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Review

Point of care optical diagnostic technologies for the detection of oral and oropharyngeal squamous cell carcinoma

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ABSTRACT

Background: Despite significant advances in treatment modalities, the 5 year survival rate in oral and oropharyngeal squamous cell carcinoma (SCC) is less than 60%. Clinical examination, white light endoscopy followed by blind biopsies and histopathological analysis remains the gold standard for diagnosis and surveillance. These modalities continue to have a limited diagnostic accuracy of less than 55%.

Methods: Novel optical-based diagnostic methods are promising new technologies for improving both screening and detection of cancer. This review will discuss their role in oral and oropharyngeal cancer detection with particular emphasis on optical imaging in oral and oropharyngeal cancer diagnosis, including the use of surface enhanced Raman spectroscopy, optical coherence tomography, fluorescence diagnosis, confocal laser endomicroscopy, confocal reflectance microscopy and narrow band imaging.

Results: Aided by the use of differing wavelengths of light, these methods are capable of detecting physical and biochemical changes that precede and mirror malignant change within tissue.

Conclusion: Our review of the currently utilized optical diagnostic modalities suggests the possibility of a cost effective, point of care diagnosis that could facilitate early detection, reduce healthcare costs and improve patient survival and quality of life.

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Introduction

The terms 'oral and oropharyngeal cancer' include a diverse group of tumours arising from the head and neck, including cancers of the buccal mucosa, hard and soft palate, tongue, and cancers of the oropharyngeal sub-sites such as tonsils, posterior pharyngeal wall and tongue base.[1] These tumours currently represent the sixth most common cancer worldwide.[2]

In Ireland, an average of 349 cases of oral or oropharyngeal squamous cell carcinoma were registered annually between 2010 and 2013. The five-year survival rate for these patients was reported to be 55% in 2011.[3] Furthermore, a study of oral and oropharyngeal cancers in Ireland identified that the diagnosis and treatment of advanced oral and oropharynegal cancer is placing a huge burden on an already overburdened healthcare system. Between 2003 and 2011, 37% of patients were diagnosed with stage IV disease, compared to 27% diagnosed with stage IV disease between 1994 to 2002.[4]

Currently, the gold standard diagnostic method for squamous cell carcinoma (SSC) is clinical examination with white light endoscopy, followed by invasive needle biopsy and histopathological analysis. From the patient's perspective, this could require up to 3 separate visits to hospital. This leads to anxiety, inconvenience and increased cost for the patient and the healthcare system while awaiting a diagnosis. Clinical limitations of these diagnostic methods including inadequate microscopic techniques and reporter-dependent bias in histopathological analysis means that early disease can easily be overlooked. Furthermore, disease progression, surgical margins, metastasis and extent of invasion are currently only monitored by diagnostic imaging methods such as X-rays, CT or PET scans, which are usually carried out prior to any surgical intervention.[5] These techniques, though clinically useful, (i) have radiation safety concerns, (ii) cannot reliably detect tumors less than 1 cm in diameter, and (iii) cannot be generated in real-time to guide surgeons intra-operatively.[6]

The fundamental concept of cancer progression is that tumours arise from the accumulation of a number of discrete genetic events including activation of oncogenes and inactivation of tumour suppressor genes that accumulate to form an invasive cancer.[7] This leads to uncontrolled cell proliferations, which only at later stages, such as with moderate to severe dysplasia, are reflected by physical changes in tissue architecture. It is well established that head and neck SCC develops through a multistep process of accumulated alterations in cellular structure and function permitting differentiation between low-grade dysplasia, high-grade dysplasia, and carcinoma.[7] such changes include the presence of irregular stratification and a lack of intercellular adherence and polarity. This combined with varying cellular features such as increased nuclear size and number and increased mitotic activity differentiates between low-grade dysplasia, high-grade dysplasia, and carcinoma.[8]

In certain cases, non-malignant epithelial cells with hyperplastic or dysplastic changes can present visually to the clinician as erythroplakia (red lesions) or leukoplakia (white lesions).[9] At the microscopic level, these lesions show varying degrees of epithelial dysplasia, from mild to severe.[10] Long-term studies have shown that the overall risk of malignant transformation of all grades of epithelial dysplasia has been reported to be approximately 16%.[11] However, it has to be noted that not all cases of true squamous cell carcinoma present with these pre-malignant changes.[12] In addition, in the absence of these visible morphological changes, white light endoscopy has limited use for pre-cancerous lesions owing to their flat appearance. Prompt surgical excision of these premalignant lesions could prevent progression to SCC. This represents the single greatest determinant of long-term patient survival and effective treatment. Therefore, it is clear that a novel, non-invasive method of identifying the sequential genetic alterations at the earliest possible time point of disease development is warranted.

Optical diagnostics is defined as the use of varying wavelengths of light to examine suspicious tissue in a non-invasive fashion *in vivo*. The penetration depth of light is dependent on its wavelength; the shorter the wavelength, the more superficial the penetration.[13] Normal endoscopic white light with a wavelength of 400–700 nm gives information about the mucosal surface only. Light in the ultraviolet (UV) region (100–400 nm) is absorbed by biomolecules and produces fluorescence. Such fluorescent molecules may be endogenous (e.g. haemoglobin) or exogenous (tumour-specific photosensitizers) and may be used to examine or probe for tumour vascularization or malignant tissue.[14] This property of light is exploited in many molecular imaging techniques such as optical coherence tomography (OCT) and fluorescence endoscopy. Light in the infrared regions (700–1000 nm) can penetrate up to 1 mm below the mucosa. In this way, optical biopsies can be produced and provide an instantaneous assessment of tissue architecture and detection of submucosal pathologies including hyperkeratosis, inflammation, dysplasia, carcinoma *in situ* and neoplasia.[15] In addition to using reflected light for imaging of pathologies, the inelastic scattering of light is utilized in optical imaging techniques such as Raman spectroscopy to provide spectral information of tissue at the molecular level.[16]

Ideally the optical diagnostic technique utilized should be minimally invasive and provide a cost effective, point of care, real-time diagnosis. This review aims to cover the current *in vivo* and immediate *ex vivo* modalities such as surface enhanced Raman spectroscopy, OCT, fluorescence diagnosis, confocal laser endomicroscopy, confocal reflectance microscopy and narrow band imaging and discuss their current application in the clinical setting.

Raman spectroscopy in cancer diagnostics

Raman spectroscopy is currently under intense investigation in oncology as a diagnostic tool for the non-invasive differentiation of normal, premalignant and malignant tissues.[17] The capability of Raman spectroscopy in differentiating between normal and dysplastic oral tissue was first shown in a pre-clinical *in vivo* study using a rat model (4NQO-treated) of oral cancer.[8]

Following some preliminary successes demonstrating major Raman spectral differences between diseased and normal human oral tissue that had been fixed[18] or frozen,[19] a study by Guze et al.[20] involving 51 patients successfully