



Assessment of the sensitivity and specificity of tissue-specific-based and anatomical-based optical biomarkers for rapid detection of human head and neck squamous cell carcinoma



Fangyao Hu^{a,1}, Karthik Vishwanath^{a,1}, H. Wolfgang Beumer^b, Liana Puscas^{b,c}, Hamid R. Afshari^d, Ramon M. Esclamado^b, Richard Scher^b, Samuel Fisher^b, Justin Lo^a, Christine Mulvey^a, Nirmala Ramanujam^a, Walter T. Lee^{b,c,*}

^a Duke University, Biomedical Engineering Department, Durham, NC, USA

^b Division of Otolaryngology – Head and Neck Surgery, Duke University Medical Center, Durham, NC, USA

^c Section of Otolaryngology – Head and Neck Surgery, Durham Veterans Administration Medical Center, Durham, NC, USA

^d Dental Service, Durham Veterans Administration Medical Center, Durham, NC, USA

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SUMMARY

Objectives: We propose the use of morphological optical biomarkers for rapid detection of human head and neck squamous cell carcinoma (HNSCC) by leveraging the underlying tissue characteristics in aerodigestive tracts.

Materials and Methods: Diffuse reflectance spectra were obtained from malignant and contra-lateral normal tissues of 57 patients undergoing panendoscopy and biopsy. Oxygen saturation, total hemoglobin concentration, and the reduced scattering coefficient were extracted. Differences in malignant and normal tissues were examined based on two different groupings: anatomical site and morphological tissue type.

Results and Conclusions: Measurements were acquired from 252 sites, of which 51 were pathologically classified as SCC. Optical biomarkers exhibited statistical differences between malignant and normal samples. Contrast was enhanced when parsing tissues by morphological classification rather than anatomical subtype for unpaired comparisons. Corresponding linear discriminant models using multiple optical biomarkers showed improved predictive ability when accounting for morphological classification, particularly in node-positive lesions. The false-positive rate was retrospectively found to decrease by 34.2% in morphologically- vs. anatomically-derived predictive models. In glottic tissue, the surgeon exhibited a false-positive rate of 45.7% while the device showed a lower false-positive rate of 12.4%. Additionally, comparisons of optical parameters were made to further understand the physiology of tumor staging and potential causes of high surgeon false-positive rates. Optical spectroscopy is a user-friendly, non-invasive tool capable of providing quantitative information to discriminate malignant from normal head and neck tissues. Predictive models demonstrated promising results for real-time diagnostics. Furthermore, the strategy described appears to be well suited to reduce the clinical false-positive rate.

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Introduction

In 2012, there were 52,610 new cases of mucosal head and neck cancers (HNC) in the United States [1]. These cancers develop through a spectrum of changes that can be pathologically identi-

* Corresponding author at: Division of Otolaryngology – Head and Neck Surgery, Duke University Medical Center, Duke Clinics Blue Zone – 3561b, Durham, NC 27710, USA. Tel.: +1 919 681 8449 (O); fax: +1 919 681 7949.

E-mail address: walter.lee@duke.edu (W.T. Lee).

¹ Contributed equally to this research.

fied as progressing from hyperplasia to dysplasia to carcinoma *in situ*, and finally, to invasive carcinoma [2–4]. Once carcinoma is identified, treatment currently involves modalities of surgery, radiation, and chemotherapy [3]. Early detection of new and locally recurrent cancers is clinically important to reduce not only cancer related mortality, but also treatment associated morbidity, as it impacts multiple organ functions including respiration, olfaction, hearing, eating, swallowing, and speaking [5].

The gold standard for diagnosing cancer is dependent on pathological examination. Thus, currently all patients with clinically suspicious lesions undergo surgical biopsies. Although these

lesions are identified during an initial clinical exam, obtaining a specimen via biopsy for analysis can be uncomfortable for patients. This may further include the use of labor, facility, and monetary resources that are expended on patients, some of whom may ultimately have no malignancy. It would be of benefit to clinicians and patients if it were possible to have an “adjunct” technique that could suitably identify those patients that would benefit from further surgical biopsy from those that likely only need follow-up clinical observations. For those patients identified as having a low likelihood of cancer, this would prevent unnecessary procedures, pain, and better utilize limited resources. The clinical value of this tool would depend on it providing rapid, non-invasive feedback could be obtained during the patient’s visit. This would be facilitated by a portable unit such that it can be used in ambulatory settings, and quantitative such that data obtained is consistent across operators and patients.

Several techniques show potential in non-invasive cancer diagnoses. Fluorescence endoscopy relies on contrast agents for staining and imaging cell nuclei [6,7]. Time-domain Optical coherence tomography (OCT) system requires a Michelson interferometer to sample lesions in *z*-direction [8]. Frequency-domain OCT system improve the image acquisition time, where information in the *z*-direction is sampled in the spatial frequency domain [9]. Reflectance confocal microscopy utilizes a pinhole to reject the out-of-focus light [10,11]. Hence, the cellular structures could be imaged in nontransparent tissues. Although these techniques show high potential in cancer diagnoses [6,12,13], the systems is expensive or requiring extra procedures. Moreover, these techniques provide only the morphological information but not the physiological information.

Diffuse reflectance spectroscopy (DRS) can provide information about tissue composition including physiological, metabolic and structural properties [14]. DRS has been used to show that malignant and normal tissues of the head and neck can be differentiated when analyzed using a variety of different techniques [15–32]. Our team has developed a quantitative DRS technique that incorporates a portable fiber-based spectrometer and a robust inverse Monte Carlo (MC) algorithm capable of extracting tissue optical properties [33,34]. The inverse model can rapidly compute total hemoglobin concentration (THb), hemoglobin oxygen saturation (SO₂), and mean reduced tissue scattering coefficient (μ'_s), which reflects the cellularity of the tissue within the probed volume. The feasibility of using DRS in patients undergoing panendoscopy has been demonstrated [16].

Although the majority of HNC are squamous cell carcinomas (>90%), signals collected from DRS might be sensitive to both SCC and the underlying tissues (the tissue below the epithelial cancer) since DRS usually lacks of optical sectioning ability. Current description of head and neck squamous cell carcinomas (HNSCC) is often based on anatomical boundaries (i.e. oropharynx, oral cavity, pharynx, larynx) [35]. Therefore, contrast detected by DRS between the tumor and normal tissues might be diminished when mixing samples with different surrounding tissue types. Other groups have tried to eliminate the effects of collecting light from beneath the epithelium when trying to diagnose epithelial cancers. Perelman et al. employed a physical model for the diffusive background originated from the stroma [36]. After removing the background, density and size distribution of the nuclei can be computed, though this method is time-consuming. Nieman et al. combined an angled illumination-collection strategy with the polarization illumination technique for reducing the optical background signals from the stromal layer [37]. Nevertheless, an angled illumination-collection probe with polarization sensitivity technique is hard to fabricate. We simply propose that by grouping the samples with similar tissue types, contrast between the SCC and normal tissues could be enhanced.

In this manuscript, the diagnostic accuracy between the anatomical and tissue-specific grouping strategies using the optical biomarkers obtained via the quantitative DRS technique was investigated for the HNSCC detection during staging panendoscopy. In addition, a comparison was made among the optical biomarkers of normal, node-positive, and node-negative malignant tissues. Finally, optical biomarkers of the malignant, pathologically confirmed normal, and clinically observed normal tissue samples were compared.

Materials and methods

Clinical study design

This study was approved by the Duke University School of Medicine Institutional Review Board (Pro00021026) and was open to all patients who were scheduled for panendoscopy and biopsy for suspected HNC at the Duke University Hospital during 2010–2012. Patients with suspicious lesions were approached and consented to undergo a non-invasive evaluation of sites to be biopsied using the optical probe. All patients were included in the study with no further sub-selection. Tissue biopsies were only obtained from the site suspected of disease and all measurements from normal appearing unaffected tissues were assumed to be normal. No biopsies were taken from normal appearing unaffected tissues. Several surgeons specialized in head and neck surgery participated in this study taking biopsies. The locations of distant normal tissue measurements were supervised by the same surgeon (W.L.) who participated in a previously published study at the Durham Veterans Administration Hospital [16] in which 25 normal tissues were biopsied and submitted for histopathology. In this study, the surgeon demonstrated 100% accuracy in correctly identifying clinically-appearing distant normal sites as histologically normal.

In each consented patient, the optical probe was placed on the surface of at least two tissue sites (“tumor” and “normal appearing unaffected tissue”). Five diffuse reflectance scans were obtained at each site and data was recorded. To co-localize the optical scans and clinical biopsies, the suspicious sites were biopsied immediately after the optical measurements were completed with the attending physician visually marking the spot of optical measurements for biopsy (which was approximately 2–5 mm in diameter).

The measurements were obtained from anatomical sites in the larynx, pharynx, or oral cavity. Four groups were built based on the structures underneath the epithelium layer and their epithelial variations. The first group consisted of measurements from the glottis. Specialized structures existed such as vocal cord in the larynx area. The true and false vocal cords are covered with stratified squamous epithelium and the ciliated pseudostratified columnar epithelium respectively [38]. The supporting ligament and muscle, vocalis muscle, also makes the underlying of the vocal cord different from the other structures in head and neck. The second lymphoid group was formed by combining measurements from the oropharynx, tonsil and base of the tongue due to the rich lymphatic drainage in the region [39]. The third muscle group consisted of measurements from tongues which consisted of majorly with striated muscle fibers. The tongue epithelium, which is modified into filiform papillae and fungiform papilla, is also distinct from other epitheliums in head and neck. The last group combined measurements from all remaining sites into a mucosal group.

Optical spectroscopy instrumentation

A portable fiber optic instrument (Fig. 1) was used to measure tissue diffuse reflectance spectra. Light from a 40 W halogen lamp (HL2000HP; Ocean Optics, Dunedin, FL), was coupled to an optical

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