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SHORT COMMUNICATION

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In-Vivo Microvascular Imaging, a Non-Invasive Diagnostic Method for Oral Surgery and Oral Medicine

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Abstract

There is a trend in the medical and dental fields to pursue alternative diagnostic and treatment strategies that are less invasive than traditional open surgical methods, while achieving equal, if not better clinical outcomes. Emerging technologies are helping to develop new diagnostic and treatment methods, many centred upon the philosophy of minimal invasive medical procedures bridging the gap between prevention and full formal surgical procedures.

In-vivo microvascular imaging is gaining popularity, with increasing recognition of the morphological changes that occur in the superficial mesodermal tissues, driven and as a direct response to the presence of certain diseases.

The Centre for Oral, Clinical and Translational Sciences, Faculty of Dentistry Oral and Craniofacial Sciences at King's College London, have developed a dedicated intra-oral video-capillaroscopy instrument, named Real Time Optical Vascular Imaging. This technology when combined with its dedicated software, Customized Angiogenesis Analyzer, has the potential to offer a real time, non-invasive diagnostic method for oral diseases, particularly, oral cancer.

There is a trend in the medical and dental fields to pursue alternative diagnostic and treatment strategies that are less invasive than traditional open surgical methods, while achieving equal, if not better clinical outcomes. Less or non-invasive procedures are the primary aim of all minimally invasive surgery [1]. One of the areas of most diagnostic significance is the incisional biopsy, a procedure much feared by patients and often used as an excuse to legitimize late or delayed presentation to healthcare services.

The last few years, healthcare has benefitted from great achievements due to technological and scientific advancements. For example, the development of laparoscopy, also known as "keyhole surgery", was facilitated by the development of adequate gas-tight access (Verres) needles, surgical instruments including endoscopes with appropriate dimensions lens and illumination configurations, capable of imaging inside the human body, while minimizing associated tissue damage [2]. The technological progress will continue to assist health care professionals in the pursue of the Hippocratic oath of "primum non nocere", meaning, "first do no harm" [3].

Emerging technologies are helping to develop new diagnostic and treatment methods [1] many centred upon the philosophy of minimal invasive medical procedures bridging the gap between prevention and full formal surgical procedures. If a disease can't be avoided by primary prevention, the onus is upon medicine to minimize the patient's treatment related morbidity, and to minimize risks from active diagnosis and treatment, while also minimizing the invasive component of monitoring in the tertiary prevention arena. This is paramount, especially in the context of cancer, as early diagnosis is crucial [4] and long-term surveillance for high risk and post-therapy patients. In this sense, it is important to develop more precise and real-time diagnostic methods that are less intrusive and more acceptable to patients, but more valuably, to accelerate the clinician's commitment to treat or to reassure and divert patients away from the cancer pathway [5].

Modern optical diagnostic techniques offer higher resolution, non-radiation based imaging and in some cases it is possible to derive a tissue "signature" based on the molecular structure (e.g. Raman based tissue interrogation) [6].

The use of differing wavelengths of light enables of detection of changes within the examined tissues and provide immediate results [7]. These diagnostic systems can be used in clinics as an adjunct to histopathological assessment or facilitating rapid diagnosis for patients [8]. Several optical devices have been developed for use in the head and neck region, such as elastic scattering spectroscopy, optical coherence tomography, autofluorescence imaging, high-resolution microendoscopy, Raman spectroscopy and narrow band imaging (NBI), to name a few [5,9,10]. NBI in particular is a contrast mechanism to enhance in-vivo macroscopic imaging of the distal circulation in mucosae and in some centres, is already used as part of routine gastrointestinal endoscopic procedures [11,12].

In-vivo microvascular imaging is gaining popularity in the medical field. Interest in studying the human microcirculation and in particular the capillaries (the smallest blood vessels in the body) is growing with increasing recognition of the morphological changes that occur in the superficial mesodermal tissues, driven and as a direct response to the presence of disease processes [13-16]. Inflammatory and mitotic conditions are known to be associated with angiogenesis (new blood vessel growth from pre-existing vasculature) [17,18]. Hence the study of angiogenesis may

allow clinicians to establish a diagnosis or at least to understand the likely mechanisms involved in the tissue disorder.

Knowledge about the link between vascular behaviour and disease, in particular cancer, prompted interest around developing in-vivo microvascular examination in different fields of medicine. Folkman and collaborators demonstrated that tumours are angiogenesis dependent [19-21]. Experimental animal models have demonstrated that angiogenesis is essential for tumour progression/ growth and that it requires a positive balance between tumour cell proliferation and cell death (apoptosis) [22]. Angiogenesis is now considered one of the hallmarks of cancer, including oral squamous cell carcinoma [17,23]. There is the potential to achieve a diagnosis of cancer through the detection of signs of angiogenesis in the microvasculature [15,24-26].

One of the most pressing decisions facing clinicians dealing with mitotic disease diagnosis, is the timely decision to enter or divert a patient away from the chemo-radio-surgical management pathways associated with oncology care.

The oral cavity offers an easily accessible anatomical site to study microvascular anatomy in health and disease, both for the diagnosis of local diseases but also as a test bed for diseases elsewhere in the body. For example, the sublingual microcirculation is currently being studied to determine the haemodynamic status of patients who suffered hypovolemic shock, most often in critically ill paediatric patients [27,28]. The importance of this assessment came from realization that conventional macro-vascular haemodynamic assessment methods (e.g. blood pressure and pulse (oximetry) do not correlate well with the microcirculation status in general and more importantly to Head & Neck clinicians, do not report the micro-circulation status local to the disease process, e.g. palatal mucosal blood flow in cleft repair, peri-tumour oximetry and blood flow as predictors of oxygenation (inversely correlating with aggression) and chemotherapeutics delivery capability, and flow in transplanted and grafted tissue.

Microvascular changes pertaining to the oral cavity have also been studied in relation to diabetes and Sjogren syndrome [29,30]. Early oral cavity microvascular studies also exist in relation to inflammatory and mitotic diseases [19,27]. Contrasting with the microvascular assessment related to a patient's haemodynamic status (microcirculation function), the morphological assessment of the microvasculature remains challenging [31,32]. Universally, previous studies were based upon a subjective analysis or if including any software, remaining dependent on examiner subjective interpretation [19,27,33,34].

A robust analytical method, able to objectively quantify microvascular anatomy in a region of interest, was totally lacking. Furthermore, there are several limitations to the currently available modalities available for in-vivo imaging of the oral cavity specifically. The Biophotonics group within the Centre for Oral, Clinical and Translational Sciences, Faculty of Dentistry Oral and Craniofacial Sciences at King's College London, have developed a dedicated intra-oral video-capillaroscopy instrument, named Real Time Optical Vascular Imaging (RTOVI) (Figure 1). This technology has been described in previous work [35,36], and it is based around a super-efficient and optically superior Hopkins' Rod type contact endoscope, as its main imaging component, permitting constant magnification contact image acquisition and an ability to access difficult sites within the oral cavity and potentially other gastro-intestinal regions with proper customization. RTOVI allows imaging of the red blood cells flowing within and therefore delineating the patent microvasculature in a field of view of 0.51 mm x 0.51 mm, permitting delineation and assessment of flow but more valuably, its morphology and architecture, already believed to reflect tissue local behaviour, demonstrating a differential pattern in relation to health and disease (Figure 2).

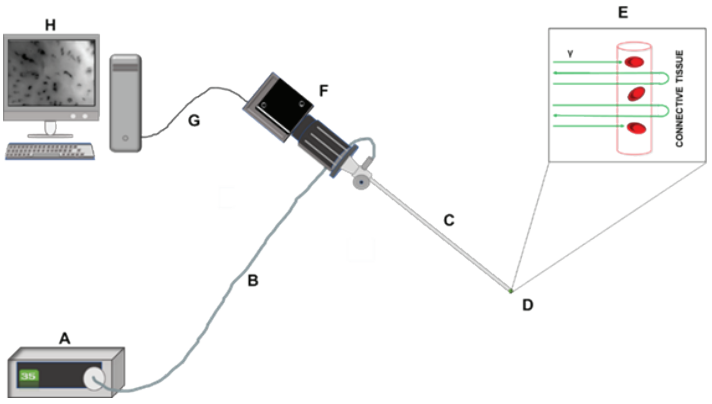

Figure 1. *Schematic representation of RTOVI system with the related components: xenon light source (A), arc lamp and a band pass filter (green) passing through an optical fiber cable (B) into an endoscope probe (C), and then scattered into the tissue being imaged (D). The photons that are reflected from the tissues (E) are captured by the probe and sent to a magnification system and a CCD camera (F). The CCD camera sends the digital signal through connecting cables (G) to a computer with a related software (H). Figure Adopted from Bastos and Cook, 2018, with permission from Mesford Publisher Inc.*

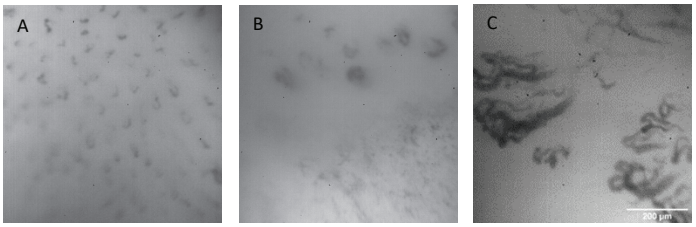

Figure 2. *In-vivo microvascular images, showing different patterns in the gingival margin of healthy tissues (A), dysplastic lesions (B) and squamous cell carcinoma (C). Image scale is represented in the white line, 200 µm.*

The true diagnostic capabilities of RTOV and the multitude of clinical applications remains vastly unexplored. The development and clinical integration of RTOVI imaging in the future has the potential to offer in-vivo and non-invasive diagnostics, guiding patients at the earliest opportunity to the correct management pathways, accelerating and streamlining their care, and address issues around oral cancer management, namely minimising diagnostic lead times and accelerating the clinicians' commitment to treat those patients, principally via tissue assessment and monitoring methods that are more acceptable to the anxious and afraid patient.

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