COMMENTARY
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# Is Carcinoembryonic Antigen the Holy Grail for Pancreatic Cyst Risk Stratification?

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See "Cyst Fluid Carcinoembryonic Antigen Level Difference between Mucinous Cystic Neoplasms and Intraductal Papillary Mucinous Neoplasms" by Ibrahim Hakkı Köker, Nurcan Ünver, Fatma Ümit Malya, et al., on page 113-121.

Incidental pancreatic cystic lesions are commonly encountered owing to the increased volume and quality of routine imaging. A study evaluating more than 2,800 patients undergoing magnetic resonance imaging (MRI) revealed that pancreatic cysts were prevalent in 2.4%.[1] Meanwhile, a more recent systematic review and meta-analysis of over 48,000 patients revealed the rate of incidentally detected pancreatic cystic lesions was 8%.[2] While many pancreatic cystic lesions are benign, some may undergo malignant transformation. Predicting which cysts will become malignant has been the illusive holy grail leading to an explosion of studies evaluating various cyst fluid biomarkers with no diagnostic silver bullet identified to date.

Carcinoembryonic antigen (CEA) was brought into prominence over 15 years ago when Brugge et al. published their landmark paper noting that cyst fluid CEA levels over 192 ng/mL differentiated mucinous from nonmucinous cysts.[3] Subsequent studies have confirmed the value of CEA in identifying mucinous cysts but have also noted its shortcomings with relatively modest sensitivity and issues with reproducibility when different assays are used.[3-5] Data on the utility of CEA to differentiate benign from malignant cysts has been even more tenuous.[6,7]

In this issue of *Clinical Endoscopy*, Köker et al.[8] from Istanbul, Turkey report on the use of pancreatic cyst fluid CEA level to differentiate low-risk (low-grade dysplasia or intermediate-grade dysplasia) intraductal papillary mucinous neoplasms (IPMN) from high-risk (high-grade dysplasia or invasive cancer) IPMN and low-risk mucinous cystic neoplasms (MCN).[8] Using endoscopic ultrasound (EUS)-guided fine needle aspiration cytology and/or surgical specimen histology for definitive diagnosis of mucinous pancreatic cyst lesions, the authors conclude that CEA cutoff of >100 ng/mL has a 100% negative predictive value in differentiating low-risk IPMN from low-risk MCN and high-risk IPMN. CEA was able to distinguish low-risk IPMN from high-risk IPMN and low-risk IPMN from low-risk MCN, but unable to separate high-risk IPMN from low-risk MCN.

While the authors present interesting data in the hopes of guiding prognostication of mucinous cystic lesions of the pancreas, there are several points that need to be addressed and clarified. First, as astutely pointed out by the authors, multiple other larger studies have reported cyst fluid CEA levels do not differentiate high-risk from low-risk mucinous cysts, and both the American College of Gastroenterology and European guidelines state CEA levels cannot differentiate malignant from benign cysts although with very low-quality evidence.[9,10] The current study has a very small sample size with 9 MCN, 16 low-risk IPMN and 15 high-risk IPMN, and while their results seem to persist when including only surgically resected samples, they may be reflective of the vicissitudes of this par-

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ticular small sample from a single center and limits external validity and generalizability to other centers.

The authors highlight a CEA cutoff to differentiate low-risk IPMN from high-risk IPMN and low-risk MCN, however, translating these findings into clinical practice may be challenging. Typically, CEA level of at least 192 ng/mL, if not higher, is used to identify mucinous cysts first as lower thresholds suffer from low specificity. Relying on EUS imaging alone to diagnose mucinous cysts is insufficient with 51% diagnostic accuracy.[3] Radiology imaging with MRI appears better for identifying mucinous cysts but still may be nondiagnostic. Therefore, what does one do with a CEA value less than 100 ng/mL if radiology and EUS imaging has not definitively identified communication between the cyst and pancreatic duct to clinch a diagnosis of IPMN? This could be consistent with a mucinous or a nonmucinous cyst for which there are typically different surveillance recommendations. On the other hand, if the CEA is greater than 100 ng/mL, we still have not definitively answered the question of whether the cyst is mucinous or not. Assuming it is a mucinous cyst, from this study, cyst fluid CEA greater than 100 ng/mL had modest specificity of 75% and only 66.7% and 78.9% positive predictive value for differentiating low-risk IPMN from low-risk MCN and high-risk IPMN, respectively. Furthermore, CEA could not distinguish between high-risk IPMN and low-risk MCN. This is important because management of high-risk IPMN and low-risk MCNs may differ. While surgical resection is typically recommended for high-risk IPMN in patients who are surgical candidates, some guidelines suggest surveillance for low-risk MCNs.[9,10]

Worrisome and high-risk features have been used to help identify higher risk pancreatic cystic lesions. While these features may differ depending on the guideline, typical findings prompting surgical referral in surgical candidates include nodule, dilated main pancreatic duct and concerning cytology. It would be interesting to know whether the high-risk IPMNs in this study had any other worrisome or high-risk features. It would also be interesting to see CEA levels amongst branch duct, main duct and mixed-type IPMN and how these compare to MCN and pancreatic ductal adenocarcinoma.

While the authors should be commended on providing us with additive literature suggesting potential use of CEA in differentiating malignant from benign IPMNs, this study simply adds to the large repertoire of mainly case series. Unfortunately, this literature to date has only yielded mixed results that make it challenging for pancreatic cyst diagnosticians to understand how best to use cyst fluid CEA. Based on currently available data, CEA will continue to assist us in differentiating mucinous from nonmucinous cystic lesions. Whether CEA can identify high-risk IPMNs remains uncertain. For risk assessment of pancreatic cysts, providers should continue to rely on EUS with cytology and pathology findings, MRI and multidisciplinary discussions.

Conflicts of Interest

The authors have no potential conflicts of interest.

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