Needle-based confocal laser endomicroscopy for the diagnosis of pancreatic cystic lesions: an international external interobserver and intraobserver study (with videos)

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Background and Aims: EUS-guided needle-based confocal laser endomicroscopy (nCLE) characteristics of common types of pancreatic cystic lesions (PCLs) have been identified; however, surgical histopathology was available in a minority of cases. We sought to assess the performance characteristics of EUS nCLE for differentiating mucinous from non-mucinous PCLs in a larger series of patients with a definitive diagnosis.

Methods: Six endosonographers (nCLE experience >30 cases each) blinded to all clinical data, reviewed nCLE images of PCLs from 29 patients with surgical (n = 23) or clinical (n = 6) correlation. After 2 weeks, the assessors reviewed the same images in a different sequence. A tutorial on available and novel nCLE image patterns was provided before each review. The performance characteristics of nCLE and the κ statistic for interobserver agreement (IOA, 95% confidence interval [CI]), and intraobserver reliability (IOR, mean ± standard deviation [SD]) for identification of nCLE image patterns were calculated. Landis and Koch interpretation of κ values was used.

Results: A total of 29 (16 mucinous PCLs, 13 non-mucinous PCLs) nCLE patient videos were reviewed. The overall sensitivity, specificity, and accuracy for the diagnosis of mucinous PCLs were 95%, 94%, and 95%, respectively. The IOA and IOR (mean ± SD) were κ = 0.81 (almost perfect); 95% CI, 0.71-0.90; and κ = 0.86 ± 0.11 (almost perfect), respectively. The overall specificity, sensitivity, and accuracy for the diagnosis of serous cystadenomas (SCAs) were 99%, 98%, and 98%, respectively. The IOA and IOR (mean ± SD) for recognizing the characteristic image pattern of SCA were κ = 0.83 (almost perfect); 95% CI, 0.73-0.92; and κ = 0.85 ± 0.11 (almost perfect), respectively.

Conclusions: EUS-guided nCLE can provide virtual histology of PCLs with a high degree of accuracy and inter- and intraobserver agreement in differentiating mucinous versus non-mucinous PCLs. These preliminary results support larger multicenter studies to evaluate EUS nCLE. (Clinical trial registration number: NCT02516488.) (Gastrointest Endosc 2017;86:644-54.)

(footnotes appear on last page of article)

INTRODUCTION

The prevalence of pancreatic cystic lesions (PCLs) on imaging studies ranges from 2.5% to 19% and is corroborated by a prevalence rate of 24% in an autopsy series.[1-4] Although the International Consensus Guidelines of 2012 (Fukuoka) permits reliable risk stratification of PCLs, the pre-surgical differentiation of these lesions remains clinically challenging.[5] The various types of PCLs include non-mucinous lesions (serous cystadenomas

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[SCAs], pseudocysts), pre-malignant mucinous lesions (mucinous cystic neoplasms [MCNs], and intraductal papillary mucinous neoplasm [IPMN]), neoplastic (cystic neuroendocrine tumors [NETs], pseudopapillary tumor), and other benign lesions (squamous-lined cysts). A combination of clinical history, imaging and EUS features, cytology, and cyst fluid carcinoembryonic antigen (CEA) levels are used to identify mucinous cysts.[6] This approach remains inadequate, reflected by an unintentional resection rate of approximately 20% for non-mucinous PCLs at 2 large tertiary care centers over the last decade.[7,8] In a solitary PCL, a nonoperative histopathologic diagnosis is inaccurate in approximately 25% of patients.[7] Although mortality rates associated with pancreatic surgery have decreased (~0.5%), the morbidity rates remain high (30%-40%), necessitating efforts to avoid unnecessary surgery.[7,8]

Confocal laser endomicroscopy (CLE) is a novel technology that provides real-time laser-assisted microscopic imaging of tissue, facilitating in vivo histopathology.[9,10] Interobserver and intraobserver agreement for CLE image patterns in the luminal tract mucosa has largely been favorable.[11-13] EUS-guided needle-based CLE (nCLE) is developing as a capable technique for pre-surgical evaluation of PCLs.[13,14] Limited imaging data from 3 clinical trials are currently the reference standard for nCLE imaging.[10,13-15] Although fewer than one-third of the patients in these studies had surgical resection and intraobserver reliability (IOR) was not assessed, it is suggested that mucinous PCLs (IPMNs or MCNs) are indicated by the presence of finger-like papillae or single band-like epithelium.[13,14] The specificity for diagnosing serous cystadenomas (SCAs) neared 100% when a characteristic superficial vascular network pattern was observed.[13,14] Specific criteria for the diagnosis of pseudocysts and cystic NETs have recently been identified.[15-17] We have recently published our experience with the technique of ex vivo CLE imaging in resected PCLs and confirmed CLE image patterns in ex vivo models of various PCLs.[16,18-20]

The objective of this study was to further characterize novel nCLE-based image criteria for the diagnosis of PCLs. In addition, we sought to externally validate and assess the diagnostic accuracy of a comprehensive panel of nCLE image patterns for differentiating PCLs, including assessment of interobserver agreement (IOA) and IOR.

METHODS

Study design and population

The study was approved by the Ohio State University Institutional Review Board. We performed a retrospective analysis of the EUS database at Ohio State University Medical Center and included all consecutive individuals who underwent EUS-guided nCLE for evaluation of PCLs from 2013 to 2016. One-third of the patients in the database included individuals who were prospectively enrolled in the INDEX study (Comparison of confocal laser endomicroscopic IN vivo Diagnosis and EX vivo examination against surgical histopathology of cystic pancreatic lesions; clinical trial registration number, NCT02516488). Our criteria for using EUS nCLE included (1) ≥18 years of age, (2) a PCL lesion size of ≥20 mm (determined by cross-sectional imaging studies), and (3) being evaluated for surgical removal based on recommended international consensus guidelines.[6] Exclusion criteria were (1) women with known pregnancy at the time of the procedure, (2) coagulopathy (international normalized ratio >1.5 and/or platelets <50,000/mL), and (3) known allergy to fluorescein.

EUS nCLE image acquisition

All EUS examinations were performed at the Ohio State University Medical Center by 3 endosonographers (S.K., J.W., S.E.) using a linear echoendoscope (Olympus America, Center Valley, Pa). All EUS examinations were performed under the direction of an anesthesiologist using intravenous (IV) propofol. In a minority of patients deemed to be high risk, elective intubation was performed at the discretion of the supervising anesthesiologist. Fluorescein (5 mL; 10% fluorescein sodium) was injected intravenously 2 to 3 minutes before CLE imaging. The AQ-Flex nCLE miniprobe (Cellvizio, Mauna Kea Technologies, Paris, France) was then advanced through the locking device into the 19G needle (Flex needle, Boston Scientific, Natick, Mass). The preloaded 19G needle was advanced under EUS guidance into the PCL. The tip of the nCLE probe was negotiated until it opposed the intracystic epithelium. Intracystic endomicroscopic images were captured for 5 to 10 minutes with permissible angulation of the 19G needle using the elevator of the echoendoscope. After image acquisition, the nCLE probe was withdrawn and the PCL was aspirated. Antibiotic (quinolone) prophylaxis was administered via the IV route on the day of the procedure followed by 3 days of oral therapy. Patients who were allergic to quinolones were administered IV ertapenem followed by oral amoxicillin/clavulanate.

nCLE image review

One gastroenterologist (S.K.), unblinded to the final diagnosis, reviewed the nCLE video records to select high-yield image sequences. All nCLE images were reviewed using dedicated software (Cellvizio Viewer, version 1.6.1; Mauna Kea Technologies, Paris, France). Because the nCLE video captures included a significant burden of low-yield intracystic non-epithelial images, they were edited (using iMovie for Mac, Apple Inc, Cupertino, Calif) to shorter durations of less than 1 minute per patient to best represent the PCL epithelium. The following edits were performed to generate high-yield sequences: