Real-Time Increased Detection of Neoplastic Tissue in Barrett's Esophagus with Probe-Based Confocal Laser Endomicroscopy: Final Results of an International Multicenter, Prospective, Randomized, Controlled Trial

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Real-time increased detection of neoplastic tissue in Barrett's esophagus with probe-based confocal laser endomicroscopy: final results of an international multicenter, prospective, randomized, controlled trial

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Abstract

Background—Probe-based confocal laser endomicroscopy (pCLE) allows real-time detection of neoplastic Barrett's esophagus (BE) tissue. However, the accuracy of pCLE in real time has not yet been extensively evaluated.

Objective—To compare the sensitivity and specificity of pCLE in addition to high-definition white-light endoscopy (HD-WLE) with HD-WLE alone for the detection of high-grade dysplasia (HGD) and early carcinoma (EC) in BE.

Design—International, prospective, multicenter, randomized, controlled trial.

Setting—Five tertiary referral centers.

Patients—A total of 101 consecutive BE patients presenting for surveillance or endoscopic treatment of HGD/EC.

Interventions—All patients were examined by HD-WLE, narrow-band imaging (NBI), and pCLE, and the findings were recorded before biopsy samples were obtained. The order of HD-WLE and NBI was randomized and performed by 2 independent, blinded endoscopists. All suspicious lesions on HD-WLE or NBI and 4-quadrant random locations were documented. These locations were examined by pCLE, and a presumptive diagnosis of benign or neoplastic (HGD/EC) tissue was made in real time. Finally, biopsies were taken from all locations and were reviewed by a central pathologist, blinded to endoscopic and pCLE data.

Main Outcome Measurements—Diagnostic characteristics of pCLE.

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Results—The sensitivity and specificity for HD-WLE were 34.2% and 92.7%, respectively, compared with 68.3% and 87.8%, respectively, for HD-WLE or pCLE ($P = .002$ and $P < .001$, respectively). The sensitivity and specificity for HD-WLE or NBI were 45.0% and 88.2%, respectively, compared with 75.8% and 84.2%, respectively, for HD-WLE, NBI, or pCLE ($P = .01$ and $P = .02$, respectively). Use of pCLE in conjunction with HD-WLE and NBI enabled the identification of 2 and 1 additional HGD/EC patients compared with HD-WLE and HD-WLE or NBI, respectively, resulting in detection of all HGD/EC patients, although not statistically significant.

Limitations—Academic centers with enriched population.

Conclusions—pCLE combined with HD-WLE significantly improved the ability to detect neoplasia in BE patients compared with HD-WLE. This may allow better informed decisions to be made for the management and subsequent treatment of BE patients.

Barrett's esophagus (BE) is the premalignant lesion for adenocarcinoma of the esophagus and gastroesophageal junction.[1] It is a condition in which the squamous mucosa of the distal esophagus is replaced by columnar mucosa, specifically, intestinal metaplasia. The current standard of endoscopy with biopsies has several limitations, including sampling error and inconsistent histopathological interpretation. Moreover, dysplastic epithelium is often inconspicuous, patchy, and macroscopically indistinguishable from metaplastic tissue. New endoscopic imaging techniques to improve the accuracy of endoscopic diagnosis have been developed, with various degrees of evaluation already performed.[2–7] These optical-based techniques, such as high-definition white-light endoscopy (HD-WLE), narrow-band imaging (NBI), and confocal laser endomicroscopy (CLE), can generally be categorized as broad-field (red-flag techniques) and focal imaging techniques. The broad-field techniques are good for providing an overview of the entire BE segment, whereas focal techniques can provide greater detail of the area of interest.

WLE has improved considerably with the availability of high-definition video endoscopes. This allows more detailed examination of the mucosal, glandular, and vascular structures.[2,3] NBI is a technique that increases the mucosal contrast without the use of dyes, based on differential light penetration in the tissue, depending on its wavelength, and can be used as a broad-field evaluation technique.[4] Probe-based CLE (pCLE) is a focal technique that provides dynamic microscopic views of the mucosa in real-time during an ongoing procedure.[8–10] This development has improved the visualization of the subtle BE lesions to a point where we can see the cellular details in vivo during endoscopy, allowing a diagnosis to be made in the GI endoscopy unit. However, the comparative sensitivities of these enhanced endoscopic techniques are not known.

STUDY AIMS

The primary aim was to evaluate the per-location sensitivity and specificity of pCLE in addition to HD-WLE compared with HD-WLE alone for the detection of high-grade dysplasia (HGD) and early carcinoma (EC) in BE patients.

Secondary aims included the evaluation of per-location sensitivity and specificity of each individual imaging modality (HD-WLE, NBI, pCLE); per-location sensitivity and specificity of pCLE in addition to HD-WLE or NBI (HD-WLE or NBI or pCLE); and activity-specific procedure time, total procedure time, procedure complexity, and potential training effect.

PATIENTS AND METHODS

Study subjects

The study protocol was approved by the institutional review board of all participating institutions and conducted according to the Declaration of Helsinki. All patients provided written, informed consent.

Consecutive patients undergoing BE surveillance and/or referred for BE-associated neoplasia (HGD/EC) evaluation and treatment were prospectively enrolled in this trial at 5 hospitals (Mayo Clinic, Jacksonville, Fla; Columbia University Medical Center, New York, NY; Veterans Affairs Hospital, Kansas City, Mo; Centre Hospitalier Universitaire, Nantes, France; Klinikum rechts der Isar, Munich, Germany). All patients enrolled in the study received proton-pump inhibitor treatment for at least 2 weeks before enrollment. Patients with erosive esophagitis, inability to obtain biopsy samples because of anticoagulation, varices, known allergy to sodium fluorescein, pregnancy, presence of an esophageal mass or nodule greater than 10 mm, and renal insufficiency were excluded from the trial.

Pre-enrollment training

Of the 11 investigators who performed pCLE procedures during the study, only 4 had previous experience with pCLE. Before enrolling the first patient, each endoscopist completed a standard training module consisting of NBI and pCLE videos and still images. The criteria used for interpreting pCLE videos were described previously.[9] Each endoscopist completed a review of 20 unknown video cases and had to repeat the test until a minimum score of 90% correct diagnoses was reached before being allowed to enroll patients.

Study design

Although not necessary for the primary aim of the study, a randomization was performed between the HD-WLE and NBI endoscopic procedures to evaluate the individual diagnostic performances and contribution of each imaging modality (Fig. 1). A tandem design was adopted in which each location/patient acted as its/his or her own control. All patients underwent examination of their BE segment by 3 imaging modalities: HD-WLE, NBI, and pCLE (procedures 1, 2, and 3). The order of procedures 1 and 2 was randomized before pCLE imaging and tissue sampling. Every attempt was made to blind the endoscopist to each patient's history and previous endoscopic findings.

Patients were randomly allocated to the 2 endoscopy sequences (HD-WLE followed by NBI, NBI followed by HD-WLE) via regulatory-compliant electronic data capture software (VISION-EDC system; Prelude Dynamics, Austin, Tex). Patients were randomized in a 1:1 ratio in blocks of 2 stratified by study site and procedure indication (BE surveillance or BE treatment). The electronic data capture system was used to collect data starting with patient screening and eligibility check and to randomize patients.

Endoscopic procedures

Procedure 1: HD-WLE—All patients underwent standard HD-WLE examination using an Olympus 180 HD endoscope (Olympus Inc, Center Valley, Pa) in white-light mode (using a 4-mm clear cap distal attachment without magnification). The BE length was measured from the gastroesophageal junction to the proximally displaced squamocolumnar junction and recorded using the Prague C & M criteria.[11] If visible lesions were identified (suspicious for neoplasia), they were graded using the Paris classification system and their distance and clock position (eg, 38 cm, 8 o'clock) were recorded.[12] Biopsy samples were not obtained until after all procedures (1, 2, and 3) were complete.

Procedure 2: NBI—Each patient also underwent NBI endoscopy examination using the same Olympus 180 HD endoscope in the NBI mode (using a 4-mm clear cap distal attachment without magnification). In addition to the recording of all visible lesions by NBI (as described for procedure 1), any abnormal mucosal and/or vascular patterns seen with NBI were also identified as suspicious locations.[6]

Unblinding and location matching: After procedures 1 and 2 were complete and all suspicious locations documented by each technique had been noted, the individual results of the first and second procedures were unblinded. Locations were paired carefully (if applicable) during the unblinding step. Any suspicious location that remained unclear was resolved by review of the photographs (by each procedure) by both endoscopists to match each site.

Procedure 3: pCLE—pCLE examination was performed using a confocal miniprobe (GastroFlex UHD, Cellvizio; Mauna Kea Technologies, Paris, France), which has a field of view of 240 μm, a lateral resolution of 1 μm, and an imaging depth of 60 μm below the tissue surface. A previously published methodology was used to precisely match the pCLE examination and the biopsy sampling.[9] The immediate vicinity of each location was "marked" using spot coagulation with argon plasma coagulation (ERBE, Tübingen, Germany). Suspicious (targeted) locations were marked first, followed by nontargeted (NBI and HD-WLE) normal random sites. After injection of sodium fluorescein (2.5 mL, 10%), the pCLE miniprobe was passed through the endoscope accessory channel and placed in gentle contact with the BE surface. pCLE imaging was performed at all suspicious (observed by either WLE or NBI) and random locations (ie, 4 quadrants every 2 cm per the Seattle surveillance protocol). The investigator made a presumptive diagnosis of dysplastic (HGD/EC) or nondysplastic at each site examined by pCLE before biopsy samples were obtained.

Additional data collection: The total time required for each procedure was recorded from endoscope insertion to removal. The time was divided into HD-WLE inspection, NBI inspection, argon plasma coagulation marking, pCLE inspection, and biopsy time. Procedure complexity was also captured prospectively during the study by grading on a 5-point Likert scale from 1 (easy) to 5 (difficult), including the ease of performing pCLE, ease of interpreting pCLE images, and ease of performing biopsies.

Histopathological assessment

Each biopsy sample was placed in a separate jar and analyzed individually. Alternatively, when placed in the same jar, the 4 biopsy samples (from 1 level, eg, 38 cm) were stained with 4 different inks representing a different quadrant (and documented). All deidentified slides were sent for central pathology and read by a single blinded expert GI pathologist. Each biopsy was classified as squamous epithelium, gastric metaplasia, intestinal metaplasia without dysplasia, low-grade dysplasia (LGD), HGD, or EC according to published standards.[13]

Data collection, analysis, and sample size

The proportions of lesions classified as suspicious or nonsuspicious by HD-WLE, NBI, and pCLE were tabulated by the presence and absence of disease (ie, HGD/EC) based on histological diagnosis (criterion standard). Estimates and 95% confidence intervals were calculated for the primary aims. Statistical significance calculations (*P* values) were performed for individual procedures (HDWLE, NBI, pCLE) and their combinations using repeated-measures log-linear models. Calculations for procedure times were also performed with analyses of covariance (including maximum BE extent) on within-subject differences

of completion times. HD-WLE, NBI, pCLE, and biopsies were compared with regard to the mean time to completion using a repeated-measures linear model with pairwise contrasts corrected for multiple comparisons using the Tukey method. All statistical testing was 2 sided at a significance level of 5% using SAS version 9.2 for Windows (SAS Institute, Cary, NC).

Based on published literature, a numerical simulation was performed assuming that HD-WLE sensitivity was 79% and specificity was 75%.[14] Power calculations indicated that, with these assumptions, the study would attain a power of 80% with 100 subjects and 10 locations per subject if the sensitivity and specificity of pCLE in addition to HD-WLE were both equal to 90%.

RESULTS

Patient characteristics

Between November 2008 and September 2009, 122 consecutive BE patients were prospectively enrolled at the 5 participating centers by the investigators at each site. Of the enrolled patients, 21 were excluded from the analysis (Fig. 1). The mean age of the patients was 65.1 years (range 27–90 years), and 14% were women (Table 1). The mean (standard deviation) Prague C & M extents were 1.91 (2.95) and 3.61 (3.24) cm, respectively. Fifty-seven patients were referred for routine BE surveillance, whereas 44 were referred for management of a history of HGD/EC.

From the enrolled patients, a total of 955 locations (from 122 patients) were identified, of which 874 were available for final analysis. Locations were excluded from the analysis for patients withdrawn or screen failures (25 locations), absence of central pathology reading because of insufficient tissue/lost slides (35 locations), or if EMR samples rather than forceps biopsy samples were obtained (21 locations).

Neoplasia distribution in study population

Using the worst location diagnosis (from any of the targeted or 4-quadrant random biopsies) to define the patient's disease status, of the 101 patients, 66 (65%) had no dysplasia (intestinal metaplasia only), 4 (4%) had LGD, 6 (6%) had HGD, and 25 (25%) had EC. Of the 31 patients with HGD/EC, 27 had endoscopically visible small lesions on examination with HD-WLE. Four were referred for routine BE surveillance and 27 for known HGD/EC. On a per-location distribution, 143 locations were suspicious on HD-WLE or NBI and 731 were true random locations. A total of 728 locations (83%) had no dysplasia, 26 (3%) had LGD, 60 (7%) had HGD, and 60 (7%) had cancer.

Primary endpoint: per-location analysis on sensitivity and specificity of HD-WLE versus HD-WLE or pCLE

A location was ruled as positive on biopsy if pathology interpretation was HGD/EC; positive on pCLE if HGD/EC was suspected based on pCLE images (Fig. 2); and positive on HD-WLE/NBI if a suspicious location was identified by the investigator. Combining modalities meant that a location was considered positive if at least 1 modality was positive. All random 4-quadrant locations were considered negative on HD-WLE and NBI.

Table 2 displays the results for the primary outcomes using these definitions. The sensitivity and specificity for HD-WLE were 34.2% and 92.7%, respectively, compared with 68.3% and 87.8%, respectively, for HD-WLE or pCLE ($P = .002$ and $P < .001$, respectively). This translated into 41 additional locations with HGD/EC being identified when pCLE was used

in conjunction with HD-WLE compared with HD-WLE alone. The relative sensitivity (using 95% CI) between HD-WLE and HD-WLE or pCLE was 2.0 ($P = .002$).

Secondary endpoints: per-location accuracy analyses

Table 3 displays the results of the per-location analyses for each imaging modality along with various combinations. NBI alone had a higher sensitivity than HD-WLE alone, but this was not statistically significant ($P = .29$). pCLE alone was more sensitive than HD-WLE alone ($P = .02$) and NBI alone ($P = .13$), while having no difference in specificity. When areas that appeared abnormal (ie, visible lesions) during HD-WLE examination were excluded, the sensitivity and specificity of pCLE alone were 51.9% and 94.7%, respectively, resulting in detection of 41 additional areas of HGD/EC. When areas that appeared abnormal (ie, visible lesions) during HD-WLE or NBI examination were excluded, the sensitivity and specificity of pCLE alone were 56.1% and 95.5%, respectively, resulting in detection of 37 additional areas of HGD/EC.

The addition of NBI to HD-WLE did not result in any statistically significant differences in sensitivity ($P = .11$), but was less specific ($P < .01$). Compared with HD-WLE or NBI, HD-WLE or pCLE had higher sensitivity ($P < .001$) but similar specificity ($P = .87$). HD-WLE or NBI or pCLE was more sensitive ($P = .01$) and less specific ($P = .02$) compared with HD-WLE or NBI, and it had similar sensitivity ($P = .25$) and specificity ($P = .05$) compared with HD-WLE or pCLE. The combination of HD-WLE or NBI or pCLE had the highest sensitivity with 37 additional HGD/EC locations identified compared with HD-WLE or NBI alone.

Secondary endpoints: per-patient accuracy analysis

Thirty-one patients were diagnosed with HGD/EC as the worst diagnosis with any 1 of the locations being read as such by central pathology (Table 4). The use of pCLE in conjunction with HD-WLE and HD-WLE or NBI resulted in identifying 2 and 1 additional HGD/EC patients compared with HD-WLE and HD-WLE or NBI, respectively, resulting in the detection of all HGD/EC patients in the second case (100% sensitivity for HD-WLE or NBI or pCLE). However, there were no statistically significant differences in sensitivity between any of the imaging strategies.

Secondary endpoints: procedure time, complexity, and training effect

The mean total procedure time was 30 minutes 7 seconds, and the mean time needed to perform pCLE examination was 9 minutes 8 seconds. To assess the presence of a potential training effect, procedure durations for the initial half of enrolled patients (n = 44) were compared with those of the second half of patients (n = 45) at the 3 clinical sites that enrolled more than 20 patients. There were no significant differences with regard to the mean duration of pCLE, HD-WLE, or NBI. There were also no significant differences between the BE extents: (C [cm]) (first half, 1.9 ± 2.8; second half, 1.5 ± 2.6; $P = .52$) or (M [cm]) (first half, 3.7 ± 3.7; second half, 3.2 ± 2.7; $P = .48$) among the enrolled patients.

With restriction to the 3 centers that enrolled more than 10 subjects, the percentages of subjects who scored 1 or 2 with regard to the ease of performing pCLE (79.3%), interpreting pCLE images (77%), and performing biopsies (81.6%) were not significantly different from each other (performing pCLE vs biopsy, $P = .70$; interpreting pCLE images vs biopsy, $P = .45$; performing pCLE vs interpreting pCLE images, $P = .71$).

Secondary endpoint: reduction in biopsies

Based on the study data, if targeted and random 4-quadrant biopsies were only performed in patients with suspicious lesions (visualized either by HD-WLE, NBI, or pCLE), 39% of patients could forego biopsies, and none of the patients with HGD/EC would be missed.

DISCUSSION

Guidelines recommend that patients with BE undergo surveillance endoscopy with the goal of detecting dysplasia and early esophageal adenocarcinoma.[15,16] HD-WLE has markedly improved the endoscopy image quality and is now widely used for surveillance endoscopy. NBI, a method of electronic chromoendoscopy, has been shown to be superior to WLE in detecting significantly more patients with dysplasia.[17] This maintains the need to rely on subsequent histopathological assessment and interpretation for patient management.

pCLE is an in vivo imaging tool that has the ability to display real-time histology to the endoscopist.[8–10] Previous studies (nonrandomized, controlled trials) have shown a high sensitivity and specificity of pCLE in diagnosing HGD/cancer in BE patients. In a pilot study, Pohl et al[9] evaluated the preliminary accuracy of pCLE for HGD and EC in BE patients. They evaluated 296 biopsy sites from 38 patients with a median BE length of 3 cm. The overall accuracy of pCLE was 88% to 93%, with sensitivity of 75% to 80%, and specificity of 89% to 94%, a positive predictive value of 44.4%, and a negative predictive value (NPV) of 98.8%. Likewise, Kiesslich et al,[18] using an integrated endoscope–based CLE system (joint venture between Pentax, Tokyo, Japan, and Optiscan Pty Ltd, Melbourne, Australia), were able to achieve a high accuracy both in the diagnosis of BE metaplasia and neoplasia (96.8% and 97.4%, respectively). The interobserver agreement using pCLE was assessed prospectively in a study by Wallace et al,[19] which constituted the training phase of the current study. There was good overall agreement on the pCLE diagnosis (κ = 0.72 [95% CI, 0.58–0.86]); endoscopists with previous pCLE experience had a much higher agreement (κ = 0.83 [95% CI, 0.64–1.0]). These results suggest that pCLE for the diagnosis of neoplasia in BE has high accuracy and reliability with a short associated learning curve. Finally, using an endoscope-based CLE system, Dunbar et al[20] also demonstrated an increased yield of neoplasia compared with a 4-quadrant biopsy protocol. Although the sensitivity of pCLE found in this study was lower than that found in some of the previous studies, this study used real-time prediction of histology, had 11 endoscopists from multiple centers, and used different criteria to interpret pCLE results, which may have contributed to the variable results.[18]

To our knowledge, this is the first international, multi-center, prospective, randomized, controlled trial that has demonstrated significantly improved sensitivity in detecting HGD/EC using pCLE. pCLE had per-location sensitivity and specificity of 62.5% and 92.7%, respectively, compared with 34.2% and 92.7%, respectively, for HD-WLE, the primary aim of the study. This resulted in a twofold increase in sensitivity for the detection of HGD/EC (from 34.2% to 68.3%), although with a minimal decrease in specificity (from 92.7% to 87.8%) when pCLE was used in combination with HD-WLE compared with HD-WLE alone. Overall, the combination of pCLE with HD-WLE led to the recognition of 41 additional locations with HGD/EC compared with HD-WLE alone. There was no statistically significant learning curve when the early patients (initial 50%) were compared with the late patients (last 50%). Furthermore, the ease of pCLE use and image interpretation was not considered more difficult by the endoscopist than that of obtaining a biopsy sample.

There are several potential clinical implications of pCLE use in the BE clinical setting. The improved sensitivity with the detection of additional neoplastic areas has a significant

impact on the clinical management in the era of endoscopic treatment of HGD/EC. If additional areas within a BE segment with HGD/EC were identified, the endoscopist may change the course of treatment with more widespread mucosal resection and/or submucosal dissection. Thus, a case can be made for real-time decision making and possible treatment with EMR or ablative therapies in selected patients after diagnosing HGD/EC using pCLE. On the other hand, a high NPV offers a higher degree of confidence in confirming the absence of HGD/EC and is highly desirable for a better informed decision as to where tissue should be sampled. In this prospective study, we were able to show that the NPV of pCLE used in combination with HD-WLE was 91% and was 95.6% when combined with both HD-WLE and NBI. This can, in turn, translate into a high degree of confidence in ruling out dysplasia during surveillance endoscopy.

There are several limitations to our study. Our study was performed at expert academic centers by endoscopists experienced in BE and pCLE. The study cohort is not representative of the general population, thereby limiting its generalizability. This also caused an artificially enriched population of patients with neoplasia. In such a population with artificially enriched HGD and EC, a lower NPV would be expected than in a traditional surveillance population. However, we found a high NPV when pCLE was used in combination with HD-WLE (and NBI). Another limitation is the inherent sampling error when performing focal examination: it is possible that pCLE images/videos did not correlate with the sites from which the biopsy samples were obtained. This risk was mitigated in our study design by the fact that all locations were marked with argon plasma coagulation in their direct vicinity to ensure the best possible correlation of biopsy- and pCLE-examined locations. The study was powered to find a difference in ability to detect locations with HGD/EC rather than patients with HGD/EC. Although HD-WLE or NBI had a higher sensitivity for patients with HGD/EC compared with HD-WLE or pCLE, there were no statistically significant differences in sensitivity between any of the imaging strategies. Consequently, it remains uncertain which imaging strategy (if any) is superior for detection of HGD/EC from a patient-based perspective. In addition, we relied on the yield of biopsy samples of suspicious lesions plus 4-quadrant random locations to determine the presence/absence of HGD/EC for each individual patient, which may have underdiagnosed HGD/EC in the study population. Finally, the cost-effectiveness of pCLE was not evaluated, and, as such, formal cost-effectiveness analyses are needed.

In conclusion, this study showed that the use of pCLE significantly improved the ability to detect neoplasia in BE patients. pCLE was easy to use, images were easy to interpret, and the learning curve was short. This technology may make surveillance endoscopy in BE more efficient and lead to better informed patient management in real time for immediate endoscopic treatment.

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Abbreviations

BE	Barrett’s esophagus
CLE	confocal laser endomicroscopy

EC	early carcinoma
HD-WLE	high-definition white-light endoscopy
HGD	high-grade dysplasia
LGD	low-grade dysplasia
NBI	narrow-band imaging
NPV	negative predictive value
pCLE	probe-based confocal laser endomicroscopy

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Take-home Message

- Probe-based confocal laser endomicroscopy is an endoscopic imaging technology that significantly improves the ability to detect neoplasia in Barrett's esophagus (BE) patients while being easy to use and having a short learning curve.
- The use of this technology may make surveillance endoscopy in BE more efficient and may lead to better informed patient management in real time for immediate endoscopic treatment.

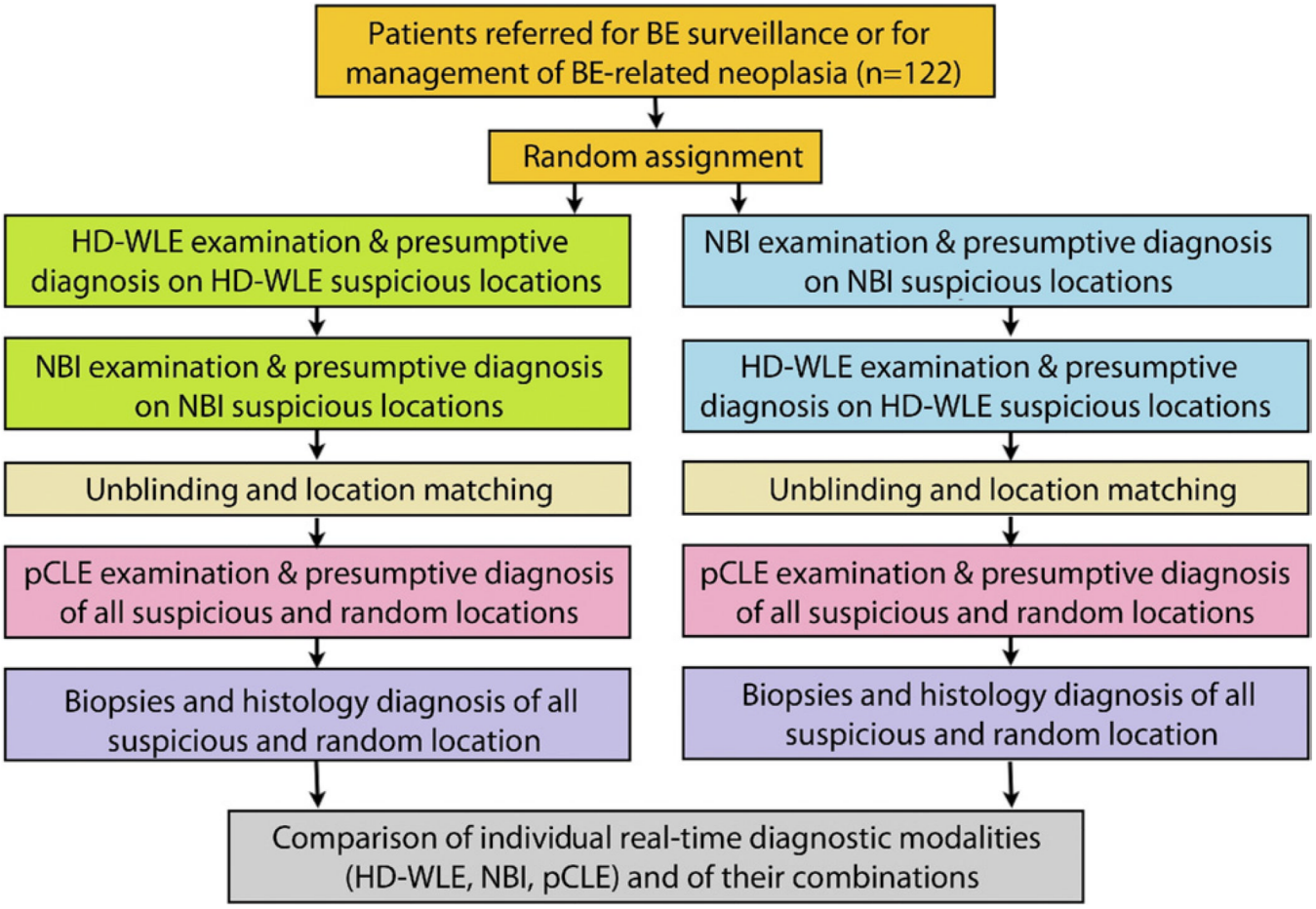

Figure 1.
Study design and flow chart. BE, Barrett's esophagus; HD-WLE, high-definition white-light endoscopy; NBI, narrow-band imaging; pCLE, probe-based confocal laser endomicroscopy.

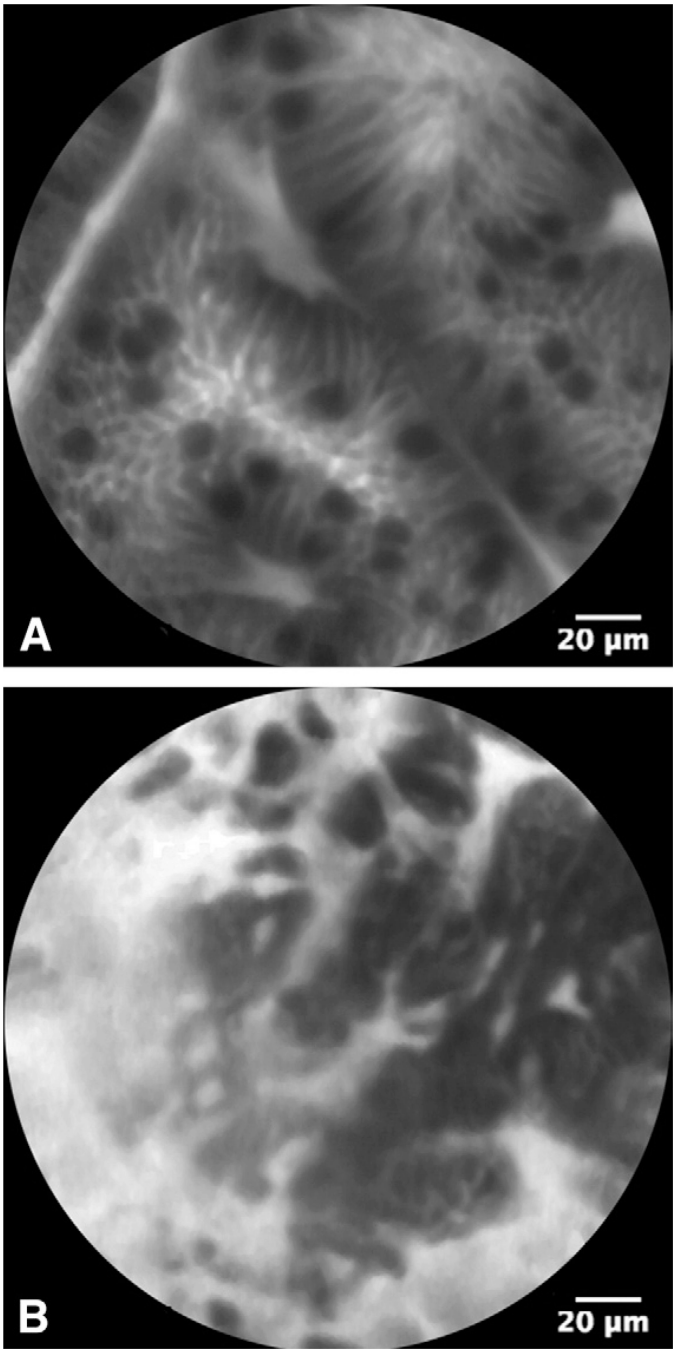

Figure 2.
Probe-based confocal laser endomicroscopy images showing nondysplastic Barrett's esophagus (BE) (**A**) and BE with early esophageal adenocarcinoma (**B**).

TABLE 1

Patient demographics and study population

Demographics	Patients (N = 101)
Age, y (range)	65.1 (27–90)
Male sex, no. (%)	86 (86)
Prague C & M, mean (SD)	
C	1.91 (2.95)
M	3.61 (3.24)
Histopathology	
No dysplasia	66
LGD	4
HGD	6
Cancer	25

SD, Standard deviation; *LGD*, low-grade dysplasia; *HGD*, high-grade dysplasia.

TABLE 2

Results: per-location analysis of sensitivity and specificity of HD-WLE versus HD-WLE or pCLE

	Sensitivity* (95% CI),%	Specificity* (95% CI),%	PPV* (95% CI),%	NPV* (95% CI),%	Areas with HGD/EC missed (total HGD/EC = 120), no. (%)
HD-WLE alone	34.2 (25.7–42.7)	92.7 (90.8–94.6)	42.7 (32.8–52.6)	89.8 (87.7–92.0)	79 (66)
HD-WLE or pCLE	68.3 (60.0–76.7)	87.8 (85.5–90.1)	47.1 (39.7–54.5)	94.6 (92.9–96.2)	38 (32)

HD-WLE, High-definition white-light endoscopy; *pCLE*, probe-based confocal laser endomicroscopy; *CI*, confidence interval; *PPV*, positive predictive value; *NPV*, negative predictive value; *HGD/EC*, high-grade dysplasia/early carcinoma.

*Sensitivity, specificity, PPV, and NPV calculated for the detection of locations with HGD/EC.

TABLE 3

Results: per-location analysis on sensitivity and specificity of HD-WLE, NBI, pCLE, and their combinations

	Sensitivity* (95% CI),%	Specificity* (95% CI)	PPV* (95% CI)	NPV* (95% CI),%	Areas with HGD/EC missed (total HGD/EC areas = 120), no. (%)
HD-WLE alone	34.2 (25.7–42.7)	92.7 (90.8–94.6)	42.7 (32.8–52.6)	89.8 (87.7–92.0)	79 (66)
NBI alone	41.7 (32.8–50.5)	90.5 (88.4–92.5)	41 (32.3–49.7)	90.7 (88.6–92.8)	70 (58)
pCLE alone	62.5 (53.8–71.2)	92.7 (90.8–94.6)	57.7 (49.2–66.2)	94.0 (92.2–95.7)	45 (38)
HD-WLE or NBI	45.0 (36.1–53.9)	88.2 (85.9–90.5)	37.8 (29.8–45.7)	91.0 (88.9–93.0)	66 (55)
HD-WLE or pCLE	68.3 (60.0–76.7)	87.8 (85.5–90.1)	47.1 (39.7–54.5)	94.6 (92.9–96.2)	38 (32)
HD-WLE or NBI or pCLE	75.8 (68.2–83.5)	84.2 (81.6–86.8)	43.3 (36.6–50.0)	95.6 (94.1–97.2)	29 (24)

HD-WLE, High-definition white-light endoscopy; *NBI*, narrow-band imaging; *pCLE*, probe-based confocal laser endomicroscopy; *CI*, confidence interval; *PPV*, positive predictive value; *NPV*, negative predictive value; *HGD/EC*, high-grade dysplasia/early carcinoma.

*Sensitivity, specificity, PPV, and NPV calculated for the detection of locations with HGD/EC.

TABLE 4

Results: per-patient analysis on sensitivity and specificity of HD-WLE, NBI, pCLE, and their combinations

Detection of HGD/EC	Sensitivity* (95% CI),%	Specificity* (95% CI),%	PPV* (95% CI),%	NPV* (95%CI),%	Patients with HGD/EC missed (total HGD/EC = 31), no. (%)
HD-WLE alone	87.10 (75.3–8.9)	71.40 (60.8–82.0)	57.40 (43.3–71.6)	92.60 (85.6–99.6)	4 (13)
HD-WLE or pCLE	93.50 (84.9–100)	67.10 (56.1–78.1)	55.80 (42.3–69.3)	95.90 (90.4–100)	2 (6)
HD-WLE or NBI	96.80 (90.6–100)	55.70 (44.1–67.4)	49.20 (36.6–61.7)	97.50 (92.7–100)	1 (3)
HD-WLE or NBI or pCLE	100 (100–100)	55.70 (44.1–67.4)	50 (37.6–62.4)	100 (100–100)	0 (0)

HD-WLE, High-definition white-light endoscopy; *NBI*, narrow-band imaging; *pCLE*, probe-based confocal laser endomicroscopy; *CI*, confidence interval; *PPV*, positive predictive value; *NPV*, negative predictive value; *HGD/EC*, high-grade dysplasia/early carcinoma.

*Sensitivity, specificity, PPV, and NPV calculated for the detection of locations with HGD/EC.