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What is This?
Confocal Laser Endomicroscopy in the Detection of Head and Neck Precancerous Lesions

Cherie-Ann O. Nathan, MD1,2, Nadine M. Kaskas3, Xiaohui Ma, MD1, Shubnum Chaudhery, MD1,4, Timothy Lian, MD1,2, Tara Moore-Medlin1, Runhua Shi, MD, PhD2, and Vikas Mehta, MD1,2

Abstract
Objective. This study aimed to determine the feasibility of using probe-based confocal laser endomicroscopy (pCLE) in the diagnostic differentiation of non-neoplastic lesions from precancerous and cancerous lesions of head and neck patients.

Study Design. Diagnostic test evaluation.

Setting. Louisiana State University Health Shreveport.

Subjects and Methods. Intravenous injection of fluorescein was given to patients with precancerous and cancerous head and neck lesions (n = 21) followed by the use of a 1.8-mm GastroFlex probe in the oral cavity with subsequent biopsies of selected areas. Probe-based confocal laser endomicroscopy images were compared to histologic evaluation of visualized sites using sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV).

Results. The dorsal surface of the tongue was not well visualized. The remaining nonkeratinized subsites, including the buccal mucosa, floor of mouth, and ventral tongue, were well visualized. Diagnoses based on pCLE images correlated well with the gold standard diagnoses based on tissue histology. The overall sensitivity for diagnosis of dysplasia versus nondysplasia was 80.0% (95% confidence interval [CI], 62.0-98.0), specificity and PPV were 100%, and the NPV was 80.0% (95% CI, 60.0-100.0). The overall specificity, sensitivity, PPV, and NPV for pCLE diagnosis of carcinoma versus nondysplasia were 100%. The overall sensitivity for diagnosis of carcinoma versus nondysplasia was 85.7% (95% CI, 73.0-99.0), specificity and PPV were 100%, and the NPV was 80.0% (95% CI, 60.0-100.0).

Conclusion. The pCLE is a promising method for differentiating between nondysplastic, precancerous, and cancerous lesions of the head and neck.

Keywords
CellVizio, GastroFlex, HNSCC, optical biopsy, pCLE

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Introduction
As the sixth most common cancer globally,1 head and neck squamous cell carcinoma (HNSCC) remains an international public health challenge. Despite optimal treatment, patients often develop local recurrences, distant metastases, and additional primaries.2,3 The overall prognosis is poor, with a 5-year survival rate of 40% to 50% for advanced stage disease.2 The lifetime risk of second primaries even for early stage disease is dramatic, and the risk, although decreased with smoking cessation, never goes back to baseline.4,5

Although the literature has ascertained that the development of HNSCC is associated with a complex multifactorial etiology to include exposure to tobacco, alcohol, and high-risk types of human papilloma virus (HPV), several factors involved in the molecular carcinogenesis remain unclear.2,6,7 A favored theory used to explicate the frequency of local recurrence and formation of multiple primaries in head and neck mucosa is that of field cancerization.2,7 Pioneered in the early 1950s by Slaughter et al, who evaluated mucosal histology surrounding oral carcinoma, field cancerization refers to a pre-neoplastic mucosal area.

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composed of epithelial cells with genetic or epigenetic changes beyond the original invasive malignancy, resulting in patients having multiple malignancies in various stages of development.\textsuperscript{7} Whereas field cancerization asserts initiation of multiple genetic clones in the entire exposed upper aerodigestive tract, the multistep carcinogenesis model supports a common clonal origin.\textsuperscript{8}

The precursor lesions of oral squamous cell carcinoma, oral leukoplakia and erythroplakia, are white and/or red mucosal patches with histology that ranges from hyperplasia to carcinoma in situ. The annual malignant transformation rate is 1\% to 2\% a year for leukoplakia.\textsuperscript{2} For lesions with dysplasia on biopsy, the 8-year rate of malignant transformation is approximately 36\%.\textsuperscript{9} As a result of field cancerization, the entire mucosa exposed to the carcinogen is often affected causing widespread leukoplakia. The treating physician is then presented with a management dilemma since resection or CO\textsubscript{2} laser ablation of diffuse mucosal areas can be crippling. It is also unclear whether this widespread treatment of the affected mucosa is necessary as only a small percentage of cases progress to malignancy. Hence, a methodology to evaluate which lesions are dysplastic without the necessity of excision and ex vivo histopathologic evaluation would be ideal.

The clinically clear margins visualized intraoperatively by the surgeon often overlook the microscopic, larger field involvement.\textsuperscript{2} Studies have found that failure to obtain adequate resection margin at the primary tumor site is the single largest cause of death for patients with HNSCC.\textsuperscript{10} Although there is a clear consensus that positive surgical resection margins contribute to greater morbidity and mortality, there is no ideal method of intraoperative resection margin surveillance in head and neck cancer.\textsuperscript{10} In current practice, intraoperative evaluation of negative margins is dependent on visual appearance, palpation, and frozen section histopathology.\textsuperscript{10,11} Although frozen section samples are an accurate and widely accepted method of intraoperative assessment, they can be unnecessary and time consuming and may be associated with unfavorable sequelae such as compromising tissue integrity. This can lead to permanent damage in sensitive areas key to function such as in laryngeal tissue.\textsuperscript{11} Furthermore, the current gold standard biopsies include a notable element of operator-dependent sampling error and may be difficult to obtain in patients with complex comorbidities.\textsuperscript{12} Therefore, a method to evaluate these margins prior to excision of the cancer would be invaluable.

A new frontier rapidly evolving to avoid unnecessary invasive biopsies is the use of optical imaging, a technology that merges the pathology laboratory with the operating room through real-time histological visualization of mucosa.\textsuperscript{13} Optical imaging techniques include narrow-band imaging, autofluorescence imaging, and confocal laser endomicroscopic imaging.\textsuperscript{12} Probe-based confocal laser endomicroscopy (pCLE) uses a single distal lens to focus the laser as well as an objective lens to transmit the tissue-generated light. Thus, by avoiding light scattering, pCLE provides focused, magnified “biopsy” images superior to that produced by conventional light microscopy.\textsuperscript{12} High-contrast visualization is enabled through the injection of contrast agents such as fluorescein, which stain the surface epithelium extracellular matrix and allow structural and architectural comparison between surface mucosa and neoplastic tissue.\textsuperscript{14}

Probe-based confocal laser endomicroscopy has been used in Barrett’s esophagus, gastric neoplasia, colorectal neoplasia, and bile duct lesions.\textsuperscript{12,14,15} It is now FDA approved for the upper gastrointestinal tract.\textsuperscript{16} In a region where clinical identification of dysplastic lesions is difficult, pCLE may have great utility in the diagnostic differentiation between non-neoplastic, precancerous, and cancerous lesions of the head and neck. We hypothesized that pCLE findings would highly correlate with the tissue histopathologic findings in head and neck lesions and therefore be feasible for use in standard practice. The use of such technology may facilitate avoiding unnecessary biopsies, attaining adequate intraoperative resection margins, and allowing adequate visualization of the field defect to locate synchronous primaries.

**Methods**

**Patients**

Twenty-one patients underwent evaluation, biopsy, and treatment of premalignant and malignant lesions (leukoplakia, n = 12; carcinoma, n = 9) of the head and neck at the Feist-Weiller Cancer Center at Louisiana State University Health Shreveport. The lesion, surrounding mucosa, and contralateral mucosa were evaluated with the pCLE. This study was approved by the Louisiana Health Sciences Center Shreveport Institutional Review Board for Human Research Subjects.

Probe-based confocal laser endomicroscopy procedures were performed either while the patients were awake in clinic (n = 8) or while under anesthesia for treatment of their precancerous or cancerous lesions (n = 13). The target lesion was first identified optically or endoscopically. An intravenous injection of 2.5 milliliters of 10\% fluorescein (Akorn Inc, Lake Forest, Illinois, USA) was then administered for tissue contrast prior to pCLE scanning. Probe-based confocal laser endomicroscopy images were obtained within 15 minutes after fluorescein injection using an ultra high-definition pCLE probe (UHD GastroFlex, CellVizio; Mauna Kea Technologies, Paris, France). The UHD pCLE probe, with a diameter of 2.5 mm and depth of 60 \( \mu \text{m} \), visualizes a 240-\( \mu \text{m} \) field of view at a resolution of 1 \( \mu \text{m} \) and magnification of 1000\( \times \) at 12 frames/s.

The probe tip was first placed on the background normal mucosa (contralateral to the lesion) to obtain a control, non-neoplastic image. The targeted lesion site and adjacent surrounding mucosa were then scanned with pCLE to obtain diagnostic images. After images were obtained, patients underwent the planned resection for malignancies or biopsy/excision for the premalignant lesions. The specimen was sent to pathology for routine histologic review.

Sixteen high-quality pCLE images (biopsy sites = 16, n = 14) with correlating tissue diagnoses obtained from pathology were selected based on the presence of interpretable epithelial
images as determined by the principal investigator and sent to 3 surgeons and 1 pathologist with prior pCLE experience. Probe-based confocal laser endomicroscopy video clips were obtained in the proprietary .mkt format and converted into MPEG format with a duration of 30 to 70 seconds. These practitioners were asked to review and categorize the pCLE images into 3 categories: normal or nondysplasia, dysplasia, or cancer. All reviewers were blinded to the patient’s medical history, histologic diagnosis, and other imaging data with removal of patient information from submitted files.

Outcome Measures

The corresponding histologic diagnoses were used as the gold standard in assessing the diagnostic accuracy of pCLE imaging through pooled sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results

Patient Characteristics

Table 1 summarizes patient demographics and their associated lesion characteristics. A total of 21 patients with head and neck lesions (leukoplakia, n = 12; carcinoma, n = 9) were enrolled in the study. There were 10 male (48%) and 11 female (52%) patients. The mean age ± standard deviation of enrolled patients was 64.2 ± 15.2 years (range, 36-83 years). On final histopathology, there were 5 nondysplastic lesions and 7 dysplastic lesions (2 low grade, 5 high grade) in 12 patients with leukoplakia. There were 4 well-differentiated and 5 moderately differentiated squamous cell carcinoma lesions identified in 9 patients. The most common lesion site identified in this study was the tongue (14 total, 4 nondysplastic lesions, 5 dysplastic lesions, and 5 carcinoma lesions).

pCLE Image Outcomes

The dorsal surface of the tongue was not well visualized due to the keratinized filiform papillae. The remaining nonkeratinized subsites, including buccal mucosa, floor of mouth, retromolar trigone, hard palate, ventral and lateral tongue, tonsil, epiglottis, and true vocal cord, were well visualized. Flat and relatively uniform polygonal epithelial cells with alternating dark and light bands were noted in normal mucosa (Figures 1A and 1B). As the tissue transitioned to low-grade dysplasia, as noted in the patient with the right lateral tongue lesion (Figures 1C and 1D), the confocal image showed an irregular epithelial lining of variable width. In high-grade dysplasia, dark, irregularly thickened, and disorganized epithelium was noted (Figures 1E and 1F). Completely disorganized epithelium with fluorescein leakage was noted in the pCLE images of ventral tongue squamous cell carcinoma in situ with focal superficial invasion (Figures 2A and 2B). Notably, this patient had field cancerization with multiple CO2 laser resections positive for high-grade dysplasia. The area surrounding her lesion showed significantly prominent vasculature in the mucosa indicating possible erythroplakia-related neovascularization (Figure 2C). Figures 3A and 3B show the pathology and pCLE images of a patient with a right lateral tongue squamous cell carcinoma. Malignancy was associated with crowded dark epithelium with a dark-gray background without identification of mucosal structures and was very similar to malignancy noted in tumors of other sites.12,15,17 In addition, keratin pearls could be visualized in the imaging of 3 squamous cell carcinoma lesions (Figures 3C and 3D).

The sensitivity, specificity, and negative and positive predictive values for offline pCLE images of 16 lesions were compared to the gold standard histologic diagnosis. The overall sensitivity for diagnosis of dysplasia versus

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Abbreviation: SCC, squamous cell carcinoma.
nondysplasia was 80.0% (95% confidence interval [CI], 62.0-98.0), specificity and PPV were 100%, and the NPV was 80.0% (95% CI, 60.0-100.0). The overall specificity, sensitivity, PPV, and NPV for pCLE diagnosis of carcinoma versus nondysplasia were 100%. The overall sensitivity for diagnosis of carcinoma versus dysplasia was 85.7% (95% CI, 73.0-99.0), specificity and PPV were 100%, and the NPV was 80.0% (95% CI, 60.0-100.0).

**Discussion**

Previous studies investigating the use of pCLE for imaging gastrointestinal, pulmonary, and urinary tracts\(^\text{12,14,17-20}\) have generated interest in applying this technology to the head and neck region.\(^\text{21}\) A preliminary report by Pogorzelski et al\(^\text{22}\) demonstrated the ability to visualize dysplastic head and neck squamous cell mucosa with the use of rigid laser endomicroscopy (n = 15), and a recent conceptual study by Just and Pau\(^\text{23}\) qualitatively indicated the intraoperative ability of a surgeon to monitor laryngeal epithelial changes with confocal endomicroscopy using a rigid endoscope. This pilot study demonstrated that diagnoses based on pCLE imaging were highly correlated with diagnoses based on the histopathologic findings in the head and neck region.

Although histopathologic review is an indispensable tool in the evaluation and treatment of head and neck lesions, the optical images obtained were highly comparable with histology, suggesting that virtual biopsy may be a good alternative. A distinctly superior aspect of in vivo imaging is the ability to evaluate the entire lesion, thereby avoiding sampling errors associated with permanent biopsies.\(^\text{13}\) Often, the tissue biopsy results do not corroborate with the resected lesion results. Probe-based confocal laser endomicroscopy can potentially decrease this discrepancy by scanning the entire lesion. Other advantages include the ability to review images multiple times as well as freeze individual

![Figure 1. Pathology pictures (40×) and probe-based confocal laser endomicroscopy (pCLE) images of normal lateral tongue mucosa exhibiting well-organized flat polygonal cells (A, B). Right lateral tongue dysplasia exhibiting irregular cells with variable epithelial lining width (C, D). Lateral tongue moderate dysplasia characterized by dark, irregularly thickened, and disorganized epithelium (E, F).](image1)

![Figure 2. Pathology pictures (40×) and probe-based confocal laser endomicroscopy (pCLE) images of ventral tongue squamous cell carcinoma (SCC) in situ with intercellular membrane and architecture breakdown, and leaky permeable fluorescein between cells (A, B). Significant vascularization possibly indicated by significant blood vessels in the mucosa (C).](image2)
frames when reviewing the offline images. The learning curve for obtaining high-quality images was short. The ability to use the probe and interpret the images occurred rapidly, as all 4 reviewers were quickly able to appropriately identify the lesions.

We found that although leukoplakia was widespread, only some areas demonstrated suspicious microarchitecture, including abnormal vasculature and disruption of membranes, which correlated with final histology. Probe-based confocal laser endomicroscopy imaging could therefore decrease the sampling errors obtained during tissue biopsy or could avoid biopsy altogether and lead to real-time management decisions.

Our study determined high accuracy rates between optical imaging and histologic diagnosis. These findings have been consistent with previous studies conducted to evaluate the diagnostic yield of CLE and pCLE imaging in other anatomic sites. A large randomized controlled trial conducted to evaluate the use of optical imaging on patients with chronic ulcerative colitis (n = 161) found that CLE was highly accurate (97.8%) in predicting neoplastic lesions, was sensitive and specific (94.7% and 98.3%, respectively), and detected almost 5 times as many neoplasias as conventional colonoscopy while reducing the number of tissue biopsies by half. A prospective, double-blind, randomized controlled trial evaluating CLE detection of endoscopically silent neoplasia found that CLE doubled the diagnostic yield for neoplasia and was equivocal to the gold standard for diagnosis of neoplasia. These findings have been corroborated by other studies evaluating the use of pCLE in detecting neoplasia in Barrett’s esophagus. A review of the literature indicates that pCLE has been empirically superior to other optical imaging techniques. A recent prospective study comparing narrow-band imaging, intrinsic autofluorescence, and pCLE for the diagnosis of gastric intestinal metaplasia using histology as the gold standard identified pCLE as the most accurate optical imaging technique.

Autofluorescence involves the sequential generation of an excitation light (370-470 nm) followed by a green light (540-560 nm), which then activates endogenous fluorophores. In the head and neck region, continuous metabolic changes and interference from intrinsic fluorescence of background tissue result in variable autofluorescence signals over time, which limits the reliability of the method. The specificity of the technique may be hindered by the possible autofluorescent changes from nearby benign tissue changes, such as scar formation.

Keereweer et al asserted that intrinsic fluorescence has no advantage over macroscopic visual clues of cancerous tissue. Studies have shown that the measured intrinsic fluorescence may not necessarily correlate with the stage of the disease. Furthermore, although spectroscopy is highly sensitive in confirming the visibility of the lesion, it cannot distinguish between benign and malignant visible lesions. A multicenter feasibility study conducted with patients with Barrett’s esophagus found that although autofluorescence increased the detection rate of high-grade dysplasia and carcinoma, a very high false positive rate of 81% was noted. A later multicenter randomized crossover study has correlated this finding, noting that intrinsic autofluorescence resulted in a high false positive rate of 79%. Our study reports significantly higher accuracy using pCLE in the diagnosis of carcinoma versus nondysplasia with both a specificity and NPV of 100%.

Narrow-band imaging (NBI; Olympus Corporation, Tokyo, Japan) involves the use of 2 filters to restrict the center wavelength to 415 and 540 nm, which limits penetration to better visualize surface structure. Narrow-band imaging has been described as too “broad-based” to be used as an effective virtual biopsy. Although the current consensus is that there may be a role for NBI in the use of colorectal polyp characterization, many have asserted that the technology’s poor light intensity precludes its routine use in practice. Buchner et al compared the sensitivity and specificity of pCLE with NBI using histopathology as the gold standard and found pCLE to be a more sensitive technique, with similar rates of specificity. Another study last year comparing the utility of pCLE and NBI in assessing polyp histology determined that pCLE demonstrated higher sensitivity in predicting histology of small polyps compared with NBI, whereas NBI had higher specificity. Compared to the pCLE specificity of 78% in the evaluation of polyp histology, our study found pCLE specificity to be 100% in the evaluation of head and neck lesions as dysplasia versus nondysplasia, carcinoma versus nondysplasia, and carcinoma versus dysplasia.

Chemoprevention studies are fraught with difficulties in determining whether biomarker endpoints are achieved or histologic changes in the grade of dysplasia have occurred. This may be attributed to the heterogeneous nature of
leukoplakic lesions of the head and neck region and the high sampling error rate at the time of biopsy. Hence, pCLE optical visualization following the administration of chemopreventive agents could potentially facilitate the measurement of end points.

The gold standard treatment for clinically evident high-grade dysplasia is excision or laser ablation, whereas it is acceptable to observe or ablate low-grade premalignancies. These consensus opinions are supported by the possibility of spontaneous regression, with the estimated rate ranging from 9% to 45%. However, a recent study by Arnaoutakis et al concluded that passive observation, even in cases of mild dysplasia, was not acceptable due to the high rates of recurrence and progression to malignancy. They found that clinical examination often cannot differentiate high-grade from low-grade lesions to determine if observation is safe. Therefore, pCLE could be used as a surveillance tool to help determine which lesions can potentially be observed rather than resected and which warrant aggressive management.

One of the limitations of our study was our sample size of 21 patients, and validation of this study in larger, multi-institutional trials is required. Another limitation of this study was that we did not include true normal patients. However, a previous autofluorescence study used the same technique by measuring contralateral spectra in the same patient, corrected for intra- and inter-individual variations. As expected, there is no evidence that the contralateral area in our patients with the oral lesions is normal, as there were no corresponding tissue biopsies. Another limitation of this study was the inability to obtain images from the dorsal tongue. This difficulty has been corroborated in a previous autofluorescence study, which found that in healthy oral mucosa, the excitation wavelengths and principal components of the dorsal tongue were outliers compared to the rest of the oral cavity. This can be attributed to the histologic differences between the dorsal tongue and the rest of the oral cavity. The keratinized mucosa as well as the presence of lingual papillae and taste buds make the autofluorescence properties of the dorsal tongue unique to the rest of the oral cavity.

One downside to the pCLE technique is that the lesion must be present in the superficial mucosa. Submucosal lesions or submucosal progression of malignancy in head and neck lesions may be missed. This limitation may be solved by the new needle-based probe.

Conclusion

This pilot study is the first to establish the feasibility of the use of novel probe-based confocal laser endomicroscopy in the diagnostic differentiation between non-neoplastic, precancerous, and cancerous lesions of the head and neck. If the results of this study are validated in larger, multi-institutional studies, use of this technology in practice may minimize the morbidity and sampling error associated with conventional biopsy, ensure adequate intraoperative resection margins, and assess the effect of treatment with novel chemotherapeutics.

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Author Contributions

Cherie-Ann O. Nathan, conception and design, acquisition/analysis/interpretation of data, drafting/revising article, final approval of the version to be published; Nadine M. Kaskas, interpretation of data, drafting/revising manuscript, final approval of the version to be published; Xiaohui Ma, acquisition/analysis of data, drafting/revising manuscript, final approval of the version to be published; Shubnum Chaudhery, analysis of data, revising manuscript, final approval of the version to be published; Timothy Lian, analysis of data, revising manuscript, final approval of the version to be published; Tara Moore-Medlin, analysis of data, revising manuscript, final approval of the version to be published; Vikas Mehta, analysis of data, revising manuscript, final approval of the version to be published.

Disclosures

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