

Accuracy of probe-based confocal laser endomicroscopy (pCLE) compared to random biopsies during endoscopic surveillance of Barrett's esophagus



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Bibliography

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ABSTRACT

Background For surveillance of Barrett's esophagus (BE), the current standard of random 4-quadrant biopsies misses 10–50% of esophageal neoplasms, and does not permit

real-time decision-making. Probe-based confocal laser endomicroscopy (pCLE) permits real-time in vivo histologic assessment of esophageal mucosa during upper endoscopy. Prospective studies comparing the accuracy of pCLE to 4-quadrant biopsies in routine clinical practice are lacking.

Methods Consecutive patients with BE underwent high definition white light and narrow-band imaging followed by pCLE and targeted biopsy or mucosal resection. Four-quadrant biopsies were obtained during the same session. Baseline variables, real-time pCLE interpretation, and histology results were prospectively recorded. Blinded expert review of pCLE sequences and histology specimens was performed. A sample size of 64 patients was calculated a priori based on 3% estimated prevalence of high grade dysplasia (HGD) or cancer.

Results In total, 66 patients were included in the study. The prevalence of HGD or cancer was 4.55%. Both real-time and blinded pCLE correctly identified all cases of cancer. For the primary outcome, real-time pCLE was 98% specific but only 67% sensitive for HGD/cancer compared to non-blinded pathologist interpretation. For HGD and cancer, inter-observer agreement was substantial between real-time and blinded endomicroscopists ($\kappa=0.6$). pCLE identified dysplasia in 75% of cases where both blinded and unblinded pathology interpretation was low grade dysplasia.

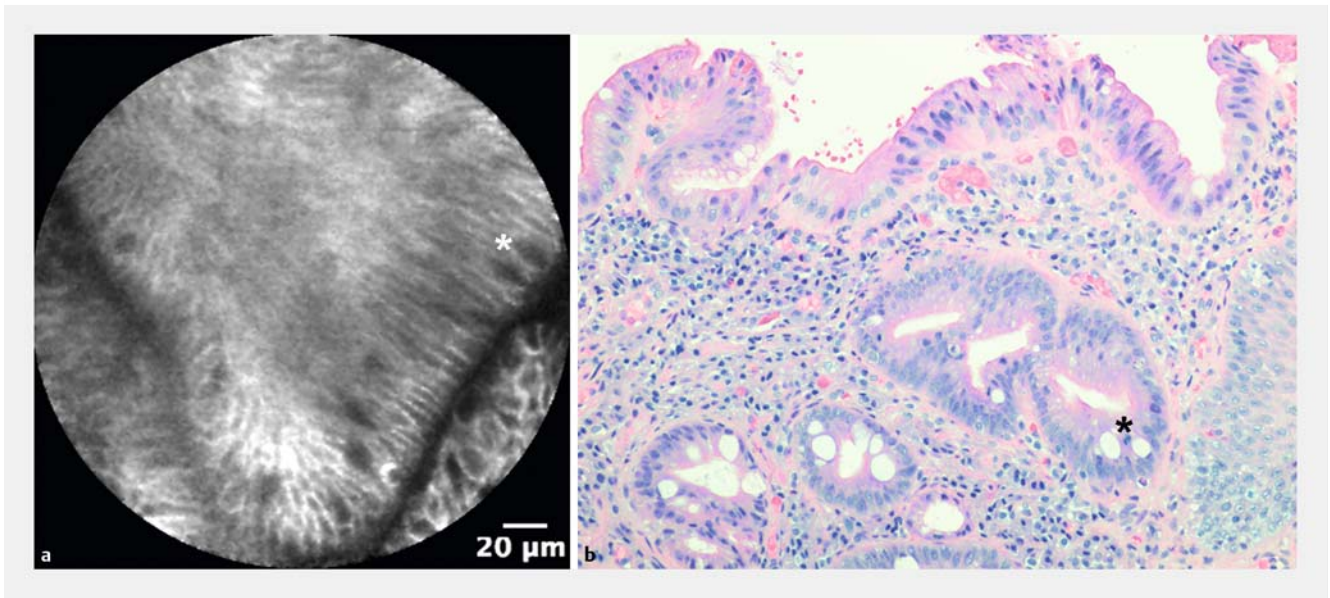
Conclusions pCLE demonstrates high specificity for detecting dysplasia and cancer, but lower sensitivity may limit its utility in routine BE surveillance. pCLE may have a role in confirming LGD in real-time before eradication therapy.

Background

The current standard for surveillance of Barrett's esophagus (BE) is to perform white-light endoscopy with targeted biopsies of any endoscopically visible lesions and random four-quadrant biopsies every 1–2 cm of the BE segment (i. e. Seattle protocol) [1]. Unfortunately, this strategy is labor intensive, may miss 10–50% of esophageal neoplasms, and may increase the risk

of bleeding from several biopsies [2, 3]. Additionally, multiple random biopsies may not be cost-effective, given the low absolute incidence of esophageal adenocarcinoma in patients with BE (0.4–0.5%) and the need for additional procedures for endoscopic eradication if dysplasia is detected [4, 5].

Confocal laser endomicroscopy (CLE) is a novel endoscopic technique that permits real-time in vivo histologic analysis of esophageal mucosa at the time of upper endoscopy. The tech-



► **Fig. 1** **a** pCLE of non-dysplastic Barrett's esophagus demonstrates uniform villiform architecture, columnar cells, and dark goblet cells (asterisk). **b** Corresponding histology at 10× magnification shows regular appearing columnar epithelium, basally situated nuclei with a low nuclear/cytoplasmic ratio, and white goblet cells (asterisk). Squamous epithelium is seen on the lower right-hand corner.

nology is based on the principle of illuminating a tissue with a low-power laser and then detecting fluorescent light reflected from the tissue [6]. The laser light is focused at a selected depth and reflected light is then refocused on the detection system by the same lens [7]. The light reflected and scattered at other geometric angles from the illuminated tissue is excluded from detection, which dramatically increases the spatial resolution of CLE [7]. Commercially available CLE is based on tissue fluorescence, with a topical or intravenous contrast agent.

Several societies have endorsed pCLE in patients undergoing surveillance of BE [8, 9]. These recommendations are based on studies that compared pCLE to white-light endoscopy, used an endoscope-based version (eCLE) that is not commercially available, marked tentative biopsy sites with argon plasma coagulation (APC), or used pCLE along with autofluorescence imaging and genetic panel testing [10–13]. To our knowledge, prospective studies comparing pCLE to random biopsies in routine clinical practice (i. e. comparative effectiveness studies) are lacking.

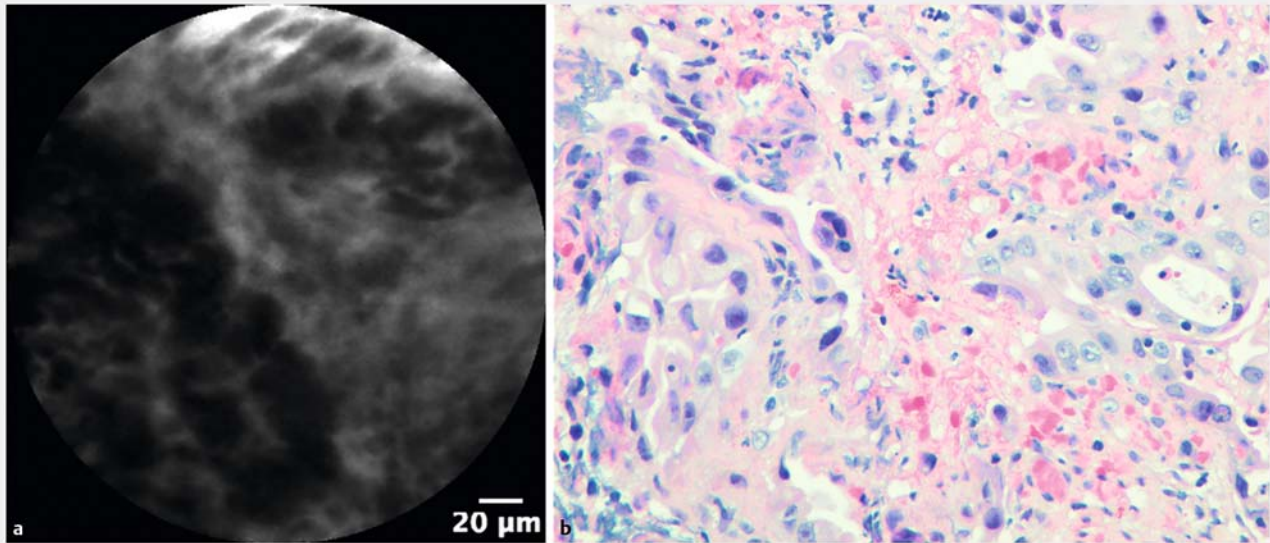
To eliminate the need for random biopsies, the American Society of Gastrointestinal Endoscopy (ASGE) initiative for the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) recommends that an imaging technology must demonstrate a per-patient sensitivity of at least 90% and specificity of at least 80% when compared to random biopsies [14]. The aim of this study was to prospectively assess if pCLE met the PIVI criteria for detecting dysplasia and cancer in routine clinical practice among patients undergoing endoscopic surveillance of BE.

Methods

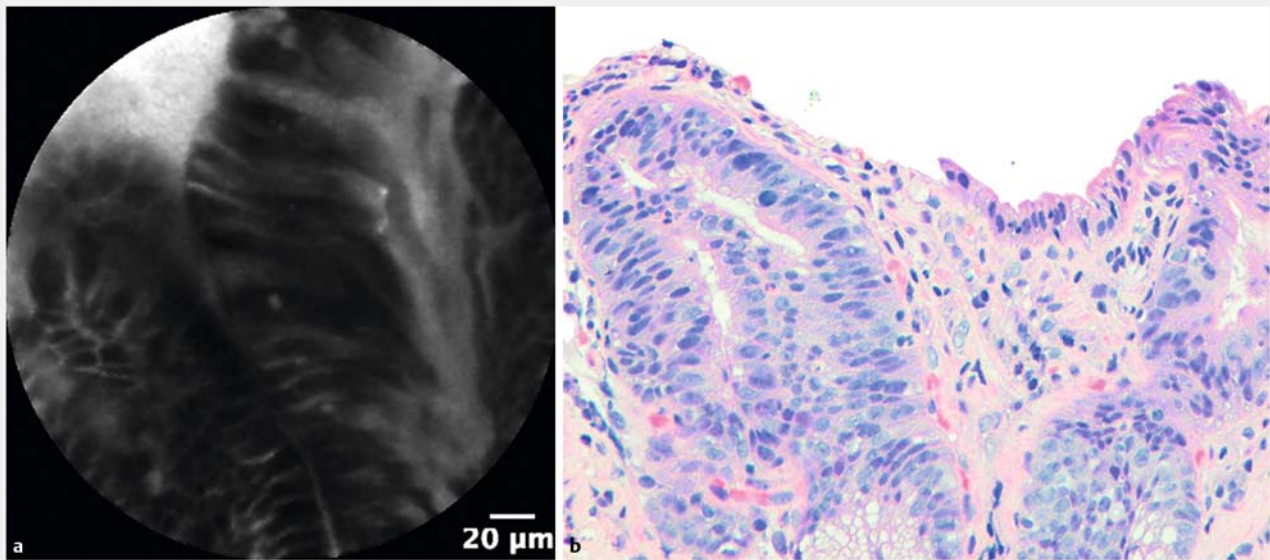
Patients and procedures

The institutional review board at the Hunter Holmes McGuire Veterans Affairs Medical Center approved the study. Consecutive patients referred for surveillance endoscopy for BE underwent high definition white-light endoscopy (HD-WLE) and narrow-band imaging (NBI) using an Olympus GIF-HQ190 adult gastroscope. Areas suspicious for dysplasia were identified on NBI based on the presence of irregular mucosal patterns, irregular vascular patterns, or abnormal blood vessels [15]. Following visual examination, pCLE examination was performed using a 2.5 mm gastroflex ultra-high definition probe (Cellvizio GI system, Mauna Kea, Paris, France) passed through the working channel of the gastroscope. The pCLE probe was placed gently on the mucosa after intravenous injection of 2.5 mL of 10% fluorescein. A transparent cap was fitted to the distal end of the scope to assist with probe stabilization. Video sequences were obtained from any areas felt to be suspicious on HD-WLE and NBI as well as in four quadrants at 1-cm intervals. Two gastroenterologists with at least 3 months of training in pCLE performed all procedures and interpreted pCLE recordings during the procedure (TS, PM). The investigators interpreted pCLE recordings based on the Miami classification as follows: non-dysplastic Barrett's esophagus (uniform villiform architecture, columnar cells, dark goblet cells) (► **Fig. 1**); adenocarcinoma (disorganized or absent villiform structures and crypts, dark columnar cells, dilated irregular vessels) (► **Fig. 2**) [16]; dysplasia (villiform structures, dark irregularly thickened epithelial borders, dilated irregular vessels) (► **Fig. 3**).

Endoscopists obtained targeted biopsies or performed endoscopic mucosal resection (EMR) of areas suspicious for



► **Fig. 2** a pCLE of adenocarcinoma demonstrates disorganized architecture with absent villiform structures and crypts, and dark columnar cells. b Corresponding histology at 40× magnification shows disorganized architecture, and irregular cells with high nuclear/cytoplasmic ratio.



► **Fig. 3** a pCLE of dysplasia shows villiform structures with dark irregularly thickened epithelial borders. b Corresponding histology shows loss of nuclear polarity and a decrease in number of goblet cells characteristic of low grade dysplasia.

HGD or cancer on HD-WLE, NBI, or pCLE. Subsequently, they obtained random four-quadrant biopsies at 1–2 cm intervals as suggested by the major American gastroenterology societies [1, 17]. In patients with diminutive islands or tongues of suspected Barrett's esophagus (i.e. ≤ 1 cm), the Seattle protocol was not feasible, so two to three random biopsies were obtained. Areas that were already sampled during targeted biopsy were not re-sampled while obtaining random biopsies. Baseline variables and real-time pCLE interpretation were prospectively recorded. As is routine at our institution, a single pathologist interpreted biopsies apart from when dysplasia or malignancy

was suspected, in which case a second pathologist confirmed the diagnosis. Non-blinded pathology results were prospectively recorded.

Blinded pCLE and pathology review

A single expert endoscopist (AZ) who had performed > 1000 pCLE procedures for BE reviewed all pCLE video sequences. The expert endoscopist was blinded to endoscopic images, real-time pCLE interpretation, and pathology interpretations. Subsequently, two endoscopists (TS, PM) reviewed video sequences for patients identified as having dys-

plasia or cancer on pCLE to assess whether they met revised pCLE criteria developed and validated by Gaddam et al. [18]. These criteria are as follows: epithelial surface: saw-toothed; cells: enlarged; cells: pleomorphic; glands: not equidistant; glands: unequal in size and shape; goblet cells: not easily identified. An expert pathologist (RL) reviewed all histopathology specimens. The pathologist was blinded to endoscopy findings, blinded and non-blinded pCLE interpretation, and non-blinded histology interpretation. Standardized criteria were used for blinded pathology interpretation [19].

Sample size

The study was a retrospective assessment of a prospectively maintained endomicroscopy database. The primary hypothesis was that specificity of real-time pCLE at detecting HGD or cancer assessed on a per patient basis is not less than 80% when compared to random biopsy. Assuming a 3% prevalence of high grade dysplasia or cancer in our tertiary referral Veterans Affairs Medical Center, expected power of 80%, and a 0.05 level of significance, we estimated a sample size of 64 patients would be necessary to evaluate the specificity of real-time pCLE to unblinded pathology review [5].

Statistical analyses

Statistical analyses were performed using SPSS IBM version 24 (Chicago, IL, USA). Baseline variables were recorded as frequencies and percentages. Accuracy was assessed by calculating sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of pCLE ± targeted biopsy compared to random biopsy. Cohen's kappa statistic was calculated to assess the degree of agreement between real time and blinded endomicroscopists as well as between blinded and unblinded pathologists [20]. Conventionally, Kappa scores of 0.41–0.6 represent moderate agreement, 0.61–0.79 represent substantial agreement, and 0.8–1.00 represent nearly perfect agreement.

Results

A total of 66 patients were included in the study. Procedures were performed from December 2014 to October 2016. The median duration for pCLE examination was 7 minutes (► **Table 1**). The median age was 66 years, and the majority of patients were white men. Mean Barrett's segment length was C2M3. Fifty-eight patients (88%) were on a proton pump inhibitor, 71% reported a history of cigarette smoking, and 86% were overweight or obese (► **Table 1**).

The overall prevalence of high grade dysplasia or cancer was 4.55% (2 cancers, 1 high grade dysplasia). Both patients with cancer had visible areas of mucosal irregularity on HD-WLE and NBI. For the primary outcome, accuracy of real-time pCLE for diagnosing HGD/cancer compared to non-blinded pathologist interpretation was as follows: sensitivity 67%, specificity 98%, negative predictive value 98%, and positive predictive value 67% (► **Table 2**). Both real-time and blinded pCLE correctly identified all cases of cancer. One patient with a flat diminutive tongue of salmon colored mucosa (C0M1) interpreted as non-dysplastic BE on real-time and blinded pCLE examination was

► **Table 1** Baseline variables (n = 66).

Median age, years	66 (range 44–73)
Gender	65 male (98%)
Race	61 White (92%) 5 Black (8%)
Median BMI	29 (range 17–46)
Mean length of Barrett's esophagus	C2 (range C0–C15) M3 (range M0 with island to M15)
Median duration of Barrett's esophagus, years	3 (range 0–22)
Median duration of pCLE exam, minutes	7 (range 2–26)
Proton pump inhibitor use (%)	Yes 58 (88%) No 8 (12%)
Current smoker (%)	Yes 21 (32%) No 45 (68%)
Prior smoker (%)	Yes 47 (71%) No 19 (29%)
Mean hiatal hernia size, cm	2 (range 0–9)

BMI, body mass index, pCLE, probe-based confocal laser endomicroscopy.

► **Table 2** Accuracy of probe-based confocal laser endomicroscopy (pCLE) compared to histology for high grade dysplasia or cancer.

	Non-blinded pathologist interpretation
Real-time pCLE interpretation	Sensitivity 67% (CI 9–99%) Specificity 98% (CI 91–100%) NPV 98% (CI 93–100%) PPV 67% (CI 20–95%)
Blinded pCLE interpretation	Sensitivity 67% (CI 9–99%) Specificity 94% (85–98%) NPV 33% (12–63%) PPV 98% (92–100%)

PPV, positive predictive value; NPV, negative predictive value; Agreement was 100% between non-blinded and blinded pathologists for HGD and cancer.

found to have HGD on random biopsy. The diagnosis of HGD was confirmed on subsequent EMR, and on blinded pathology review. For HGD and cancer, inter-observer agreement was moderate between real-time and blinded endomicroscopists (kappa = 0.6), and was perfect between blinded and non-blinded pathologists (kappa = 1).

The prevalence of LGD in our cohort varied substantially from 6% to 29% depending on the modality (pCLE vs. biopsy) and physician (blinded vs. non-blinded) (► **Table 3**). Real-time pCLE identified LGD in 11 patients (17%), whereas blinded pCLE review diagnosed LGD in only 6% of patients. When two non-blinded pathologists evaluated the specimens, LGD was found in 8% of patients, whereas blinded histology review using standardized criteria identified dysplasia in 29% of patients. Specificity of real-time pCLE for LGD was greater than 80%

► **Table 3** Accuracy of probe-based confocal laser endomicroscopy (pCLE) compared to histology for low grade dysplasia.

	Non-blinded pathologist interpretation (n = 5)	Blinded pathologist interpretation (n = 19)
Real-time pCLE interpretation (n = 9)	Sensitivity 60 % Specificity 87 % NPV 96 % PPV 27 %	Sensitivity 32 % Specificity 89 % NPV 76 % PPV 55 %
Blinded pCLE interpretation (n = 4)	Sensitivity 0 % Specificity 93 % NPV 92 % PPV 0 %	Sensitivity 11 % Specificity 96 % NPV 73 % PPV 50 %

PPV, positive predictive value; NPV, negative predictive value.

► **Table 4** pCLE and targeted biopsy/mucosal resection findings in patients with nodularity or irregularity on high definition white light or narrow-band imaging.

Patient	Sampling method	pCLE interpretation	Pathology interpretation
1	Biopsy	Real-time Adenocarcinoma Blinded Adenocarcinoma	Unblinded Adenocarcinoma Blinded Adenocarcinoma
2	Mucosal resection	Real-time HGD Blinded HGD	Unblinded No Barrett's esophagus Blinded No Barrett's esophagus
3	Mucosal resection	Real-time LGD Blinded LGD	Unblinded No Barrett's esophagus Blinded
4	Biopsy	Real-time NDB Blinded NDB	Unblinded NDB Blinded NDB
5	Biopsy	Real-time LGD Blinded HGD	Unblinded NDB Blinded NDB
6	Mucosal resection	Real-time LGD Blinded NDB	Unblinded Indefinite Blinded LGD
7	Mucosal resection	Real-time HGD Blinded LGD	Unblinded Indefinite Blinded LGD
8	Mucosal resection	Real-time NDB Blinded NDB	Unblinded No Barrett's esophagus Blinded No Barrett's esophagus
9	Biopsy	Real-time Adenocarcinoma Blinded HGD	Unblinded Adenocarcinoma Blinded Adenocarcinoma

NDB, non-dysplastic Barrett's esophagus; LGD, low grade dysplasia; HGD, high grade dysplasia.

when assessed against both non-blinded and blinded pathology interpretations; specificity of blinded pCLE interpretation for LGD was greater than 90% (► **Table 2**). Sensitivity of pCLE for LGD was low when compared to random biopsies, particularly in the blinded pCLE group (► **Table 3**). For LGD, inter-observer agreement was poor between real-time and blinded endomicroscopists ($\kappa=0.2$) as well as between blinded and non-blinded pathologists ($\kappa=0.2$). Among the 20 patients who had LGD on either unblinded or blinded pathology review, only three patients had visible areas of nodularity or irregularity on HD-WLE or NBI (► **Table 4**). Real-time pCLE identified LGD in three of four patients (75%) who were diagnosed as LGD by both unblinded and blinded pathologists. All patients identified as having dysplasia or cancer on real-time or blinded pCLE re-

view met at least one of the revised criteria proposed by the ASGE Technology Committee [7].

Discussion

Sharma et al. demonstrated improved sensitivity of pCLE compared to WLE [12]. However, in clinical practice, the utility of the technology would rest on its ability to eliminate the need for random biopsies, which are time consuming with resulting low adherence [21]. The aim of our study was to determine whether pCLE met PIVI criteria to consider replacing random biopsies for surveillance of BE in clinical practice [14]. The technology did meet the primary outcome of specificity >80% for HGD and cancer when compared to random biopsies. However, both patients with cancer had visible areas of mucosal irregu-

larity or nodularity on HD-WLE or NBI, so pCLE did not provide any incremental benefit.

Additionally, pCLE did not meet the >90% sensitivity threshold for dysplasia and cancer recommended by the PIVI initiative. Sensitivity was not the primary outcome, so we cannot rule out the possibility that the study was underpowered to minimize type II error. Yet, our results are consistent with those of Bajbouj et al. [10], who marked tentative biopsy sites using argon plasma coagulation (APC), assessed the sites with pCLE, and then obtained biopsies from the sites. In their study, pCLE demonstrated high specificity but sensitivity of only 12–28%. Although their study was not entirely reflective of typical clinical practice, their findings do help corroborate our findings. In our experience, pCLE allows for multiple “optical biopsies” but does not generally permit *in vivo* histologic analysis of the entire BE segment. Also the distal cap improves probe stabilization, but image optimization is not always feasible. These technical limitations may explain the lower sensitivity of the technology. In the one patient with HGD on random biopsy and EMR, we speculate that the pCLE probe did not contact the dysplastic area. Canto et al. demonstrated improved sensitivity of CLE compared to random biopsy using an endoscope-based version of the technology (eCLE, Pentax Medical, Montvale, NJ, USA) that included a wider surface area and provided a more stable image. Unfortunately, this technology is no longer commercially available [11].

For LGD, there was poor inter-observer agreement between pathologists as well as between physicians performing pCLE interpretation. These difficulties in making a conclusive histologic diagnosis of LGD are well documented in the literature, even among gastrointestinal pathologists with a special interest in BE [22]. In our study, the blinded pathologist used standardized criteria that optimized sensitivity, which may account for the high prevalence of LGD (29%) on blinded pathology review [19]. In routine clinical practice, pathologists may be more conservative in their assessment knowing that a diagnosis of LGD could trigger discussion with regard to multiple repeat endoscopies and ablation. Indeed, the prevalence of LGD as assessed by the unblinded pathologists was only 8%. The physician performing blinded pCLE interpretation did not know the clinical history and did not view the endoscopy images, factors that could bias real-time pCLE interpretation. For instance, an endoscopist may lean toward diagnosing dysplasia in patients with a visible nodule, ultra-long segment BE, or prior histologic diagnosis of LGD. These factors may in part account for the inter-observer variability between real-time and blinded pCLE assessments. Despite all of these limitations, both real-time and blinded pCLE demonstrated high specificity (>85%) for the diagnosis of LGD. Additionally, real time pCLE identified LGD in 75% of patients in whom both blinded and unblinded pathologists agreed on the diagnosis. Given the known limitations of histology, patients referred to tertiary referral centers for ablation of LGD frequently undergo a repeat diagnostic endoscopy with biopsies for expert pathologist review. Confirming a diagnosis of LGD with real-time pCLE at the time of repeat endoscopy could increase confidence in the diagnosis, and permit ablation during the same session.

Strengths of the study include its prospective design with a priori sample size calculations, real-time and blinded expert review of pCLE sequences, and interpretation of pathology specimens by unblinded pathologists as well as a blinded expert pathologist. Unlike previously published studies, our goal was to examine the use of pCLE in routine clinical practice (i.e. comparative effectiveness). To our knowledge, this is the first study that attempts to differentiate pCLE findings of LGD from HGD. A limitation of our study is that investigators were not required to strictly adhere to Miami criteria, because the aim was to assess accuracy in routine clinical practice. We did not use validated criteria to distinguish HGD from LGD during real-time pCLE interpretation, and there was significant disagreement between blinded and unblinded pathologists. Although inclusion of subjects was limited to a single tertiary Veterans Affairs (VA) medical center, the demographics of these patients closely resemble those of BE patients in the community setting. We did not collect information to calculate “per optical biopsy” accuracy because our aim was to assess “per patient accuracy” as suggested by the ASGE PIVI. Only three patients in our study had HGD or cancer, which has implications for estimating predictive values of pCLE. However, these findings were well within our sample size estimates, and highlight the cost-effectiveness barriers that any imaging technology faces when used for routine BE surveillance.

In summary, our study demonstrates a high specificity for dysplasia and cancer using pCLE. The relatively low sensitivity and lack of incremental benefit over HD-WLE and NBI may limit its utility in routine surveillance of BE. The technology may have a more limited role for real-time confirmation of LGD, but further study is needed to validate pCLE for this specific indication.

Competing interests

None

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