccuracies in identifying advanced neoplasia and whether the surveillance of all pancreatic cysts is warranted.[10-12]

The purpose of our study was to determine the short-term accuracy of the AGA guidelines in detecting advanced neoplasia and to propose an alternative approach to pancreatic cyst evaluation and management. As with any retrospective analysis that attempts to model historical data, it is difficult to estimate the accuracy of a test over an extended period of time because different criteria and treatment strategies were followed previously. Thus, we limited our analysis to the short-term sensitivity and specificity of the AGA guidelines. In addition, as opposed to using a cohort of resected pancreatic cysts, which is often constrained by referral and selection bias, we chose to analyze a consecutive population of 225 patients who were evaluated by EUS-guided FNA and molecular analysis. Although diagnostic pathology was unavailable for most cases, the fluid aspirates from all pancreatic cysts were molecularly profiled for *KRAS*, *GNAS*, *VHL*, *TP53*, *PIK3CA,* and *PTEN*. Several studies have shown that mutations in *KRAS* and/or *GNAS* are highly specific for IPMNs and MCNs, whereas *VHL* alterations are only identified in SCAs.[13-18] Further, IPMNs with advanced neoplasia are associated with mutations in *TP53*, *PIK3CA,* and/or *PTEN*.[15,19-21] Considering that EUS-FNA data were available for the entire study population and have been shown to be superior to abdominal magnetic resonance imaging (MRI) for diagnosing both neoplasia and malignancy, we assessed the AGA guidelines at the point of EUS-FNA using the AGA clinical decision support tool.[22,23]

METHODS

Study cohort

Study approval was obtained from the University of Pittsburgh Institutional Review Board (IRB no. PRO13020493). A cytopathology database search was performed to identify pancreatic cysts in patients who underwent EUS-FNA with corresponding molecular analysis between January 2014 and May 2015 at the University of Pittsburgh Medical Center. Main duct IPMNs were specifically excluded from this search. In total, 225 patients with pancreatic cysts were identified. For each patient, demographic information, clinical presentation, EUS findings (including size, location, main pancreatic duct dilatation, presence of a mural nodule, and impression of cyst subtype), cytopathology results, carcinoembryonic antigen (CEA) values, and molecular reports were recorded. An elevated CEA was defined as >192 ng/mL. Patients were cross-referenced with a surgical pathology database to identify corresponding surgical resection material. Pathology slides were reviewed for each surgical specimen, and diagnoses for all pancreatic cysts were rendered based on standard histomorphologic criteria.[24]

The AGA guidelines were retrospectively applied to the study cohort using criteria for surgery that includes at least 2 of the following: cyst size ≥ 3 cm, an associated dilated main pancreatic duct, and a mural nodule or malignant cytopathology. A dilatation of the main pancreatic duct was defined by a diameter ≥ 5 mm by EUS.[6] A mural nodule was defined as a uniform echogenic nodule of any size without a lucent center or hyperechoic rim.[25] The same cohort was also applied to an alternative approach with inclusion criteria and management as outlined in Figures 1 and 2. Malignant cytopathology was defined as either at least suspicious for adenocarcinoma