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Chapter 36

Optical Coherence Tomography of Malignancies of the Head and Neck

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Introduction

In 2014, The American Cancer Society estimates over 42,000 new cases of oral and pharyngeal cancer, and over 12,000 new cases of laryngeal cancer will be diagnosed in the United States [1]. The majority of these malignancies are head and neck squamous cell carcinomas (HNSCC), a particularly aggressive form of cancer, for which tobacco and alcohol use are major risk factors. Despite novel molecular targeting therapies (e.g., epidermal growth factor receptor), expanded roles for chemotherapy (e.g., neoadjuvant treatment for laryngeal cancer), and new irradiation techniques (e.g., hyperfractionated radiotherapy), the long-term survival rates for advanced-stage HNSCC remain low [2, 3]. Between 2004 and 2010, 65 % of the newly diagnosed cancers of the oral cavity (OC) and pharynx were advanced-stage tumors (regional or distant metastasis); 40 % of laryngeal cancers were in advanced stage [4]. One explanation for the delayed diagnosis of head and neck cancer is that many early stage cancerous lesions are subtle and do not demonstrate clinical characteristics of advanced lesions including ulceration, induration, pain or associated cervical lymphadenopathy [5]. Furthermore, premalignant lesions are often undetectable to the naked eye and are highly heterogeneous in presentation, frequently mimicking benign or reactive conditions. Hence, a practical and accurate imaging modality which may improve the incidence of early stage diagnosis and allow for screening of head and neck cancer is needed.

Diagnostic evaluation of head and neck cancer patients begins with a thorough history and physical examination. The head and neck examination includes visual and digital assessment of hard

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and soft tissues within the OC and oropharynx (OP). Examination of the pharynx and larynx may be accomplished with an indirect mirror examination or, for more comprehensive evaluation, with transnasal flexible laryngoscopy. Panendoscopy (bronchoscopy, esophagoscopy, and direct laryngoscopy) is often performed for a more thorough preoperative assessment and tumor staging. All aforementioned diagnostic techniques provide information on the color and surface pattern of mucosal tissue only and therefore are unable to detect subepithelial pathology. Computed tomography (CT), positron emission tomography CT (PET-CT), and magnetic resonance (MR) imaging are commonly used imaging modalities in the management of head and neck cancer. However, these technologies lack adequate spatial resolution to differentiate between benign, premalignant, and malignant lesions at the substructural or cellular level. Screening of the OC for cancerous lesions may be attempted with toluidine blue staining, fluorescence staining, exfoliative cytology, and brush biopsy [6]. However, these tests lack standardized methodology, have variable reported diagnostic sensitivity and specificity, or lack randomized controlled trials.

Histopathological analysis of excised tissue remains the gold standard of care for achieving a definitive diagnosis of suspicious lesions. However, office-based or operative biopsy is not a pragmatic option for routine screening. A single lesion may require multiple biopsies to avoid overlooking the most dysplastic region of pathology. Biopsy is also associated with patient morbidity and may pose risk for long-term speech or swallowing sequela. Hence, a less invasive imaging modality which can delineate mucosal substructure in vivo, identify tumor margins and screen for occult foci of pathology has the potential to improve the management of head and neck cancer patients.

Principles of OCT

OCT is a minimally invasive imaging modality which combines nonionizing near-infrared light with principles of low coherence interferometry [7]. A light source (e.g., laser or superbright light emitting diode) is split into a reference arm (mirror) and a sample arm (biological sample). Back-reflected light from each path is recombined and detected to construct a two-dimensional reflectivity profile (A-line) as a function of tissue depth with up to 2 mm optical penetration. Adjacent A-lines are combined to yield high-resolution (~10 μm), 3D cross-sectional images of tissue. Early OCT systems were developed using a time-domain (TD-OCT) configuration. Later, OCT systems based on Fourier-domain (FD-OCT) detection were constructed, either with a spectrometer configuration (spectral-domain OCT) or a frequency-swept

source (swept-source OCT). FD-OCT systems spectrally resolve the interference signal to measure the echo time delay of backscattered light. The advantages of FD-OCT over TD-OCT include faster imaging speeds, higher sensitivity, and greater resolution [8–10]. Polarization-sensitive OCT (PS-OCT) augments conventional OCT by detecting changes in the polarization state of reflected light [11, 12].

OCT imaging of laryngeal tissue can be accomplished in contact or near-contact modes using an endoscopic probe during operative microlaryngoscopy or office-based upper-airway endoscopy. Some research groups have evaluated long-range imaging of the vocal folds by integrating OCT sampling arms with operative microscopes, while others have adapted handheld laryngoscopes for transoral endoscopic OCT imaging of the larynx.

Oral and Pharyngeal Cancer

The OC and pharynx are the most common sites for neoplasm of the head and neck. Precancerous lesions include leukoplakia (white), erythroplakia (red), mixed red-white lesions, and verrucous hyperplasia. Leukoplakias develop in 1–4 % of the population, with malignant transformation in approximately 0.13–33 % of these lesions [13, 14]. Up to 85 % of erythroplakias carry risk for malignant transformation [14]. Accurate differentiation between benign, premalignant and malignant pathology requires assessment of the structure and integrity of the epithelium and subepithelial layers. Potential applications of OCT in the management of oral and pharyngeal cancer include identification of transition zones between different histological states (e.g., definition of tumor margins to guide therapy), evaluation of basement membrane integrity for suspicious lesions and longitudinal monitoring of disease progression. Figure 36.1 depicts OCT images from normal and cancerous tissue of the floor of the mouth, acquired by Betz's group (Munich, Germany) using a commercially available system. A loss of layered substructural integrity is noted in cancer tissue, secondary to the downgrowth of malignant epithelial cells and breakdown of the basement membrane. The transition zone between both regions is demonstrated in Fig. 2 using a research TD-OCT system.

Animal and Ex Vivo Studies

The hamster cheek model is frequently used to evaluate OCT of premalignant and malignant lesions followed by image correlation with histological section [15–24]. In 2004, Matheny et al. reported in vivo and, following excision, in vitro OCT (central wavelength $\lambda = 1310$ nm) and optical Doppler tomography (ODT) of induced dysplasia and malignancies in hamster cheek pouches [16]. Their OCT images of dysplastic lesions demonstrated epithelial thickening

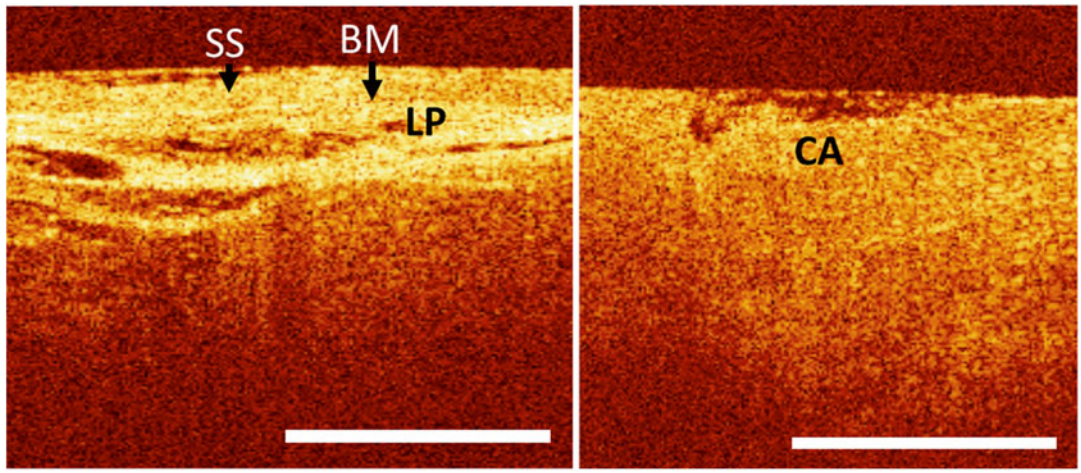

Fig. 1 OCT images of normal epithelial tissue (**a**) and squamous cell carcinoma (**b**) from the floor of the mouth, acquired from a commercially available system. *SS* nonkeratinized stratified squamous epithelium, *BM* basement membrane, *LP* lamina propria, *CA* cancer. *White bar* = 1000 μm

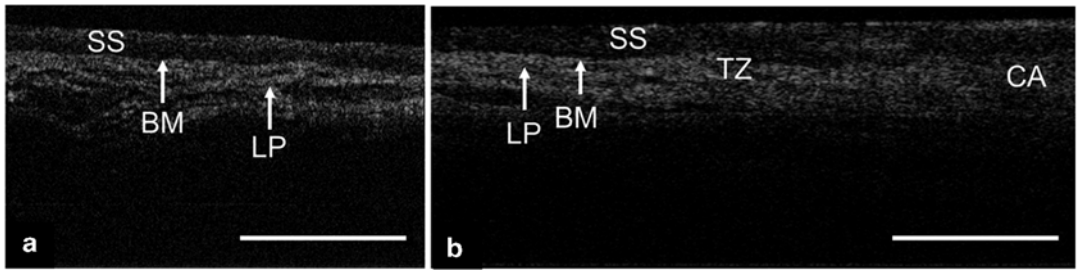

Fig. 2 OCT images of normal epithelial tissue (**a**) and the transition zone (**b**) between normal tissue and squamous cell carcinoma of the floor of mouth, acquired from a research system. *SS* nonkeratinized stratified squamous epithelium, *BM* basement membrane, *LP* lamina propria, *TZ* transition zone, *CA* cancer. *White bar* = 1000 μm

into the underlying connective tissue; cancerous regions appeared to have higher levels of scattering and absorption, thus reducing the overall optical penetration depth in these tissues. In 2011, Ahn et al. performed longitudinal in vivo FD-OCT (center wavelength $\lambda = 1310$ nm) to image the development of carcinogenesis including epithelial migration, loss of basement membrane integrity, and subepithelial invasion [23]. Multiple reports of OCT of precancerous and cancerous lesions of the human OC in the immediate ex vivo phase have allowed for diagnostic sensitivity and specificity measurement by direct comparison with histopathology [25–29].

Clinical Studies

In vivo OCT evaluation of normal human OC/OP mucosa is described in the literature [30–34]. These reports have helped establish standards for OCT-based identification of substructural

tissue layers within the OC and OP and provide a reference for differentiating noncancerous from cancerous lesions. In vivo human studies have demonstrated the efficacy of OCT in differentiating premalignant and malignant lesions of the OC/pharynx [35–39]. In 2006, Ridgway et al. imaged normal and pathologic lesions within the OC and OP in 41 patients using a TD-OCT system (central wavelength $\lambda = 1310$ nm) and a flexible endoscopic probe mechanically supported in a rigid, stainless steel cylinder [36]. Their OCT images of histologically proven oral cancer depicted ablation of subepithelial tissue and a progressive loss of layering and basement membrane integrity at tumor margins. Tsai et al. performed in vivo swept-source FD-OCT in 32 patients to evaluate OC lesions at different oncologic stages [37]. By computing the lateral variation of multiple A-line parameters (standard deviation of signal intensity fluctuation, exponential decay constant, epithelial thickness), their image analysis offered objective diagnostic indicators to differentiate between premalignant and malignant lesions.

Field Cancerization

Field cancerization describes the process in which an invasive cancer within a mucosal surface is surrounded by multiple molecular lesions with cancer-associated genetic or epigenetic alterations [40, 41]. With high resolution and high diagnostic sensitivity, OCT has the unique capability of identifying transition zones between normal and cancerous subepithelial tissue and the potential to detect subclinical pathologic foci [18, 23, 25]. Tsai et al. used a swept-source FD-OCT system (central wavelength $\lambda = 1310$ nm, axial resolution 8 μm) to image OC cancer ex vivo and analyzed the lateral variation of A-scan profiles across the margin of lesions [25]. Intensity decay constants were calibrated by plotting exponential fitting curves of OCT signal intensity as a function of tissue depth. Their data showed a decreasing trend of the decay constant as the A-line scan point moved across the margin from normal to abnormal tissue. Secondly, they analyzed the fluctuation extent (standard deviation) of OCT signal intensity in A-scans; this parameter increased significantly as the A-line scan point was moved across the transition zone from normal to abnormal tissue. Hence, OCT has potential as a screening tool for identifying margins of disease, satellite foci, or neighboring secondary tumors within the upper aerodigestive tract.

Laryngeal Cancer

The larynx is the second most common site for malignancy in the upper aerodigestive tract, with over 12,000 new cases annually in the United States [1]. Approximately 85–95 % of malignant laryngeal tumors are squamous cell carcinomas (SCC) [42]. The layered

microanatomy of the vocal fold is described in the literature and reviewed elsewhere in this text [43]. While excisional biopsy remains the gold standard for diagnosis of suspicious lesions, this procedure may result in soft tissue deficits and/or vocal fold scarring, both events which may adversely affect postoperative voice quality [44]. OCT offers a less invasive means of acquiring an "optical biopsy" to assess the structural architecture of the vocal fold. Similar to applications in the OC/pharynx, OCT of laryngeal precancerous or cancerous lesions would allow for delineation of tumor margins to guide laser therapy or excisional biopsy, evaluation of basement membrane integrity and penetration depth for suspicious lesions, and monitoring of disease progression. The transition zone between normal laryngeal epithelial tissue and SCC is marked by a gradual loss of basement membrane, which separates the optically distinct stratified squamous epithelium and lamina propria (Fig. 3). OCT of laryngeal SCC demonstrates a lack of clear epithelial borders, without delineation of a basement membrane (Fig. 4).

comprehensive review of research in OCT imaging of vocal fold anatomy and vibrational parameters is provided in an alternate chapter in this text. Select laryngeal OCT studies in porcine and primate models are included here for review purposes [45–48]. These reports provided a basis for understanding OCT-based delineation of the layered microstructure of the vocal fold. Additional reports of OCT in human *ex vivo* larynx specimens are described [49, 50].

Clinical Applications

In 1997, Sergeev et al. first reported in vivo endoscopic OCT of healthy and cancerous laryngeal tissues under direct laryngoscopy in the operating room [51]. Their TD-OCT system (central wavelength $\lambda = 830$ nm, scanning rate 30 cm/s) included a flexible sampling arm integrated into the working channel of a standard

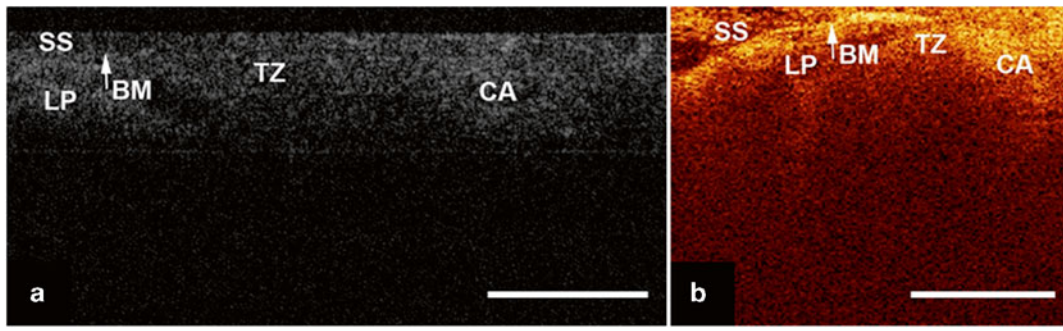

Fig. 3 OCT image of the transition zone between normal epithelium and squamous cell carcinoma of the true vocal fold, acquired from a research system (**a**) and a commercially available system (**b**). *SS* stratified squamous epithelium, *LP* lamina propria, *BM* basement membrane, *TZ* transition zone, *CA* cancer. *White bar* = 1000 μm

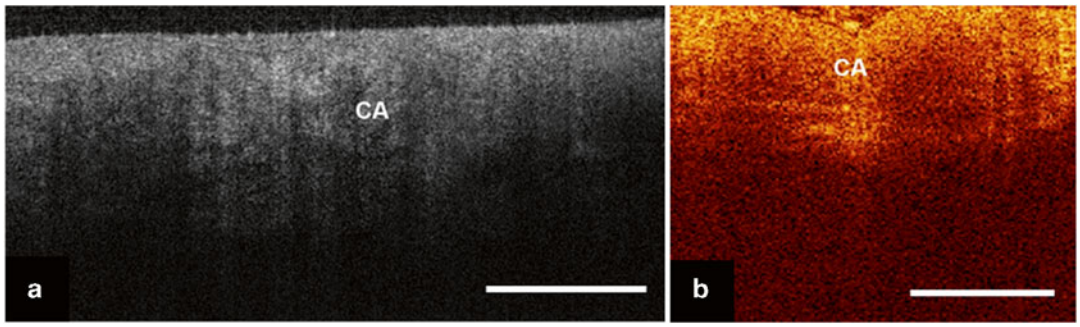

Fig. 4 OCT images of squamous cell carcinoma of the true vocal folds, acquired from a research system (**a**) and a commercially available system (**b**). *CA* cancer. *White bar* = 1000 μm

endoscope. The distal fiber tip was positioned 5–7 mm away from the tissue of interest and swung by a galvanometric plate to scan tissue in a lateral motion with a 2 mm wide optical beam. Their results contrasted healthy and cancerous laryngeal tissue using OCT, revealing a disruption of substructural anatomy and a greater degree of optical backscattering and vascularization in tumor tissue. Similar experiments of tandem OCT-endoscopy of the larynx have been described for operative and office-based settings [52, 53].

Multiple groups have performed OCT of laryngeal cancer during microlaryngoscopy and operative endoscopy by manually inserting a fiber-based probe through the lumen of a surgical laryngoscope or mechanically integrating the probe with a laryngoscope [54–60]. In 2001, Shakhov et al. used endoscopic TD-OCT to identify laryngeal tumor margins during microlaryngoscopy and transoral laser surgery [54]. They noted that OCT allowed for identification of tumor margins up to 3 mm beyond the margins visually identified under microlaryngoscopy. Kraft et al. prospectively compared the intraoperative diagnosis of 217 laryngeal lesions including 41 precancerous and 46 malignant lesions using microlaryngoscopy with and without OCT; all diagnoses were confirmed with histopathology [57]. During microlaryngoscopy, the surgeon used a handheld applicator to apply the probe in direct contact with laryngeal tissue. They determined that microlaryngoscopy with OCT yielded a correct diagnosis in 93 % of malignant lesions and correctly predicted the exact grade of dysplasia in 71 % of lesions. Microlaryngoscopy with OCT presented a higher sensitivity than microlaryngoscopy alone in predicting invasive tumor growth (93 % vs. 87 %) and epithelial dysplasia (78 % vs. 66 %).

Vokes et al. first described OCT integrated with a surgical microscope to conduct hands-free, noncontact imaging of the vocal cords in 10 patients, including five cases of laryngeal SCC [61]. The fiber terminus of their sampling arm was positioned

40 cm from laryngeal tissue, limiting the lateral resolution (50 μm) as a result of diffraction. Nonetheless, their OCT images delineated the epithelium-lamina propria border and provided cross-sectional images to a depth of 1.6 mm. The integrated, hands-free OCT-microscope system offered multiple advantages compared to handheld contact or near-contact OCT probes: (1) minimizing of motion artifact, (2) eliminating OCT instrumentation in the body of a laryngoscope and, as a result, (3) offering surgeons an improved field of view. Just et al. integrated a commercially available FD-OCT system (Spectral Radar; Thorlabs HL AG, Lubeck, Germany; central wavelength $\lambda = 840$ nm) with the camera port of an operating microscope to image suspicious laryngeal lesions during microlaryngoscopy [60]. By adjusting the zoom on their OCT-microscope system they were able to control the size of the lateral imaging field (2–8 mm). They noted additional advantages over endoscope-based OCT systems, including a longer working distance and visualization of the scanning plane with a pilot beam which allowed for unobstructed, precise localization of biopsy sites.

In 2005, Luerssen et al. first reported office-based OCT of normal vocal cords using a contact endoscopic probe [45]. Later generations of office-based OCT systems included integration of the sampling arm with a handheld rigid laryngoscope [48, 62]. With an increasing number of laryngeal diagnostic and therapeutic procedures being conducted in office-based settings, OCT of the laryngeal airway in the awake patient has considerable utility for monitoring lesions, real-time identification of pathologic margins and guidance for office-based excisional biopsy or laser therapy.

OCT Limitations

While advanced generations of OCT technology have led to higher resolution, imaging speeds, and diagnostic sensitivity, a number of factors preclude OCT to serve as an independent diagnostic imaging modality. A primary limitation of OCT in the diagnosis of cancer is the optical penetration depth. Achieving adequate signal penetration to assess basement membrane integrity is critical to differentiating dysplastic lesions such as hyperkeratosis from malignancy. Most research and commercial systems report a maximum imaging depth of 2 mm. Larger, exophytic lesions which exceed OCT signal range cannot be identified and require biopsy for confirmation of diagnosis. Secondly, despite the ability to delineate substructural features, most OCT systems lack adequate resolution to resolve cellular (e.g., cellular maturation) and subcellular features (e.g., nuclear pleomorphism). Hence, OCT may not adequately and independently differentiate subtle lesions such as benign dysplasia and carcinoma-in-situ where invasion is not present. Ultra-high resolution OCT systems (axial resolution 1–5 μm) may offer

promise for cellular resolution. Lastly, technical issues such as motion artifact (minimized with video-rate imaging speeds), probe stabilization, probe signal strength, and imaging range may all affect OCT image quality.

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