Suboptimal accuracy of carcinoembryonic antigen in differentiation of mucinous and nonmucinous pancreatic cysts: results of a large multicenter study CME

Srinivas Gaddam, MD,[*,1] Phillip S. Ge, MD,[*,3] Joseph W. Keach, MD,[2] Daniel Mullady, MD,[1] Norio Fukami, MD,[2] Steven A. Edmundowicz, MD,[1] Riad R. Azar, MD,[1] Raj J. Shah, MD,[2] Faris M. Murad, MD,[1] Vladimir M. Kushnir, MD,[1] Rabindra R. Watson, MD,[3] Kourosh F. Ghassemi, MD,[3] Alireza Sedarat, MD,[3] Srinadh Komanduri, MD,[4] Diana-Marie Jaiyeola, MD,[4] Brian C. Brauer, MD,[2] Roy D. Yen, MD, MPH,[2] Stuart K. Amateau, MD, PhD,[2] Lindsay Hosford, BS,[2] Thomas Hollander, MS,[1] Timothy R. Donahue, MD,[5] Richard D. Schulick, MD,[2] Barish H. Edil, MD,[2] Martin McCarter, MD,[2] Csaba Gajdos, MD,[2] Augustin Attwell, MD,[2] V. Raman Muthusamy, MD,[3] Dayna S. Early, MD,[1] Sachin Wani, MD[2,6]

St. Louis, Missouri; Centennial, Denver, Colorado; Los Angeles, California; Chicago, Illinois, USA

Background and Aims: The exact cutoff value at which pancreatic cyst fluid carcinoembryonic antigen (CEA) level distinguishes pancreatic mucinous cystic neoplasms (MCNs) from pancreatic nonmucinous cystic neoplasms (NMCNs) is unclear. The aim of this multicenter retrospective study was to evaluate the diagnostic accuracy of cyst fluid CEA levels in differentiating between MCNs and NMCNs.

Methods: Consecutive patients who underwent EUS with FNA at 3 tertiary care centers were identified. Patients with histologic confirmation of cyst type based on surgical specimens served as the criterion standard for this analysis. Demographic characteristics, EUS morphology, FNA fluid, and cytology results were recorded. Multivariate logistic regression analysis to identify predictors of MCNs was performed. Receiver-operating characteristic (ROC) curves were generated for CEA levels.

Results: A total of 226 patients underwent surgery (mean age, 61 years, 96% white patients, 39% female patients) of whom 88% underwent Whipple's procedure or distal pancreatectomy. Based on surgical histopathology, there were 150 MCNs and 76 NMCNs cases. The median CEA level was 165 ng/mL. The area under the ROC curve for CEA levels in differentiating between MCNs and NMCNs was 0.77 (95% confidence interval, 0.71–0.84, $P < .01$) with a cutoff of 105 ng/mL, demonstrating a sensitivity and specificity of 70% and 63%, respectively. The cutoff value of 192 ng/mL yielded a sensitivity of 61% and a specificity of 77% and would misdiagnose 39% of MCN cases.

Conclusions: Cyst fluid CEA levels have a clinically suboptimal accuracy level in differentiating MCNs from NMCNs. Future studies should focus on novel cyst fluid markers to improve risk stratification of pancreatic cystic neoplasms. (Gastrointest Endosc 2015;82:1060-9.)

Abbreviations: AUC, area under curve; CEA, carcinoembryonic antigen; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; MCN, mucinous cystic neoplasm; NMCN, nonmucinous cystic neoplasm; ROC, receiver-operating characteristic; SD, standard deviation.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this article.*

*Drs Gaddam and Ge contributed equally to this article.

See CME section; p. 1105.

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2015.04.040

Received January 30, 2015. Accepted April 26, 2015.

Current affiliations: Division of Gastroenterology and Hepatology, Washington University School of Medicine, St. Louis, Missouri (1), Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Centennial, Colorado (2), Division of Digestive Diseases, David Geffen School of Medicine at UCLA, Los Angeles, California (3), Division of Gastroenterology, Feinberg School of Medicine Northwestern University, Chicago, Illinois (4), Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California (5), Division of Gastroenterology and Hepatology, Veterans Affairs Medical Center, Denver, Colorado (6), USA.

Presented in part at Digestive Diseases Week 2014, May 3-6, 2014, Chicago, Illinois (Gastroenterology 2014;146(suppl 1):S872-3).

Reprint requests: Sachin Wani, MD, Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, 1635 Aurora Ct., Rm. 2.031, Aurora, CO 80045.

The increasing use of high-resolution abdominal cross-sectional imaging such as CT and magnetic resonance imaging has led to increased detection of pancreatic cysts. The overall prevalence of pancreatic cysts in asymptomatic patients is about 2.5%,[1-3] but is substantially higher in patients who undergo imaging for suspected pancreatic disease.[4] In addition, the prevalence of pancreatic cysts increases with increasing age.[1,5,6] Although the risk of cancer in certain pancreatic cystic lesions is well-known,[7] the criteria for accurate identification of patients in whom cysts are likely to progress to cancer have not been well established[8] and continue to evolve.[3,9-12] Pancreatic cystic neoplasms are generally classified into 2 main groups: mucinous cystic neoplasms (MCNs), including mucinous cystadenomas, cystadenocarcinomas, and intraductal papillary mucinous neoplasms (IPMNs), which are premalignant or malignant, and nonmucinous cystic neoplasms (NMCNs), which are nearly always benign. The main goal of evaluating pancreatic cysts is to make this distinction, which is an important factor in determining further management (surgery, surveillance, or neither). Currently, EUS with FNA is routinely performed for the evaluation of a newly discovered pancreatic cystic neoplasm.[13]

The differentiation between MCNs and NMCNs is critical because a misdiagnosis of an MCN can lead to a missed opportunity to prevent potential pancreatic cancer, which has a dismal 5-year survival rate.[14] On the other hand, misdiagnosis of an NMCN can result in unnecessary surgery or surveillance that is associated with high morbidity and costs[15] and a negative impact on quality of life. The increasing incidence of pancreatic cysts with unclear risk of progression and the continued poor outcomes of pancreatic cancer represent a significant burden on our health care resources.

Carcinoembryonic antigen (CEA) was first reported to be elevated in the serum of patients with pancreatic cancer in the 1970s[16] and was later found to correlate with the stage of pancreatic cancer.[17] Subsequent studies showed that CEA levels were elevated in the pancreatic cyst fluid.[18,19] In 2004, a multicenter, blinded study by Brugge et al[20] showed that, at an optimal cutoff of 192 ng/mL, cyst fluid CEA levels were capable of differentiating an MCN from an NMCN with a high degree of accuracy (sensitivity of 73%, specificity of 84%). However, subsequent small case series have shown that CEA levels may not be accurate as previously reported (sensitivity of 28%–100%, specificity of 25%–100%).[21-37]

AIM

The aim of this study was to evaluate the diagnostic performance characteristics of CEA levels in differentiating pancreatic cystic neoplasms (MCNs vs NMCNs) in a large multicenter cohort of consecutive patients undergoing surgical resection of a suspected pancreatic cystic neoplasm.

METHODS

Consecutive patients undergoing EUS-FNA for the evaluation of pancreatic cysts at 3 academic tertiary medical centers (Washington University School of Medicine in St. Louis, Missouri; University of Colorado Hospital in Denver; and University of California, Los Angeles Medical Center in Los Angeles) between 2006 and 2011 were enrolled in the study. The study was approved by the institutional review boards at each of the participating centers. Data in this study are reported in accordance with the STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guidelines.[38]

Patients and data collection

Consecutive patients undergoing surgical resection of the pancreas for pancreatic cystic neoplasms were included in the study. Patients undergoing surgery without previous EUS evaluation were excluded from this study. Patients were also excluded if FNA was unsuccessful or if the aspirate was insufficient for analysis. For the purposes of this study, pancreatic cysts diagnosed as neuroendocrine tumors and lymphoma were excluded from the final analysis.

Patients who underwent EUS for the evaluation of pancreatic cystic lesions were identified from a prospectively maintained endoscopy database. Patient demographic data were collected at each of the participating centers by study members who reviewed the electronic medical records. These data were then entered into a Microsoft Access database (Microsoft Corporation, Redmond, Wash). Based on our data collection experience in a pilot set of patients, a standardized set of guidelines for data collection was formulated and used by all 3 centers. This included a review of outpatient and inpatient notes in the preceding 6 months to obtain information.

Definitions

Demographic, laboratory, and EUS information was collected by reviewing electronic medical records. Evaluation and interpretation of abdominal cross-sectional imaging or EUS was based on the final read reported by the physician interpreting/performing the procedure. Surgical notes and histopathologic information were gathered by review of patient records. If reports were inconclusive, they were reported as such, and no further efforts were made to draw a conclusion in an effort to prevent inadvertent bias. Patients were considered to have premalignant or malignant lesions based on resected specimens. Patients with a diagnosis of an NMCN by surgical histopathology were considered to have a benign cyst. Similarly, patients with a diagnosis of an IPMN, MCN, or associated adenocarcinoma were assigned to the MCN group.

Physicians at all 3 academic centers performed EUS according to the current standard of care.[39] Patients