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Detection of oral potentially malignant disorders using liquid saliva in a novel optofluidic photonic crystal fiber

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Abstract: In this work we demonstrate novel optofluidic photonic crystal fiber to study biomarker changes associated with oral potentially malignant diseases from liquid saliva. The results show good agreement with *in vivo* tissue Raman measurements. © 2025 The Author(s)

1. Introduction

Oral potentially malignant disorders (OPMD) are characterized by abnormal changes in oral tissues, such as leukoplakia and actinic cheilitis, and can increase the risk of developing oral cancer by up to 35%. According to the World Health Organization, oral cancer is the 16th most common cancer worldwide and presents with 5-year survival rate below 50%, due to late diagnosis at advanced stages of the disease [1]. Therefore, early diagnosis and monitoring are crucial for preventing malignant transformation, but current diagnostic methods, such as biopsies and histopathology, are invasive and are not suitable for routine disease monitoring. Saliva, as a non-invasive biofluid, offers promise in detecting OPMD biomarkers due to its direct interaction with oral lesions. However, traditional methods for saliva analysis, like Raman spectroscopy, face challenges in detecting low-concentration analytes in liquid samples. The drying process, often used to enhance analyte concentration, risks altering molecular structure and reducing diagnostic reliability. To address this, we propose the use of optofluidic photonic crystal fibers (PCF) for real-time saliva analysis, preserving the molecular integrity of the liquid sample while enhancing light-sample interactions to achieve improved signal levels. This novel approach avoids the need for interfering substrates, such as nanoparticles, that can obscure analyte signals, offering a more accurate, label-free alternative for saliva-based diagnostics in oral cancer screening. In this work, we present results from proof-of-concept study where Raman signals from *in vivo* tissue measurements were correlated with PCF-based liquid saliva measurements from 11 participants.

2. Methods

This preliminary study involved 11 participants, including 5 healthy individuals and 6 participants with OPMD lesions. Approval for the data collection was granted by the Cork Research Ethics Committee (CREC) at University College Cork (UCC), under references ECM 4 (y) 13/4/2021 and ECM 3 (aaaa) 12/09/2023. Unstimulated saliva was collected by gentle drooling process and *in vivo* tissue data were recorded using custom Raman system described elsewhere [2]. PCFs fabricated at XLIM Research Institute - Limoges, France were used [3]. The core size and length of the PCFs were experimentally optimized to achieve best signal-to-noise ratio by varying the core size (2.5 μm, 3 μm, 3.5 μm) and length (4 – 16 cm) and recording data from the same healthy participant saliva. Filtered saliva samples were filled inside a syringe and injected into the PCF at a constant speed of 50 μL/min with a syringe pump. The PCF was subsequently placed on a XYZ stage and Raman signal from liquid saliva was measured using system shown in Figure 1 (a). Briefly, the system consists of two illumination channels: (1) green light for visual guidance and (2) 785 nm single mode laser for Raman excitation. The filtered Raman signals are measured using Teledyne (LS785, f/2) spectrometer and Teledyne CCD camera (Blaze 400HR). The liquid saliva spectra were recorded from each prepared fiber for 4 s with 22 mW laser power and averaged over 5 accumulations for better signal-to-noise ratio. Collected data were calibrated along x-axis and y-axis using Neon-Argon and white light lamps from IntelliCal spectral calibration system (Teledyne) and by standard spectra of acetaminophen and naphthalene. Data was normalized with standard normal variate analysis and Savitzky–Golay filter (order = 2, window = 7) was used for noise filtering.

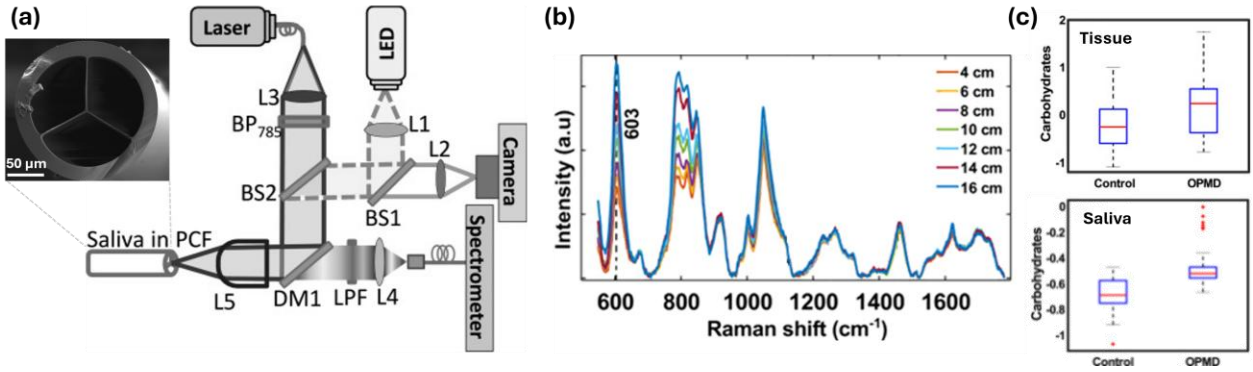

Fig. 1. (a) Design of system used for PCF measurements (inset shows the SEM image of the PCF), (b) Results showing changes in Raman signal as a function of PCF length, (c) Boxplot showing comparison of tissue (top) and saliva (bottom) signals for 1123 cm^{-1} corresponding to changes in carbohydrates.

3. Results and discussion

Figure 1(b) shows the average Raman intensity for different fiber lengths. The results reveal a strong silica background at 603 cm^{-1}, associated with the PCF, which clearly increases with fiber length. Similarly, the signals from saliva, with several distinctive peaks above 1000 cm^{-1}, also increase with fiber length. Taking this into account, to balance minimizing the interfering signals from silica while maximizing the saliva signals for optimal intensities across the entire spectrum, we selected a PCF length of 9–10 cm for all analyses. Likewise, the optimal core size was identified as 3.5 µm. Three spectral markers related to carbohydrates, proteins, and lipids—at 1123, 1251, and 1454 cm^{-1}, respectively—were identified in both tissue and saliva experiments, showing significant differences ($p < 0.05$) between healthy and OPMD groups. Consistent with previously published research [4], we observed that the features representing carbohydrates at 855 and 1123 cm^{-1} are more pronounced in OPMD spectra, reflecting their critical role in cellular processes. The corresponding statistical analysis plots for the 1123 cm^{-1} peak are shown in Fig. 1(c). The enhanced expression of these saccharide molecules on cancer cell membranes facilitates disease progression and their entry into the bloodstream and saliva.

4. Conclusions

Our primary objective was to explore the potential of using optofluidic PCF for liquid saliva analysis and to provide insights into both the molecular composition and structural changes associated with the early onset of OPMD. To achieve this, we investigated the Raman spectra of healthy and OPMD in vivo tissue and correlated them with PCF-based liquid saliva measurements. The optical confinement within the PCF core significantly enhances the interaction between incident light and the sample, allowing us to overcome the challenges of conventional liquid saliva Raman analysis. The spectral trends observed in liquid saliva aligned with changes in the in vivo tissue of the same participants, confirming that the variations detected in liquid saliva are related to OPMD. Significant spectral variations in carbohydrate, protein, and lipid levels were observed. These results suggest that PCF-based Raman spectroscopy holds promise as a real-time, non-invasive diagnostic platform for OPMD screening and disease monitoring by enabling the visualization of subtle molecular changes in liquid saliva.

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