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Non-Invasive multimodal spectroscopic Diagnosis for Early-Stage Oral Cancer

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Abstract: This study aims to develop a multimodal scheme for diagnosing oral cancer non-invasively in its early stages and to assess the performance of an integrated diagnostic platform comprising of Raman and diffuse reflectance spectroscopy systems.

1. Introduction

Oral cancer along with other head and neck tumours is the sixth most common cancer worldwide [1]. More than 90% of oral cancers are squamous cell carcinomas (OSCC). Use of tobacco, alcohol, areca nut and betel quid are the most common etiological factors of OSCC. Early diagnosis followed by appropriate treatment can significantly improve the survival rate and post treatment quality of life by reducing the need for extensive enervating treatments. Diagnosis of early-stage oral cancer is often complex due to uncertain development of a benign lesions into cancer.

This study aims to develop a multimodal scheme for diagnosing oral cancer non-invasively in its early stages and to assess the performance of an integrated diagnostic platform comprising of Raman spectroscopy (RS) and diffuse reflectance spectroscopy (DRS) systems. This study consists of two parts, an *ex vivo* saliva screening followed by the *in vivo* tissue analysis. Patients undergoing biopsy or histopathological examination will be recruited to participate.

2. System design

Raman spectroscopy (RS) is used to investigate the chemical signature of the tissue which allows the detection of structural, conformational, and compositional changes in the sample with high specificity [2]. To this end, we have customized a RS system, which is compact, mobile and easy to use as compared to commercially available systems with an aim to provide rapid point of care diagnostics. The system was designed to be fully reconfigurable as depicted in figure 1 (A-C). For *ex vivo* analysis, the system can be set up in an epi-configuration where Raman signals from the specimen are captured in the reflective mode. Microscope stage design can be modified according to the dimensions of the samples. Alternatively, the system can also be configured in a transmission mode stage for liquid specimen analysis with a hollow-core photonics crystal fibre to increase light-sample interaction length, thereby improving detection sensitivity. For *in vivo* analysis, the system is coupled to an optical fiber, which acts both as a laser-delivery as well as a signal collection conduit. Figure 1 represents the new Raman system.

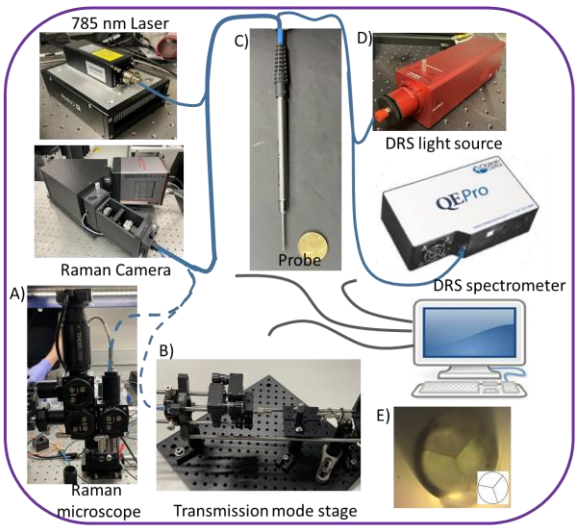

Figure 1: Home built Raman system coupled with optical microscopy

3. *Ex vivo* analysis on saliva specimen for oral cancer diagnosis

Patients undergoing histopathological examination in Cork University Hospital (CUH) have been enrolled in this study. Informed consent was be obtained from all the participants. *Ex vivo* measurements were carried out on saliva specimens using surface enhanced Raman scattering (SERS), with the aim to detect salivary biomarkers for oral cancer detection. gold nanoparticles (AuNPs) were used to enhance the Raman signals. Also, a photonic crystal fiber (PCF) was employed for transmission mode analysis to increase the sampling volume and thus enhance repeatability and sensitivity. Figure 1 (D) represents a microscopic view of the PCF that was used for the saliva analysis with its geometry in the inset of 1(D). In an initial study, a transmission mode stage was used to optimize the length of PCF (9cm- 13cm) by using vegetable oil as the analyte because oil is a strong Raman scatterer. The results shown in figure 2 (A) represents maximum Raman signal for 9cm and 10 cm PCF length. This figure also illustrates the Raman signal enhancement in PCF as compared to 2D CaF substrate. Figure 2(B) represents some preliminary SERS spectra of uric acid at different concentration to show the performance of newly designed system. We have used uric acid as a test analyte because it can serve as a potential biomarker for oral cancer.

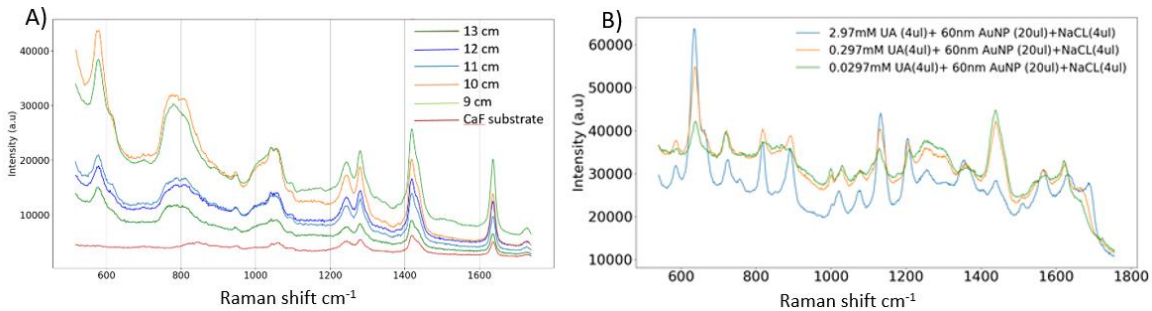

Figure 2: A) Length optimization of PCF with transmission mode stage using oil as an analyte B) Raman signal of uric acid at different concentration

Advantage of using PCF is improved sensitivity due to long light-molecule interaction length in a relatively small volume (20 - 100nL range). By virtue of the excitation of localized surface plasmons in AuNP-analyte mixture, the biomolecules near the particle surface also experience strong excitation due to enhanced electromagnetic field in that area yielding an overall amplified Raman signal. Prior to collecting *ex vivo* saliva samples, the participants were asked to fast for half an hour and rinse their mouth with water to avoid any food debris. The collected specimens were centrifuged to separate in supernatant and cell pallet and will be divided in parts to freeze. Later on, for label free analysis, specimen will be thawed and mixed with nano particles. The mixture will then be injected in a PCF and will be analysed in transmission and reflection mode with Raman system.

4. *In vivo* analysis for oral cancer diagnostics

The *in situ* studies were based on RS and DRS. Informed consent was obtained from all the participants. *In vivo* analysis involved measurements on healthy and malignant tissue using a multimodal fiber-optic probe that incorporates RS and DRS. During the tissue measurements, the optical probe was carefully positioned on the tissue of interest specified by the clinician. It included the spectroscopic measurements on the parts of the lesion where biopsy is to be performed and contralateral site of the oral cavity. Later on, clinician performed a normal biopsy procedure and histopathological analysis, which served as gold standard to determine the sensitivity and specificity of the spectroscopy techniques. Figure 3 represents typical Raman data from one of the patients showing the difference between lesion on cheek mucosa and healthy contralateral site.

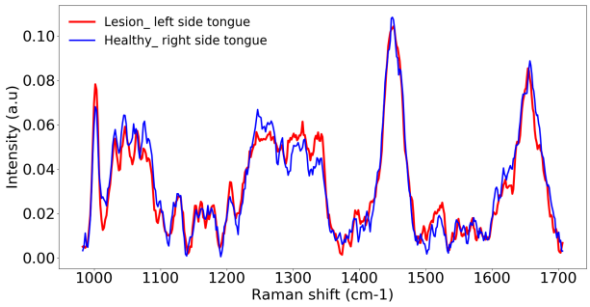

Figure 3: Representative *in vivo* Raman spectra from a participant depicting comparison between a lesion on the left side of tongue and healthy contralateral tissue on right side of tongue

5. Conclusion and future perspective

The obtained spectra from saliva specimen were analysed to differentiate between the saliva from participant having cancer and healthy person on the basis of proteomic biomarkers in saliva. The data obtained from *in vivo* analysis allows for the identification of cancerous tissues and it can further be used to analyse accurate margins of the tumor.

6. References

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