Confocal laser endomicroscopy in Barrett’s esophagus and endoscopically inapparent Barrett’s neoplasia: a prospective, randomized, double-blind, controlled, crossover trial

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Background: The detection of high-grade dysplasia and cancer in Barrett’s esophagus (BE) can be challenging. Confocal laser endomicroscopy (CLE) allows in vivo visualization of mucosal histology during endoscopy.

Objective: To determine whether CLE with optical biopsy and targeted mucosal biopsy improves the diagnostic yield of endoscopically inapparent, BE-associated neoplasia compared to standard endoscopy with a 4-quadrant, random biopsy protocol.

Design: Prospective, double-blind, randomized, crossover study.

Setting: Single, tertiary-care academic center.

Patients: This study involved patients with BE undergoing routine surveillance or referred for treatment of non-localized, endoscopically inapparent, BE-associated neoplasia.

Intervention: All participants underwent both a confocal endomicroscopy with a targeted biopsy procedure and standard endoscopy with a 4-quadrant biopsy procedure in a randomized order.

Main Outcome Measurements: Increase in diagnostic yield for neoplasia, reduction in mucosal biopsy number, final pathologic diagnosis.

Results: CLE with targeted biopsy almost doubled the diagnostic yield for neoplasia and was equivalent to the standard protocol for the final diagnosis of neoplasia. Two thirds of patients in the surveillance group did not need any mucosal biopsies at all.

Limitation: Single-center study.

Conclusion: CLE with targeted biopsy significantly improves the diagnostic yield for endoscopically inapparent BE neoplasia compared to a standard endoscopy with a random-biopsy protocol. CLE with targeted biopsy also greatly reduces the number of biopsies needed per patient and allows some patients without neoplasia to completely forgo mucosal biopsy. (This trial was registered at www.clinicaltrials.gov, ID number NCT00487695.)

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Abbreviations: BE, Barrett’s esophagus; CA, cancer; CLE, confocal laser endomicroscopy; CLE-TB, confocal laser endomicroscopy with targeted biopsy; EMR, endoscopic mucosal resection; HGD, high-grade dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; SE-RB, standard endoscopy with random biopsy.

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Barrett’s esophagus (BE) increases the risk of esophageal adenocarcinoma, and surveillance for neoplasia is recommended for patients with BE. Current guidelines for endoscopic surveillance recommend a systematic biopsy protocol involving 4-quadrant, random biopsies every 1 to 2 cm for the length of BE. Despite advances in endoscopic imaging and multiple mucosal biopsies, detection of neoplasia in BE can be difficult. Rigorous biopsy protocols still miss high-grade dysplasia (HGD), particularly in flat mucosa without obvious mucosal abnormalities. Furthermore, despite multiple biopsies, the diagnostic yield for neoplasia during surveillance of BE is highly variable depending upon the patient population and prevalence of dysplasia. Hence, during surveillance endoscopy of BE, a large number of biopsy specimens are obtained with a relatively low yield for dysplasia or cancer.

Confocal laser endomicroscopy (CLE) can be used to image the GI mucosa during endoscopy, allowing in vivo microscopic examination of tissues throughout the GI tract. CLE has been used to image neoplasia in the colon, stomach, and esophagus with accurate prediction of mucosal pathology in both normal and abnormal tissues. By using CLE, microscopic images of the mucosa are produced at up to 1250-fold magnification with imaging from the mucosal surface to 250 µm below the surface. With this level of magnification, the specialized intestinal metaplasia and goblet cells of BE can be identified accurately.

The first published study of CLE for BE proposed an endomicroscopy classification system, the Confocal Barrett’s Classification, incorporating vascular structure and cell patterns to distinguish between gastric mucosa, BE, and neoplasia (HGD and cancer) (Table 1). Endomicroscopic changes suggesting the presence of HGD or cancer include the presence of irregular, black cells with a loss of the normal cellular pattern and distorted subepithelial capillaries with leakage of fluorescein. In this study, mucosal biopsy specimens were routinely obtained to allow calculation of CLE performance characteristics. Mucosal pathology was used as the reference standard, and this study showed that the classification system had a sensitivity of 92.9%, specificity of 98.4%, and accuracy of 97.4% for predicting BE-associated neoplasia. These performance characteristics were based upon blinded reading of CLE images after the endoscopic examinations were complete. Furthermore, because the study was designed to develop a CLE classification system for BE, patients with esophageal masses were included. To date, there are no published studies that have validated the Confocal Barrett’s Classification in a prospective, blinded, controlled fashion with in vivo endomicroscopic imaging as the basis for diagnosis. Preliminary data suggest that in vivo CLE imaging may be highly accurate and potentially may enable targeted mucosal biopsy or selective endoscopic treatment within the same procedure, with the patient sedated only once.

The aim of this study was to determine whether CLE with optical biopsy and targeted mucosal biopsy (CLE-TB) improves the diagnostic yield of BE-associated neoplasia compared to standard endoscopy with a 4-quadrant, random biopsy (SE-RB) protocol in patients referred for suspected nonlocalized, endoscopically inapparent HGD or cancer and in patients undergoing routine surveillance of BE.

**PATIENTS AND METHODS**

**Study design and setting**

This prospective, controlled, double-blind (endoscopists and pathologists), crossover trial was conducted at a single, tertiary-care, academic medical center. Each patient underwent confocal endomicroscopy and standard endoscopic examinations, but the order in which CLE-TB and SE-RB were performed was randomized (Fig. 1). Randomization was 1:1 in blocks of 4, according to a computer-generated list.

One endoscopist (M.C.) performed all CLE procedures, whereas a second endoscopist (P.O.) performed all SE procedures. Both endoscopists had more than 10 years of endoscopic experience and clinical practice, including experience with BE and BE-neoplasia patients. The endoscopist performing CLE had completed 30 supervised and 85 independent endomicroscopy procedures. Both endoscopists were aware of the indication for the procedure (routine surveillance or suspected neoplasia) but were blinded to the prior endoscopy and pathology results. The second procedure was performed 2 to 6 weeks after the first, to allow healing of prior biopsy sites and minimize bias during the second procedure.

**Patients**

Patients with BE or BE with suspected nonlocalized, endoscopically inapparent HGD were recruited from the gastroenterology clinics at Johns Hopkins University in...
Baltimore, Maryland, from April 2007 through May 2008. The study was approved by the Johns Hopkins University institutional review board (clinicaltrials.gov NCT00487695). The inclusion criteria were as follows: adults with (1) biopsy-proven BE or (2) biopsy-proven BE with suspected nonlocalized, endoscopically inapparent HGD. Exclusion criteria for the study were known esophageal adenocarcinoma, BE with a biopsy-proven malignant lesion, allergy to fluorescein sodium, coagulopathy, cardiopulmonary instability, active wheezing, or a history of anaphylaxis. All patients enrolled in the study completed a standardized questionnaire used for the Johns Hopkins Barrett’s Esophagus Registry that recorded patient demographics, GI symptoms, duration of BE, and other relevant medical history.

### Standard endoscopy procedure

During the standard endoscopy procedure, the endoscopist performed a videocapsule endoscopic examination by using the Olympus video upper endoscope (GIF 160; Olympus Corporation, Tokyo, Japan). Endoscopic landmarks, including the level of the gastroesophageal junction, Z line, and BE length and pattern (circumferential, tongues, and islands) were recorded. The presence of esophagitis was described by using the Los Angeles classification. The endoscopist evaluated the size, morphology, and location of any visible lesions, which were described by using the Japanese classification of esophageal cancer. Then, biopsy specimens of any discrete lesions were obtained, followed by 4-quadrant, random biopsies of the flat BE mucosa every 1 cm (for suspected neoplasia) or 2 cm (for BE surveillance), beginning at the gastroesophageal junction, moving proximally to the Z line.

### Confocal endomicroscopy procedure

The Pentax endomicroscope (EC3870KCIILK, joint venture between Pentax, Tokyo, Japan, and Optiscan Pty Ltd, Notting Hill, Melbourne, Australia) was used for all endomicroscopy examinations. The endomicroscope is the length of a standard gastroscope, with a 12.8-mm diameter and 2.8-mm channel. The shaft of the endomicroscope is labeled in 1-cm increments to allow accurate measurement of location. The endomicroscope laser has a wavelength of 488 nm, with maximum laser output of <1 mW at the mucosal surface. All images were collected at a scan rate of 0.8 frames per second, giving a resolution of 1024 × 1024 pixels. The field of view is 500 × 500 μm,

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### Table 1. Confocal Barrett’s esophagus classification

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Vessel pattern</th>
<th>Cell pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric epithelium</td>
<td>Capillaries of regular shape visible in the deeper mucosa.</td>
<td>Regular columnar epithelium with round gland openings and cobblestone pattern.</td>
</tr>
<tr>
<td>Barrett’s esophagus</td>
<td>Capillaries of regular shape seen in deeper and upper mucosal layers.</td>
<td>Columnar epithelium with dark, mucin-containing goblet cells in the upper mucosal layer. Deeper mucosa shows dark, cylindrical cells arranged in a villous pattern.</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Irregular capillaries visible throughout the mucosal layer. Vessel leakage leads to heterogeneous and bright lamina propria.</td>
<td>Black cells with irregular borders in contrast to surrounding tissue.</td>
</tr>
</tbody>
</table>


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**Figure 1.** Overall study design. Patients are referred for evaluation of Barrett’s esophagus or Barrett’s esophagus with high-grade dysplasia. All patients have confocal laser endomicroscopy (CLE) with targeted biopsy and standard endoscopy with random biopsy in a randomized order. For patients randomized to CLE first, endoscopist A performs CLE and targeted biopsy. Two to 6 weeks later, the patient has standard endoscopy with 4-quadrant, random biopsies. All biopsy specimens undergo histopathologic examination, and the yields for neoplasia between CLE and standard endoscopy are compared. BE, Barrett’s esophagus; CLE, confocal laser endomicroscopy; HGD, high-grade dysplasia; RB, random biopsy; SE, standard endoscopy; TB, targeted biopsy.
with lateral resolution of 0.7 μm and an optical slice thickness of 7 μm. At each imaging site, multiple images were collected from the surface down to the maximum imaging depth of 250 μm. The standard videoendoscope built into the confocal endomicroscope was used to examine the esophagus, similar to that previously described for the standard endoscopy procedure, recording endoscopic landmarks, BE characteristics, and lesions.

Confocal endomicroscopy was then performed. Five mL of 10% fluorescein sodium (Ak-fluor, Akorn Pharmaceuticals, Lake Forest, Ill) was administered intravenously, and images were acquired by placing the tip of the endomicroscope against the mucosal surface, using suction to stabilize the tip for image acquisition. Discrete lesions were imaged first, then 4-quadrant optical biopsy specimens of the flat BE mucosa were acquired every 1 cm (for suspected neoplasia) or 2 cm (for BE surveillance). Optical biopsy specimens were obtained by imaging from the mucosal surface to a depth of 250 μm to visualize the epithelial cells, lamina propria, and blood vessels. At each optical biopsy site, the endoscopist used the CLE images to predict the histology expected on mucosal biopsy, interpreting each image according to the Confocal Barrett’s Classification,11 differentiating neoplasia from BE and gastric epithelium. For CLE imaging sites suspicious for neoplasia, targeted mucosal biopsy specimens were acquired, guided by the suction polyp created by endomicroscopic imaging. For CLE imaging sites that did not suggest neoplasia, no biopsy specimens were taken. No random mucosal biopsy specimens were acquired during the endomicroscopy procedure.

### Endoscopic mucosal resection

Informed consent was obtained on all patients prior to endoscopy for possible endoscopic mucosal resection (EMR) at the end of the second procedure, if there was endoscopic or CLE evidence of HGD. At the end of the second endoscopic procedure, the study coinvestigator (K.D.) was allowed to unblind the endoscopist and disclose the prior pathologic diagnoses and the location of any areas of biopsy-proven HGD. If an area of localized HGD was detected by endomicroscopy, or if the specific location of HGD was known from prior endoscopy, then EMR was performed by using the Duette multiband ligation device (Cook Medical, Bloomington, Ind). Alternatively, if the second endoscopist felt that a mucosal lesion was highly suspicious for HGD or early cancer, EMR could be performed.

### Pathology

Mucosal biopsy specimens were placed in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin as well as periodic acid-Schiff/Alcian blue stain for identification of goblet cells. Mucosal biopsy specimens were reviewed by the GI pathology service and were rereviewed by an expert BE pathologist (E.M.) who was blinded to the outside pathology results, endoscopic procedure type, endoscopic findings, and CLE diagnoses. Each individual biopsy specimen was graded according to the Vienna classification of GI epithelial neoplasia.19 The individual mucosal biopsies were counted for each procedure for a given patient.

### Statistical analysis

Results for each patient were analyzed in a paired fashion, comparing each patient’s CLE procedure with the patient’s standard endoscopic procedure. The final per-patient histopathologic diagnoses for CLE-TB and SE-RB were compared by using a McNemar test. The primary endpoint, the diagnostic yield (the number of mucosal biopsy specimens showing HGD or cancer divided by the total number of mucosal biopsy specimens), was calculated per patient for each procedure and compared by using the Wilcoxon signed rank test. The secondary endpoints of the mean number of biopsy specimens obtained per patient and mean number of biopsy specimens with HGD were compared by procedure type by using the signed rank test. The prevalence of HGD in lesions and flat mucosa was calculated. Two-tailed $P$ values of <.05 were considered statistically significant.

### Sample size calculation

The sample size calculation was based on the predicted yield for neoplasia by using standard endoscopy and CLE. Based on published studies and prior data collected at Johns Hopkins, the yield for neoplasia of SE-RB was estimated to be 10%, and the neoplasia yield for CLE-TB was estimated to be 40%.6,11 By using an alpha of 0.05 and power of 90%, we calculated a sample size of 37 patients when using a paired design. To allow for dropouts, we planned to enroll 48 patients. Statistical analysis was performed with Stata 9.0 (Stata Corporation, College Station, Tex).

### RESULTS

#### Patient characteristics

Fifty-two patients with BE or suspected BE neoplasia were screened for participation. Six of the screened patients declined to participate, leaving 46 patients who enrolled in the study (18 with suspected HGD and 28 for BE surveillance). A total of 39 patients completed the study, including 16 patients with suspected neoplasia and 23 patients for BE surveillance (Fig. 2). The characteristics of the study participants are listed in Table 2. The mean length of BE was greater in the high-risk group (mean = 6 cm, range 1-11 cm) than in the surveillance group (mean = 4 cm, range 1-10 cm) (Table 3). Half of the high-risk patients and one third of the surveillance patients had circumferential BE. Esophagitis (Los Angeles classification grade B) was identified in only 2 of the study
participants who were enrolled in the surveillance group. No patients were found to have masses or nodules greater than 0.5 cm. In the high-risk group, 9 patients were found to have subtle lesions. There were no lesions in the routine surveillance group.

**Final pathologic diagnosis**

We established the final pathologic diagnosis by recording the highest grade of neoplasia from the blinded reading of the 2 sets of mucosal biopsy specimens from the SE-RB and CLE-TB procedures (Table 2).

In the high-risk group referred for suspected non-localized neoplasia, 13 cases of HGD and no cancers were identified. CLE-TB and SE-RB each detected 11 cases of HGD, and there was no statistically significant difference in neoplasia detection by the 2 methods ($P = 1.0$). Four patients in the study had discordant final diagnoses. For the 2 cases of neoplasia detected only by SE-RB, the random biopsy protocol found a single biopsy specimen showing focal HGD. For the 2 cases of neoplasia detected by CLE-TB alone, CLE found areas of HGD not detected by standard endoscopy: 1 area of HGD in 1 case and 2 areas of HGD in the second case.

In the surveillance endoscopy group, 1 patient had a single biopsy specimen obtained in the setting of esophagitis during SE-RB interpreted as focal HGD, which could not be confirmed on 3 subsequent endoscopic procedures performed after treatment with double-dose proton pump inhibitors. Otherwise, no cases of neoplasia were identified in the surveillance group by SE-RB or CLE-TB.

**Mucosal biopsy number per procedure and the diagnostic yield for neoplasia**

In the 16 patients with suspected high-grade dysplasia, CLE-TB led to a significant, 59% decrease in the number of mucosal biopsy specimens taken per patient during endomicroscopy compared to SE-RB (9.8 biopsies vs 23.8 biopsies; $P = .002$) (Table 4). Furthermore, despite fewer total biopsies, the mean number of mucosal biopsy specimens per patient showing HGD or cancer was not significantly different between the groups, with 3.1 and 3.7 neoplastic biopsy specimens obtained during CLE-TB and SE-RB, respectively ($P = .89$). The diagnostic yield for neoplasia with CLE-TB was 33.7% (95% CI, 15.2%-52.2%), whereas the diagnostic yield for neoplasia during SE-RB was 17.2% (95% CI, 6.2%-28.2%), giving a difference in yield of 16.5% (95% CI, 5.2%-27.8%; $P = .01$) (Table 4). In BE patients undergoing surveillance, the mean number of mucosal biopsies was 87% lower during CLE-TB than during SE-RB (1.7 vs 12.6; $P < .0001$) (Table 4). Sixty-five percent of the 23 patients undergoing surveillance endoscopy did not need any mucosal biopsies during CLE-TB, as the in vivo endomicroscopic imaging did not suggest BE with neoplasia. No patient in the surveillance group was found to have HGD. Hence, the diagnostic yield for HGD for both CLE-TB and SE-RB was zero.

**Prevalence of HGD or cancer in lesions**

No patients in the surveillance group were found to have lesions during the study period. Nine of 16 patients (56%) in the high-risk group had 17 subtle mucosal
lesions. One patient had 4 lesions, 1 patient had 3 lesions, 3 patients had 2 lesions, and 4 patients had 1 lesion. Of the 17 lesions identified, 9 were Japanese classification type 0-IIa (superficial flat, slightly elevated), 2 were type 0-IIc (superficial flat, slightly depressed), 2 were type 0-I (superficial protruding), and 4 were type I (small polypoid lesions) (Table 2). Only 9 out of 17 (53%) of the mucosal lesions contained HGD or cancer by mucosal biopsy or EMR. The other 8 lesions in the high-risk patients contained nondysplastic BE, BE with low-grade dysplasia (LGD), BE with indefinite dysplasia, or gastric cardia.

**CLE-guided EMR**

Two patients had EMR during their CLE-TB procedures. The decision to perform EMR was based on CLE images of flat mucosa suggesting HGD. In 1 patient, a small, flat, BE island was found to have changes suggestive of HGD by using CLE: dark, irregular cells and loss of the normal glandular pattern (Fig. 3). EMR was performed, and subsequent histopathologic examination confirmed the presence of HGD (Fig. 3). The second patient with flat, endoscopically apparent HGD also underwent EMR, based on endomicroscopic imaging, and histopathology confirmed the presence of HGD. Four EMRs were performed at the end of the SE-RB procedure. Of these, 2 were based on endoscopic appearance of the mucosa suspicious for neoplasia, as lesions were present. One EMR showed LGD, whereas the other had nondysplastic BE on histopathology. The other 2 EMRs were performed per protocol when the endoscopist was unblinded and informed by the study coordinator about the location of biopsy-confirmed HGD found during prior CLE. The results of these EMRs showed HGD for 1 patient and LGD for the other.

**CLE imaging time**

Procedure times were not a major endpoint of the study. The study protocol did not allow complete recording of the time needed to perform CLE and acquire mucosal biopsy specimens. However, approximate times were available for a subset of the study sample. Esophageal imaging with CLE added a median of 18 minutes to the procedure time (interquartile range [IQR] 12-22 minutes). In contrast, the time spent acquiring targeted mucosal biopsy specimens during CLE (median 1.5 minutes, IQR 0-5 minutes) was shorter than the time needed for biopsies during SE-RB (median 9 minutes, IQR 5-15 minutes) (P < .001). For patients with long BE (>6 cm), the median imaging time was 23.5 minutes (IQR 20-32.5 minutes). The median time spent acquiring mucosal biopsy specimens during CLE in patients with long BE was 5 minutes (IQR 1-6 minutes) compared to 14.5 minutes (IQR 10-18.5 minutes) during SE-RB (P < .001). For patients with short BE
(<3 cm), the median time spent imaging was 10 minutes (IQR 7-16 minutes). The median time spent acquiring targeted mucosal biopsy specimens in short BE was 0 minutes (IQR 0-2 minutes) during CLE, compared to 4 minutes (IQR 3-6 minutes) during SE-RB (P <.02).

**Complications**

All study-related procedures were performed with intravenous propofol administered by the anesthesiology department. There were no serious complications related to SE-RB or intravenous fluorescein sodium during CLE.

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**TABLE 4. Diagnostic yield for neoplasia, per-patient analysis**

<table>
<thead>
<tr>
<th></th>
<th>High-risk group, n = 16 (suspected HGD or CA)</th>
<th>Surveillance group, n = 23</th>
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<tbody>
<tr>
<td></td>
<td>CLE-TB</td>
<td>SE-RB</td>
</tr>
<tr>
<td>Mean number of biopsies with HGD or CA (range)</td>
<td>3.1 (0-15)</td>
<td>3.7 (0-19)</td>
</tr>
<tr>
<td>Mean number of mucosal biopsy specimens obtained (range)</td>
<td>9.8 (1-22)</td>
<td>23.7 (3-41)</td>
</tr>
<tr>
<td>Mean diagnostic yield (% biopsy results positive for HGD or CA)</td>
<td>33.7%</td>
<td>17.2%</td>
</tr>
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</table>

CA, Esophageal adenocarcinoma; CLE-TB, confocal laser endomicroscopy with targeted mucosal biopsy; HGD, high-grade dysplasia; SE-RB, standard endoscopy with random mucosal biopsy.

**Figure 3.** A, Unmagnified, standard white-light endoscopic image of a tiny island of Barrett’s esophagus obtained with the endomicroscope prior to endoscopic imaging. B and C, Confocal endomicroscopy images of the island show glands with irregularly shaped, distorted, dark cells; indistinct cell borders; and loss of normal crypt architecture, suggestive of high-grade dysplasia. D, Histopathology confirmed Barrett’s esophagus with high-grade dysplasia in the endoscopic mucosal resection specimen (H&E, orig. mag. ×100).
One postprocedure pneumonia occurred after a CLE procedure. This resulted in a 2-day hospitalization and complete resolution of the infection after antibiotic therapy.

**DISCUSSION**

This is the first prospective, randomized, controlled, blinded trial that validates the Confocal Barrett’s Classification for in vivo prediction of mucosal histopathology. It also demonstrates the potential role of in vivo endoscopic diagnosis with CLE for the surveillance of BE. By combining in vivo CLE diagnosis with targeted mucosal biopsy, we demonstrated significant reduction in the number of mucosal biopsies required for surveillance of BE in patients undergoing routine surveillance and those referred for suspected endoscopically inapparent, nonlocalized neoplasia. There was an almost 60% reduction in the number of mucosal biopsies required to make a diagnosis of neoplasia, comparing CLE-TB to SE-RB. Importantly, the detection of HGD by using CLE-TB and SE-RB was comparable, despite CLE-TB obtaining significantly fewer biopsy specimens. Hence, CLE-TB almost doubled the diagnostic yield of mucosal biopsies for neoplasia compared to SE-RB (33.7% vs 17.2%). In addition, almost two thirds of patients in the routine surveillance group did not need any mucosal biopsies during CLE because of the absence of neoplasia during in vivo imaging. The biopsy reduction in these patients without suspected neoplasia was even greater, with an 86% reduction in the number of biopsies needed during CLE-TB compared to SE-RB. The first CLE study by Kiesslich et al in BE reported a potential reduction of neoplasia during in vivo imaging. The biopsy reduction was calculated based on the study data plus CLE, with the endomicroscopist performing both procedures on the same patient. This was not feasible but not prospectively studied. Our study demonstrates that CLE led to a reduction in the number of biopsies needed during CLE-TB compared to SE-RB. The first CLE study by Kiesslich et al in BE reported a potential reduction in the number of mucosal biopsies needed, as only 30 of 156 (19.2%) CLE sites in 63 patients examined would have required a mucosal biopsy for confirmation of the diagnosis of neoplasia. However, this potential biopsy reduction was calculated based on the study data but not prospectively studied. Our study demonstrates that CLE led to a reduction in the number of biopsies needed. Furthermore, all CLE interpretation in this study was performed in real time, which differs from other studies of endomicroscopy in BE. The performance characteristics for the in vivo diagnosis of BE and associated neoplasia are not well-characterized and require further investigation. This study could not assess accuracy because mucosal biopsy was not routinely performed during the CLE procedure if in vivo CLE imaging did not show HGD or cancer. The final pathologic diagnoses suggest comparable detection of neoplasia between SE-RB and CLE-TB.

We chose a crossover design for this study to help ensure a fair comparison between CLE and standard endoscopy. To reduce the potential for bias and to minimize interobserver variability in CLE image interpretation, one endoscopist performed all CLE-TB procedures and a second endoscopist performed all SE-RB procedures. Both endoscopists were blinded to the details of prior endoscopies and pathology results to reduce the potential for bias. In addition, the study GI pathologist examined all the study biopsy specimens and was blinded to the suspected diagnosis, endoscopy findings, and CLE findings. We excluded patients with known masses and lesions from this study and focused on patients with nonlocalized, endoscopically inapparent neoplasia. Some subtle lesions were identified during the study, but only 53% of the lesions showed HGD, and none showed cancer. This is comparable to other published reports. In 1 study of high-resolution endoscopy, only 17 of 30 (57%) suspicious lesions were shown to have HGD or cancer on biopsy. Thus, even when mucosal lesions are present in BE, accurate endoscopic identification of HGD and cancer is still challenging. Our study demonstrates the potential clinical utility of in vivo CLE for localization and detection of HGD in flat BE mucosa. In our study, EMR was possible in 2 high-risk patients with endoscopically inapparent HGD who had CLE as the second procedure. By comparison, 3 of the 4 EMRs performed on endoscopically suspicious mucosal lesions at the end of the standard endoscopy procedure were unnecessary. The use of CLE could potentially impact in vivo decision-making for the treatment of localized HGD or early cancer by allowing EMR during the same procedure, potentially reducing the difficulty of relocating the precise site of HGD at a later time. Our study was not designed to compare the potential clinical impact of the CLE diagnosis on the decision to perform EMR. Future studies should examine how in vivo endomicroscopic diagnosis might allow selective and immediate application of EMR. The additional time needed to perform CLE after SE was not a major endpoint of this study, but it is an important issue. This would be best addressed by a study comparing the time difference of SE alone versus SE plus CLE, with the endomicroscopist performing both procedures on the same patient. This was not feasible with the design of this study. With current CLE imaging technology, the additional time needed to perform CLE beyond SE is influenced by BE length, prevalence of neoplasia, and operator experience. From our study data, the time needed for acquisition of mucosal biopsy specimens was shorter with CLE than with SE, particularly in patients with long BE. A multicenter study of CLE in BE is also planned to address this issue.

There are several limitations to our study. Our study is relatively small and based in a single-center, tertiary-care academic referral center. However, despite the small sample size, the crossover, paired-study design provided significant power (90%) for our study results. The participants in this study may not be representative of the general U.S. population, as our hospital is a referral center for BE and endoscopic therapy of neoplasia; however, our study population included both an enriched population of patients with suspected nonlocalized neoplasia.
neoplasia as well as patients undergoing routine surveillance. In addition, we excluded patients with obvious cancers and lesions, which differs from prior studies. The interobserver variability for the in vivo endomicroscopic findings is unknown, and we were unable to evaluate in vivo interobserver agreement, because only one endoscopist performed CLE. This was not a primary endpoint of our study but is an important issue that needs to be addressed by future studies of CLE. Preliminary data on the interobserver agreement of the interpretation of selected CLE images appears to be moderate to substantial, particularly with respect to GI neoplasia. The in vivo interobserver agreement of the interpretation of selected CLE images appears to be moderate to substantial, particularly with respect to GI neoplasia. The in vivo interpretation with CLE is likely to be influenced by technical factors, operator experience, and disease prevalence. Finally, the only contrast agent available at our institution for CLE is fluorescein sodium, which does not stain the nuclei of cells. However, high-grade neoplasia and cancer can still be distinguished from nondysplastic BE with pattern recognition by using the published Confocal Barrett’s Classification. In the future, improvements in endomicroscopic imaging technology and molecular markers may obviate the need for imaging with nonspecific agents such as fluorescein. This may enhance the application of CLE to BE surveillance. The current Pentax endomicroscope is equipped only with standard videomicroscopic resolution without mucosal enhancement features. The diagnosis of BE-associated neoplasia might be significantly altered if high-resolution endoscopy is used with other mucosal enhancement techniques, such as narrow-band imaging, autofluorescence, or chromoendoscopy. However, at this time, none of the newer imaging modalities have been clearly shown to be significantly better than endoscopy with a 4-quadrant, random biopsy protocol or high-resolution endoscopy alone. Hence, the current standard of practice for detection of neoplasia in BE involves a systematic biopsy protocol after careful white-light endoscopy.

CONCLUSIONS

In summary, our study shows that in vivo imaging with CLE and targeted mucosal biopsy of imaging abnormalities is superior to standard endoscopy with 4-quadrant, random biopsy for detection of endoscopically inapparent neoplasia in Barrett’s esophagus. The number of biopsies required to make a diagnosis was significantly lower, and the diagnostic yield for neoplasia was higher, suggesting that CLE-TB may assist the endoscopist with doing “smarter” biopsies. Our study demonstrates how CLE can enable more selective sampling of the mucosa, without the need for the gastroenterologist to replace the pathologist. Future studies will need to evaluate the clinical impact of in vivo diagnosis with CLE on the immediate endoscopic treatment of BE with associated neoplasia.

REFERENCES


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