Clinical optical coherence tomography in head and neck oncology: overview and outlook

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Abstract

Objective
Optical coherence tomography is a high-resolution and minimally invasive optical imaging method, which provides in vivo cross-sectional images of living tissue in real-time. Our intention is to present a contemporary and comprehensive review on the role of optical coherence tomography in head and neck oncology.

Recent findings
Promising results have been published in small, single-centre studies applying optical coherence tomography in clinical settings for the diagnostic workup of superficial pathologies of the upper aerodigestive tract, showing that it can be a helpful adjunct to standard white light endoscopy. Using optical coherence tomography, microanatomical structures of healthy and diseased mucosa can easily be identified, allowing for a differentiation between benign, premalignant and early malignant lesions with high sensitivity and specificity. Also, it may be helpful in the evaluation of neoplastic thyroid disease and in the preclinical diagnosis of (chemo) radiation therapy-related mucositis.

Summary
Optical coherence tomography enables in vivo, real-time visualisation and diagnosis of healthy and diseased mucosa of the upper aerodigestive tract, and might be useful for other indications. Larger, multicentre trials are needed to validate the current findings and further define the method’s clinical role. With the expected technical advances in acquisition speed and resolution, as well as a wider public acceptance of the method, optical coherence tomography seems to have a bright future in head and neck oncology.

Introduction
Even though white light endoscopy followed by invasive tissue biopsy is still the gold standard for evaluating upper aerodigestive tract (UADT) lesions, novel optical imaging methods such as magnification, digital imaging, optical coherence tomography (OCT), confocal microscopy, narrow band imaging and fluorescence imaging have recently been subjected to thorough evaluations with respect to improving the sensitivity and specificity of standard white light endoscopy and to decrease the number of unnecessary biopsies1,2. Optical imaging techniques thus seem to quickly emerge as invaluable tools during cancer diagnosis and treatment because of their ability to non-invasively provide information about the tissue surface and subsurface structures in real-time at the point of care. This article is aimed at reviewing early clinical applications of OCT as one such optical imaging technology.

OCT has found its way into routine clinical use in ophthalmology, and vascular surgery and has been recently used in clinical studies in the head and neck region. It has a distinctive capability to obtain high-resolution images of tissue microstructures that resemble typical histology cross-sections in real time3. At the same time, OCT is non-invasive, easily performed, safe and harmless. These characteristics may help otolaryngologists in a whole range of applications, for example for guidance of biopsy and surgery and for post-treatment surveillance.

Technical background of OCT
OCT is an optical imaging method using near infrared light to provide high-resolution and cross-sectional images of living tissue. It is often compared with ultrasound as they both rely on reflection (light for OCT, sound for ultrasound) to create an image. Sound waves travel relatively slower (approximately 1500 m/s) compared with light waves (3 × 108 m/s), thus leading to a much higher resolution in OCT imaging compared with that in ultrasound.

Figure 1 illustrates a comparison between OCT and other imaging methods used in the UADT with respect to penetration depth of tissue interrogation versus resolution. As illustrated, OCT has excellent in-depth resolution when compared with conventional imaging methods. Its resolution is about 10 times that of high frequency ultrasound and 100 times that of standard ultrasound, and its penetration depth is conveniently higher compared with confocal microscopy.

Fundamental, method-specific limitations of OCT imaging are the penetration depth and the spatial resolution. Human tissue contains many components that naturally reflect near
Critical review

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ously. Being independent of mechanically moving parts within the system, images are therefore created at a much faster rate, allowing for ‘video-rate’ display of B-scans as well as the generation of three-dimensional and four-dimensional sequences in reasonable time67.

Last but not the least, additional information from the acquired signal can be used to derive more information from the tissue investigated. For example, intravascular speed or vocal cord vibrations can be determined via measurement of Doppler shift (Doppler-OCT)8, or certain tissue structures such as fibrous proteins can be highlighted by detecting the polarisation state of the back-reflected light (polarisation sensitive or PS-OCT)9.

Clinical applications in head and neck

OCT has recently been investigated in terms of its applicability in otolaryngology. The current review is focused on its clinical application in head and neck cancers, mostly for the differentiation of premalignant and early invasive lesions of the UADT. This review also discusses its use in aiding thyroid cancer diagnosis as well as in judging the severity of UADT mucositis as a side-effect of radiation therapy. Other interesting application fields of OCT in otorhinolaryngology which are not discussed in this paper include its use in otology for visualisation of the tympanic membrane, functional assessments of vocal cord mobility and function and neonatology for three-dimensional reconstruction of the upper airway.

The Medline database was searched for appropriate and relevant publications in February 2013 via PubMed using the following search strings: ‘optical coherence tomography’ and ‘optical imaging’ in combination with ‘oral cavity’, ‘larynx’, ‘thyroid’ and ‘mucositis’.

Early tumour diagnosis in the UADT

As tissues have different optical backscattering properties, OCT allows one to visualise and to differentiate the most superficial tissue layers of the UADT. As demonstrated in Figure 3, it thus provides microanatomical information on the integrity or disruption of the epithelium, basement membrane (BM) and supporting lamina propria.

The earliest studies on clinical applications of OCT in the UADT were reported from Russia. In 1997, Sergeev et al. were the first to report imaging of the larynx as part of the UADT with OCT in vivo10. Normal tissue and cancerous tissue was visualised with OCT and the authors observed ‘a loss of normal tissue stratification in tumours’ and thought that OCT would be ‘an interesting tool for early diagnosis of tumours and for guidance of biopsies’. In 2001, Shakhov et al. published a descriptive study on TD-OCT examinations in 26 patients with small laryngeal squamous cell carcinomas (SCC)11. The authors concluded that a ‘stratification seen in OCT images is a criterion for a healthy larynx’ and that ‘disappearance of such stratification is a sign of pathologic tissue alterations’. In addition to rather recently published, site-specific ‘normal values’ for epithelial thicknesses within the larynx12 and the oral cavity13, their findings thus form the basis for our current interpretation of OCT images in the UADT with regard to diagnosis of early invasive SCC versus premalignancy. This can be illustrated by Figures 4 (dysplasia of the tongue) and 5 (early SCC of the floor of the mouth). Other clinically challenging diagnoses, such as differentiating hyperplasia versus dysplasia, might also be possible using real-time OCT14,15 as dysplastic lesions seem to show a persistently higher decrease in signal intensity over the axial run of the epithelial layer than hyperplastic lesions.

Larynx

The larynx is the most frequently investigated location with OCT in the UADT, as its sturdy structure as well as its relatively thin epithelium in healthy conditions makes it an optimal location for optical imaging6,11,12,14,16. OCT has been studied in >500 patients in single-centre trials as an adjunct diagnostic tool for its value in assessing and diagnosing early stage laryngeal pathologies7,11,12,14,16-25, but with consistently and significantly positive results with regard to sensitivity, specificity and correlation with biopsy results. In most cases, OCT imaging probes were placed directly onto the tissue during microlaryngoscopy. However, non-contact OCT image acquisition via 90° rigid laryngoscopy or flexible
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from the aforementioned general biopsies. On the downside and apart from the current spatial resolution of OCT, the authors concluded that OCT is a simple, rapid and reliable aid in the early diagnosis of laryngeal disease.

In 2011, Burns et al. used PS-OCT and conventional OCT to image laryngeal disease. The authors found PS-OCT to be useful especially when differentiating between normal vocal cord tissue and scar tissue, because the increased collagen content in the scar tissue led to different birefringence patterns. Also, PS-OCT was found to be useful for determining the exact extent of malignant invasion and submucosal spread into adjacent normal structures. However, larger studies are needed to determine the true value of PS-OCT.

In conclusion, OCT appears to be an ideal imaging tool for evaluating discrete and superficial laryngeal abnormalities. To date, its application helps in locating the best site within the larynx (such as the anterior commissure) can be difficult to image, and certain conditions such as hyperkeratosis and ulcerations can be hard to interpret. With upcoming technical advances and following more thorough investigations, however, the method has the potential to gain a much more widespread acceptance in laryngology.

**Oral cavity**

Fewer but not less interesting single-centre studies have been published on the clinical use of OCT in the oral cavity. As early as 2004, Fomina et al. investigated 43 patients with 56 intraoral lesions. The authors were able to detect SCC versus all other pathologies with a sensitivity of 83% and a specificity of 98%. A composite and helpful series of OCT images of a variety of normal and pathologic states from oral and oropharyngeal mucosa were published by Ridgway et al. in 2006. In 2009, Wilder-Smith studied 50 patients with dysplastic and malignant oral lesions and found OCT to have 93.1% sensitivity and 97.3% specificity for detecting SCC versus all other pathologies with an excellent intra- and inter-observer agreement ($\lambda = 0.844$–$0.896$). Similarly, promising results were reported by Volgger et al. who studied 100 UADT lesions (66% oral cavity and oropharynx, 34% larynx) and were able to distinguish non-invasive lesions from invasive lesions with a sensitivity of 88.9% and a specificity of 89.0%.

Similar to the larynx, OCT has been found to be useful in the differentiation between benign, premalignant and malignant mucosal changes. In addition, OCT can be used in the oral cavity for screening, monitoring existing lesions, guiding biopsies (and thereby reducing the number of biopsies necessary), surgical guidance and post-treatment surveillance. The oral cavity is thereby easily accessed, and the OCT investigations (usually performed by direct placement of an imaging probe onto the tissue) can be performed in an outpatient setting. Compared to the larynx, the oral cavity’s normal epithelium is thicker in average and shows a greater intra- and inter-individual variability, so a definitive identification of the BM (especially in cases of benign hyperplasia) is often difficult. Also, oral (pre)malignancies are often associated with hyperkeratosis, which has a negative influence on the image quality. Therefore, this site might be slightly less suitable for OCT-based diagnosis than the larynx.

**Thyroid cancer workup**

According to two ex vivo studies performed on thyroid tissue, OCT might be helpful for biopsy guidance during open, minimally invasive, endoscopic or robot-assisted thyroid surgery or could be used as an adjunct to fine needle aspiration under ultrasound imaging for the screening of thyroid nodules. With a fundamental knowledge of histopathology, OCT might enable the surgeon properly to distinguish between lymph nodes, parathyroid glands and the thyroid gland and to identify normal, degenerative, hyperplastic, adenomatous and malignant thyroid tissue by revealing characteristic image features that relate to comparable histopathological findings (Figure 6). Obviously, these results need to be confirmed in larger investigations.

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Diagnosis of (chemo) radiation-induced mucositis

Mucositis is a common complication of head and neck cancer treatment that often cannot be diagnosed until changes are visible on clinical evaluation or the patient reports pain. Mucositis results from the deleterious effects of radiation and chemotherapy on the basal epithelial cells of the oral mucosa. Physicians are in need of a method to identify the earliest stages of mucositis, allowing for early intervention with the goal of increasing the patients' quality of life and decreasing the total cost of patient care. Muanza et al. found that OCT revealed thinning of the epithelium of the oral mucosa in mice before any clinical signs or symptoms were apparent. Others have confirmed these findings in vivo in humans. In 2013, Calantog et al. reported that specific imaging-based changes were a consistent predictor of clinical mucositis. Mucositis progression thus shows a decrease of epithelial thickness, followed by loss of the BM and layer distinction. OCT might thus be used in an office setting for early detection and monitoring of mucositis in the future.

Conclusion

OCT is a young, non-invasive imaging method that provides high-resolution, cross-sectional images of the most superficial tissue layers and that seamlessly integrates into other diagnostic procedures. It has shown highly promising results in smaller clinical studies which have applied OCT for the diagnostic workup of superficial pathologies of the UADT, mainly dysplastic, precancerous and micro-invasive early canerous lesions. For this indication, certain conditions such as pronounced hyperkeratosis and/or epithelial hyperplasia, as well as mucosal ulcerations, have a negative impact on the interpretability of the acquired images. Apart from its application for the diagnosis of superficial UADT lesions, OCT may also be helpful in the evaluation of neoplastic thyroid disease and in the preclinical diagnosis of (chemo) radiation therapy-related mucositis.

In conclusion, OCT is a very attractive technology that has the capability to satisfy several vital needs in head and neck oncology: high-risk population screening, guiding biopsy and surgical procedures and enhancing post-treatment surveillance. Larger, multi-centre trials are needed to validate the current findings and further define the method's clinical role. With the expected technical advances in acquisition of speed and resolution, as well as a wider public acceptance of the method, OCT seems to have a bright future in head and neck oncology.

Abbreviations list

BM, basement membrane; FD-OCT, frequency-domain optical coherence tomography; OCT, optical coherence tomography; PS-OCT, polarisation sensitive optical coherence tomography; SCC, squamous cell carcinoma; TD-OCT, time-domain optical coherence tomography; UADT, upper aerodigestive tract.

References


