Comparative diagnostic performance of volumetric laser endomicroscopy and confocal laser endomicroscopy in the detection of dysplasia associated with Barrett's esophagus

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Background and Aims: Probe-based confocal laser endomicroscopy (pCLE) and volumetric laser endomicroscopy (VLE) (also known as frequency domain optical coherence tomography) are advanced endoscopic imaging modalities that may be useful in the diagnosis of dysplasia associated with Barrett's esophagus (BE). We performed pCLE examination in ex-vivo EMR specimens and compared the diagnostic performance of using the current VLE scoring index (previously established as OCT-SI) and a novel VLE diagnostic algorithm (VLE-DA) for the detection of dysplasia.

Methods: A total of 27 patients with BE enrolled in a surveillance program at a tertiary-care center underwent 50 clinically indicated EMRs that were imaged with VLE and pCLE and classified into neoplastic (N = 34; high-grade dysplasia, intramucosal adenocarcinoma) and nonneoplastic (N = 16; low-grade dysplasia, nondysplastic BE), based on histology. Image datasets (VLE, N = 50; pCLE, N = 50) were rated by 3 gastroenterologists trained in the established diagnostic criteria for each imaging modality as well as a new diagnostic algorithm for VLE derived from a training set that demonstrated association of specific VLE features with neoplasia. Sensitivity, specificity, and diagnostic accuracy were assessed for each imaging modality and diagnostic criteria.

Results: The sensitivity, specificity, and diagnostic accuracy of pCLE for detection of BE dysplasia was 76% (95% confidence interval [CI], 59-88), 79% (95% CI, 53-92), and 77% (95% CI, 72-82), respectively. The optimal diagnostic performance of OCT-SI showed a sensitivity of 70% (95% CI, 52-84), specificity of 60% (95% CI, 36-79), and diagnostic accuracy of 67%; (95% CI, 58-78). The use of the novel VLE-DA showed a sensitivity of 86% (95% CI, 69-96), specificity of 88% (95% CI, 60-99), and diagnostic accuracy of 87% (95% CI, 86-88). The diagnostic accuracy of using the new VLE-DA criteria was significantly superior to the current OCT-SI ($P < .01$).

Conclusion: The use of a new VLE-DA showed enhanced diagnostic performance for detecting BE dysplasia ex vivo compared with the current OCT-SI. Further validation of this algorithm in vivo is warranted. (Gastrointest Endosc 2016;83:880-8.)

(footnotes appear on last page of article)

Barrett's esophagus (BE) is the strongest risk factor for the development of esophageal adenocarcinoma, a disease with rising incidence in the United States.[1] Detection of dysplasia associated with BE is of critical importance in determining the risk of progression to cancer and need for endoscopic ablation therapy. Advanced imaging techniques have been shown to significantly increase detection of dysplasia and in some studies reduce the number of suggested biopsies in patients with BE.[2]

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Confocal laser endomicroscopy (CLE) is an optical imaging modality that can generate in vivo images of esophageal mucosa at histologic level resolution. The use of probe-based confocal laser endomicroscopy (pCLE) has been shown to enhance detection of BE-associated dysplasia compared with high-definition white-light endoscopy alone.[3] pCLE, however, has limited imaging depth and a very limited field of view. In addition, pCLE requires administration of intravenous fluorescent

contrast agents in order to visualize the esophageal mucosa.

Frequency domain optical coherence tomography imaging, also known as volumetric laser endomicroscopy (VLE), is a second-generation optical coherence tomography (OCT) device that, in conjunction with a balloon-imaging catheter, can generate wide-field cross-sectional views of the entire distal portion (4-6 cm) of the human esophagus. VLE allows for comprehensive assessment of the esophageal mucosa and submucosa; however, its lateral resolution of about 30 μm is approximately 10 times lower than that of pCLE. VLE can effectively distinguish normal squamous epithelium from BE and uses an established OCT scoring index (OCT-SI) to detect dysplasia.[4,5]

pCLE and VLE have unique advantages and disadvantages for the detection of dysplasia associated with BE. This study aims to compare the diagnostic performance of VLE and pCLE by using their respective diagnostic criteria for BE dysplasia. In addition, we introduce and perform preliminary validation of a novel diagnostic algorithm designed for VLE.

METHODS

Patient and EMR specimens

EMR specimens were obtained from patients enrolled in a tertiary-care BE unit at Mayo Clinic, Rochester Minnesota. The patients consented to participate in this study. All patients had a history of high-grade dysplasia (HGD) or intramucosal adenocarcinoma (IMC). Endoscopic resection was performed by a single endoscopist (K.K.W.) with experience in the endoscopic management of BE, by using either the cap-snare (Olympus USA, Center Valley, Pa) or the band-ligation technique (Wilson-Cook Medical, Winston-Salem, NC).[6] This study was approved by the Mayo Clinic Institutional Review Board.

Specimen processing

In this study, EMR specimens were used as a tissue platform to establish a direct correlation between pCLE, VLE, and histology. Immediately after endoscopic resection, the specimens were rinsed with phosphate-buffered saline solution, oriented along the longitudinal axis, and marked with an ink dot on the lateral margin at the 12 o'clock position. VLE imaging was performed on each individual EMR specimen by using the Nvision VLE imaging system (Nvision, Cambridge, Mass). Specimens were then incubated in 0.5 μM 2-[N-(7-nitrobenz-2-oxa-1,3-diaxol-4-yl) amino]-2-deoxyglucose (2-NBDG) for 20 minutes at room temperature as previously described.[7] This agent supplies fluorescent contrast to dysplastic cells being incorporated through the glucose transporter. After the incubation period, the specimens were rinsed with phosphate buffered saline solution and imaged by using pCLE (Cellvizio, Mauna Kea Technologies, Paris, France). All EMR specimens were submitted for histopathologic evaluation by a GI pathologist (T.C.S., V.O.) for the presence and extent of dysplasia. (Fig. 1).

Specimens were considered neoplastic if the highest grade of dysplasia contained in the EMR specimen was HGD or IMC. Given that the diagnostic performance of both pCLE and VLE are limited in their differentiation of low-grade dysplasia (LGD), EMR specimens were grouped as nonneoplastic if they contained either nondysplastic BE or focal LGD.

Image acquisition and selection

The Nvision VLE imaging system used in this study consisted of a console, monitor, and optical probe. The optical probe is designed to fit through a therapeutic endoscope's instrument channel (3.7 mm). The probe used in this study is centered by a 25-mm balloon that is 6 cm in length. Imaging is performed by automatic helical pullback of the probe from the distal to the proximal end of the balloon over 90 seconds. VLE images have an axial resolution of 7 μm, a transverse resolution of about 30 μm, and can reach an imaging depth of up to 2 to 3 mm. A total of 1200 cross-sectional images are acquired over a 6-cm VLE scan. VLE scans are viewed by using a software interface that allows simultaneous examination of cross-sectional transverse and longitudinal views. In this study, VLE imaging was performed by direct application of the VLE balloon over the EMR specimen oriented along its longitudinal axis with gentle pressure to avoid distortion of EMR specimen structures.

The pCLE imaging system used in this study consists of a console, monitor, and optical probe. The optical probe used was a high-definition probe (Gastroflex UHD, Mauna Kea Technologies, Paris, France) designed to fit through a diagnostic gastroscope's instrument channel. pCLE has a field of view of 240 μm, with a lateral resolution of <5 μm. In our study, the pCLE image probe was stabilized by using a mechanical probe holder adapted over a translational mechanical stage as previously described.[7] Orientation of EMR specimens was preserved along the longitudinal axis, and pCLE videos were captured at a rate of 12 frames per second in a grid scanning pattern across the entire surface area of each specimen.

pCLE and VLE image acquisition was performed by 2 authors (C.L.L., M.A.) who reviewed videos and scans for image quality while remaining blinded to histology.

CLE fluorescence criteria

The CLE fluorescence intensity criteria were developed for the detection of BE-associated dysplasia by using 2-NBDG as a fluorescent agent in EMR specimens.[7] The components of these criteria are described in Figure 2. These criteria have been reported to have a sensitivity of 74% and specificity of 86% in the diagnosis of dysplasia in BE.[7]