Needle-Based Confocal Laser Endomicroscopy: A New Promising Armamentarium for Diagnostic Endoscopic Ultrasound

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Abstract

With increasing use of cross-sectional imaging in diagnosis of various diseases, incidence of asymptomatic pancreatic cyst has increased dramatically in last decade. In management of such asymptomatic pancreatic cyst differentiation of pre-malignant cyst and benign cyst remains an utmost important parameter. Though various endoscopic ultrasound (EUS) criteria have been developed, differentiation between these two entities still remains a challenge in many patients. Confocal laser endomicroscopy (CLE) has shown promising results in diagnosis of various gastrointestinal cancers and colonic polyps. However, CLE criteria have not been prospectively validated in asymptomatic pancreatic cyst to differentiate pre-malignant vs benign cysts. Similarly, CLE criteria are also not defined for diagnosis of various gastric sub-epithelial lesions. In this news and views we have discussed two important articles regarding role of needle based CLE (nCLE) in these lesions. While one is a multicentric trial which prospectively validates previously defined nCLE criteria for characterizing pancreatic cystic lesion, second developed criteria for diagnosis of various gastric subepithelial lesions based on nCLE findings.

Keywords
- ► Pancreatic cystic neoplasm
- ► Gastric sub-epithelial lesions
- ► Endoscopic ultrasound
- ► Gastro-intestinal stromal tumour

Because of its ability to acquire high-resolution images, endoscopic ultrasound (EUS) has emerged as an excellent tool for imaging of various gastrointestinal (GI) and surrounding structures. Advent of linear EUS and the consequent ability to perform EUS-guided fine-needle aspiration (FNA) has vastly expanded the role of EUS in the diagnosis of various GI and non-GI disorders. With the use of fine-needle biopsy and presence of onsite pathologist, diagnostic yield of EUS-guided tissue sampling has improved further. However, EUS-guided tissue sampling has its own limitations, with sensitivity and specificity varying between 80% and 90%, sampling error, and limited availability of onsite cytopathologist.[1-3] Confocal laser endomicroscopy (CLE) is a novel endoscopic imaging technique which enables subcellular visualization during endoscopy. It is being used for diagnosis of various gastrointestinal cancers and colonic polyps.[4-7] In past few years, needle-based probes have been developed which can be passed through 19G needle during EUS-FNA and visualization of subcellular structure in area of interest can been performed. This needle-based confocal laser endomicroscopy (nCLE) probe provides real time imaging at a microscopic levels and thus acts as an "optical biopsy."[8]

With routine use of computed tomography (CT) or magnetic resonance imaging (MRI) for various abdominal conditions, asymptomatic pancreatic cysts are being increasingly diagnosed.[9,10] In such asymptomatic pancreatic cysts it is of utmost importance to differentiate a mucinous cyst from a nonmucinous cyst as mucinous cystic neoplasm and intraductal mucinous neoplasm are associated with increased risk of malignancy while others are not. Though use of EUS and its characteristics like wall thickness and intramural nodule have been used to differentiate premalignant versus benign cystic neoplasm, accurate diagnosis is not possible in many cases who finally have to undergo long follow-up

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and multiple radiological investigations periodically.[11] Role of nCLE has been explored for differentiation of mucinous versus nonmucinous pancreatic cystic lesions in few studies. nCLE criteria have also been developed that helps to discriminate between these two lesions.[12,13] Similar to pancreatic cystic lesions, definitive diagnosis of various gastric subepithelial lesions is also difficult to make. So, various endoscopic sampling techniques like endoscopic partial resection with unroofing technique, fixed flexible snare biopsy, and EUS-trucut biopsy have been described to increase diagnostic yield.[14,15] However, role of nCLE have not been explored in various gastric SELs. In this news and views article, we will discuss two articles that explore the interesting diagnostic role of nCLE. One is a multicentric trial which prospectively validates previously defined nCLE criteria for diagnosis of pancreatic cystic lesions. Second article evaluated the role of nCLE in diagnosis of gastric subepithelial lesions where in the authors developed criteria for diagnosis of various gastric SELs after correlation with histopathology of resected specimen.

Napoleon et al[16] conducted multicentric prospective validation study of nCLE criteria in patients with single noncommunicating pancreatic cystic lesion. Primary objective of this study was to validate the previously defined nCLE criteria for diagnosis of noncommunicating single pancreatic cyst using surgical histopathology or EUS-FNA cytohistological analysis as a reference standard. They also checked performance of nCLE in differentiating benign versus premalignant lesion and mucinous versus nonmucinous lesion in comparison to standard EUS imaging and CEA levels. Patients with age ≥18 years with single pancreatic cyst on CT or MRI without communication with main pancreatic duct and size ≥20 mm were included in the study. Patients underwent standard EUS imaging and lesions were characterized based on their location, size, and characteristic features like wall thickness, presence or absence or septa, number of cavities, and wall calcification. nCLE was performed using 19-gauge needle (ECHO-19; Cook Ireland Limited, Limerick, Ireland) and fluorescein sodium (2.5 mL, 10% solution). Previously defined nCLE criteria for final diagnosis of pancreatic cystic lesion were used.[12,13] Presence of "epithelial border" was used as criterion for mucinous cystadenoma. Presence of "superficial vascular network" was used criterion for serous cystadenoma. Similarly, presence of "papilla," "dark aggregates of cells surrounded by gray areas of fibrosis and vessels," or "field of bright, gray or black particles" were used criteria for diagnosis of intraductal papillary mucinous neoplasm, neuroendocrine tumor, and pseudocyst, respectively. After completion of nCLE examination, cystic fluid and sometimes cyst wall fragments were sampled. The samples were tested for CEA levels and also sent for cytohistopathological analysis. CEA cutoff of 192 ng/mL was used to differentiate mucinous from nonmucinous lesion and 5 ng/mL was used to differentiate benign from premalignant lesions. For reference diagnosis, each cytopathological or surgical specimen with conclusive diagnosis at a primary center was reviewed by two central pathologists who were blinded to the patient's medical history and procedural outcomes. Only patients with conclusive reference diagnosis were included in the study.

Seventy-eight patients with reference diagnosis (39 resected cysts and 39 cytohistopathological analysis) of pancreatic cystic lesion were included in the study. Out of 78 lesions, 7 had inconclusive nCLE findings. So, finally 71 patients with conclusive nCLF findings were compared with reference diagnosis (made with either cytohistopathological sample or surgical histopathological analysis). nCLE showed very high sensitivity and specificity in diagnosis of various pancreatic cystic lesion. For diagnosis of serous cystadenoma, nCLE showed sensitivity and specificity of 0.95 and 1. For diagnosis of mucinous cystadenoma and neuroendocrine tumor nCLE showed sensitivity and specificity of 0.95 and 1, 1, and 0.95, respectively. For premalignant lesion nCLE showed sensitivity and specificity of 0.96 and 0.95. nCLE also had high sensitivity (0.95, 0.68, and 0.79, respectively), specificity (1, 0.95 and 0.85, respectively) and area under receiver operating curve (AUROC) (0.98, 0.81, and 0.82, respectively) compared with CEA and EUS morphology for differentiating mucinous from nonmucinous lesion. nCLE had high sensitivity (0.95 and 0.87, respectively), specificity (0.96 and 0.83, respectively) and AUROC (0.96 and 0.85 respectively) compared with CEA for differentiating benign versus premalignant lesions. However, EUS morphology had similar sensitivity, specificity, and AUROC for differentiating benign versus premalignant lesion. In this study, however, there were only two patients with pseudocyst, so accuracy of nCLE in diagnosis of same couldn't be evaluated.[16] The authors concluded that the diagnostic performance of nCLE was better than that of EUS and CEA titration for differentiating mucinous from nonmucinous lesions and benign from premalignant PCLs.

Zhang et al conducted single-center prospective study to evaluate the diagnostic efficacy, feasibility, and safety of endoscopic ultrasound-guided nCLE in patients with gastric subepithelial lesions (SELs). Patients with age between 18 and 75 years with gastric SELs ≥2cm were included in this study.[17] Initially, linear EUS was performed and the location, diameter, layer of origin, internal echogenicity, and outer margin of gastric SEL's was noted. Thereafter, EUS-nCLE was done with use of miniprobe (AQ-Flex 19; Mauna Kea Technologies, Paris, France) through 19-gauge needle (ECHO-19, Cook Ireland Limited, Limerick, Ireland). Fluorescein sodium (3 mL, 10% solution) was injected 3 minutes before the procedure. The to and fro movements of the needle in the lesion were restricted to reduce chances of bleeding and consequent obscuring of confocal imaging. The final diagnosis was established by histopathological evaluation of resected specimen (either by endoscopic resection or by surgery) and the histopathologist was blinded to the EUS and nCLE findings. After diagnosis, nCLE characteristics of different lesions were evaluated by correlating nCLE images with histological findings in an open label manner. Three months after establishment of nCLE criteria for different gastric SELs, the nCLE videos recorded from the study patients were reviewed offline by the same endoscopist in a blinded manner. For assessing interobserver agreement, three endomicroscopist were shown randomly selected nCLE videos from study patients and they made their diagnosis in a blinded manner.

The authors enrolled 33 patients with gastric SELs undergoing EUS during their study period. 60% of patients were treated with endoscopic resection and rest were treated with surgical resection. Fourteen (42.4%) patients had GIST, 8 (24.2%) had ectopic pancreas, 6 (18.2%) had leiomyoma, and 5 (15.2%) had carcinoma after histopathological examination of resected specimen. After diagnosis they established criteria for these diseases based on nCLE. Fascicular architecture with mild or heterogenous fluorescein leak was the most consistent with low-risk or high-risk GIST. Similar features without fluorescein leak was correlated with leiomyoma. Presence of regular, dark, lobular structures with "coffee beans" appearance was consistent with ectopic pancreas. Presence of atypical or irregular glands with dilated and distorted vessels was consistent with carcinoma.

After formulating these criteria for nCLEs for gastric SLEs, experienced endosonologist reviewed previously stored videos. Though, nCLEs had higher sensitivity and specificity for diagnosis of gastric SLEs compared with EUS alone, it was not statistically significant. However, overall accuracy of offline nCLE was higher that of EUS alone (87.9% vs. 63.6%; $p = 0.02$). Interobserver agreement was "excellent" for ectopic pancreas; however, it was only moderate for rest of the lesions. None of the patients had adverse events related to the procedure. The authors concluded that their study demonstrated that EUS-nCLE was feasible and safe to accurately diagnose gastric SETs.[17]

Commentary

In recent years, interventional EUS has expanded its indications from mere transmural drainage of pancreatic collections to EUS guided biliary drainage, EUS-guided liver biopsy and various EUS-guided vascular intervention. Similar to interventional EUS, various new armamentariums have been added in diagnostic EUS as well. In recent years, EUS elastography has shown its promising role in differentiation and diagnosis of various solid pancreatic mass and malignant lymph nodes. EUS elastography have been also used to differentiate GIST from leiomyoma with promising results.[18] Similarly, contrast-enhanced EUS has also shown promising results to differentiate pancreatic adenocarcinoma from various other causes of pancreatic head mass. Contrast-enhanced EUS has also been explored for differential diagnosis of various gastric SELs.[19] Use of these new techniques enables gastroenterologist to differentiate malignant versus benign pathologies more precisely. Moreover, these diagnostic methods in combination may increase yield of EUS-FNA and may even obviate the need of same in future.

In recent years, nCLE has shown promising results in differentiation and diagnosis of various pancreatic lesions and even lymph nodes. Giovannini et al had developed criteria of various pancreatic solid lesions based on nCLE images and had shown accuracy up to 96% for nCLE images in diagnosis of various solid pancreatic mass.[20] Similarly, Benias et al also explored role of nCLE in differentiation of malignant versus benign lymph nodes.[21] Use of nCLE for differentiating mucinous versus nonmucinous lesions have been explored in earlier studies; however, it has been prospectively validated by Napoleon et al. In this study authors have included only patients with confirmed reference histological diagnosis to increase validity of the study. In this study nCLE outperformed both EUS morphological characteristics and cystic CEA levels in differentiation of mucinous versus nonmucinous cyst and also to differentiate premalignant versus benign cyst. With advent of this new tool, patients might get confirm diagnosis more precisely obviating need for unnecessary surgery or long-term follow-up. Zhang MM et al explored role of nCLE in differentiation of various gastric SELs and developed criteria for same by correlating with histological images. However, further large multicentric studies are required for validation of these criteria. Moreover, small sample size and inclusion of only few types of gastric SEL's were important limitations of this study.

These studies highlight the future of diagnostic EUS which is at present heavily dependent of EUS-FNA. With development of these newer techniques in diagnosis and differentiation of various pancreaticobiliary and gastric subepithelial pathologies, indications and burden of EUS-FNA and subsequent cytohistopathological examination might reduce.

Conflict of Interest
None.

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