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Biophotonics diagnostics of oral cancer using Raman spectroscopy

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ABSTRACT

Oral cancer (OC) is one of the most common oral malignancies. Despite significant advances in medical devices, the five-year survival rate of OC remains low. Current technologies based on tissue pathology are insufficient to diagnose OC at early stages. Molecular sensitive technique such as optical spectroscopy, on the other hand, has the potential for early-stage diagnostics and non-invasive tissue interrogation. Raman spectroscopy (RS), for instance, is a powerful vibrational spectroscopy that allows highly sensitive detection of low concentration analytes, as well as molecular fingerprints of bio samples to be studied non-invasively. Additionally, higher spatial resolution, narrow peaks, better sensitivity and minimal sample preparation makes RS a potential tool for analysing oral cancer in a clinical setting. In this study, we will validate the potential of Raman spectroscopy (RS) and surface enhanced Raman spectroscopy (SERS) for oral cancer diagnostics. Patients having biopsy and histopathological examination were involved in this study. *Ex vivo* measurements were performed on saliva specimen using SERS while in-vivo analysis was performed by RS. Integration of *in vivo* tissue and *ex vivo* sample analysis could potentially improve early-stage OC detection, and hence the overall survival rate of OC.

1. INTRODUCTION:

Oral cavity cancer is some time referred as the mouth cancer or oral cancer (OC). It can occur in any part of the oral cavity including cheeks, gums, lips, tongue, floor of mouth and palate. A lesion in the oral cavity can start from a red (erythroplakia) or white (leukoplakic) flat patch having variable degree of dysplasia that represents the extent of the premalignancy [1]. Which sometimes can lead to a non-healing ulcer in later stages[2]. Early diagnosis and timely treatment can improve the survival outcome. Current gold standard procedure for diagnosing oral cancer is invasive biopsy followed by an expensive histological examination of biopsied tissue. This type of diagnosis has its own limitations and is subjective to sampling. Accurate diagnosis depends on many important factors such as type of biopsy, biopsy site and adequate specimen submission to the laboratory, quality of specimen and correct interpretation of biopsy[3-5]. Clinically innocuous oral premalignant lesions could be multifocal and can easily go undetected [5] or sometimes, inappropriate sampling during biopsy could result in overlooking some important features. This problem could be more intensified with the heterogeneity in the tissue. Other advocating techniques for early-stage oral cancer diagnosis include vital staining, cytology, chemiluminescence and optical imaging. Some of these diagnostic techniques show potential for oral cancer screening and early diagnosis but none of them have yet proved better than the conventional visual examination and histopathology of biopsied tissue. There is plenty of research devoted to developing less invasive but more effective diagnostic modalities that can facilitate selection of a more suitable lesion site for biopsy and determination of any oral premalignant lesion that should be completely excised [6].

In this regard, Raman spectroscopy (RS) could play an important role. It can provide the chemical signature of the sample being studied. Raman spectroscopy combined with saliva analysis is an emerging biofluid spectroscopy for oral cancer diagnosis. As water is a weak Raman scatterer, it is an ideal spectroscopy for analysing aqueous samples. Change in the concentration of biomolecules, any mutation or tissue deformation during cancer progression provides notable change in Raman signals[7, 8]. This study reports the development of a novel non-conventional method to diagnose oral cancer in early stages by identifying the biochemical changes in saliva specimen.

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2. MATERIALS AND METHODS

A customised Raman system shown in figure 1 is used for the *in vivo* Raman and *ex vivo* SERS analysis. The detail of system fabrication is described in another manuscript[9]. Patients suffering from oral squamous cell carcinoma and other malignant diseases going through biopsy or histopathological examination are currently being enrolled in this study approved by the Clinical Research Ethics Committee CREC of the university. Informed consent was obtained from all the participants. Saliva sample analysis was performed using surface enhanced Raman spectroscopy (SERS). To collect ex vivo saliva sample, the participants were asked to fast for half an hour and rinse their mouth with water to avoid any food debris. The collected specimen was separated in supernatant and cell pallet. Later, specimen was thawed and mixed with nanoparticles to induce surface enhancement. *In vivo* analysis involved measurements on healthy and malignant tissue using fiber optic probes for Raman systems. The probes were sterilized in between patient measurements. During the tissue measurements, the optical probe was carefully positioned on the tissue of interest specified by the clinician. Experiment included spectroscopic measurements on the parts of the lesion where biopsy is to be performed, adjacent normal mucosa and contralateral site of the oral cavity. Later, clinician will perform a normal biopsy procedure and histopathological analysis, which served as gold standard to determine the sensitivity and specificity of the spectroscopy techniques.

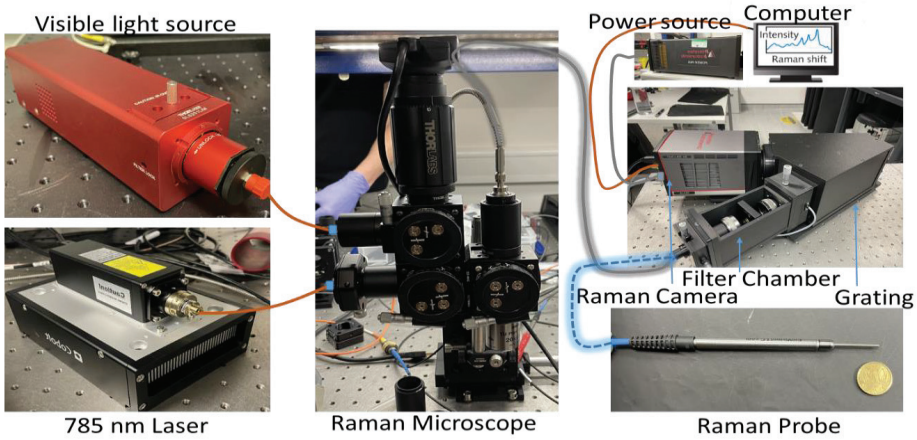

Figure 1: Customised Raman system coupled with optical microscopy

3. RESULTS AND DISCUSSION

The obtained spectra from Saliva specimen were analysed to differentiate between the saliva from participant having a malignant lesion and healthy person based on different biomarkers in saliva and a machine learning model will be developed with the help of collected data for future use. Which will eventually help in developing a screening method for oral cancer diagnosis. Figure 2 represents preliminary results from a healthy volunteer and a participant having a malignancy in the oral cavity. This data presents change in lipid, glycogen and amide I with the development of malignancy.

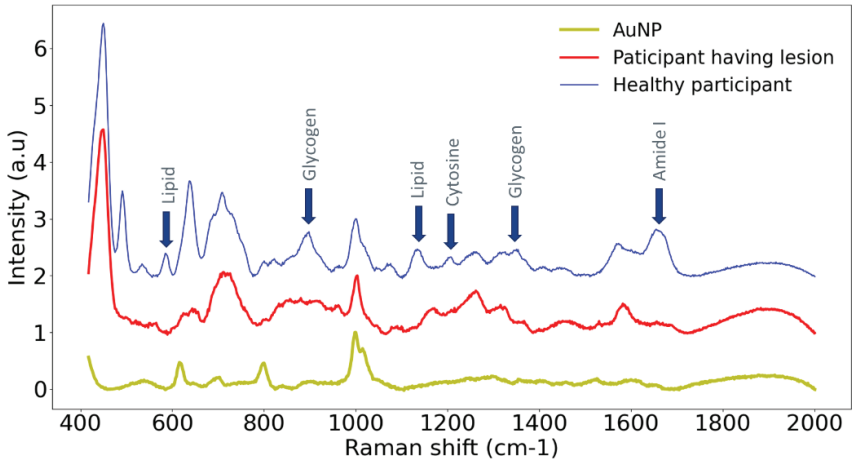

Figure 2: Preliminary SERS data from the saliva specimen of a healthy volunteer and a participant having lesion in oral cavity

Figure 3 represents preliminary *in vivo* Raman signal from four participants having a lesion in the oral cavity at different locations. Data was collected from the lesion and the healthy contralateral tissue. The difference in healthy tissue and lesion is obvious from Raman spectra. The difference in relative peak ratio of DNA with respect to protein and blood with respect to protein can be seen from the box plot.

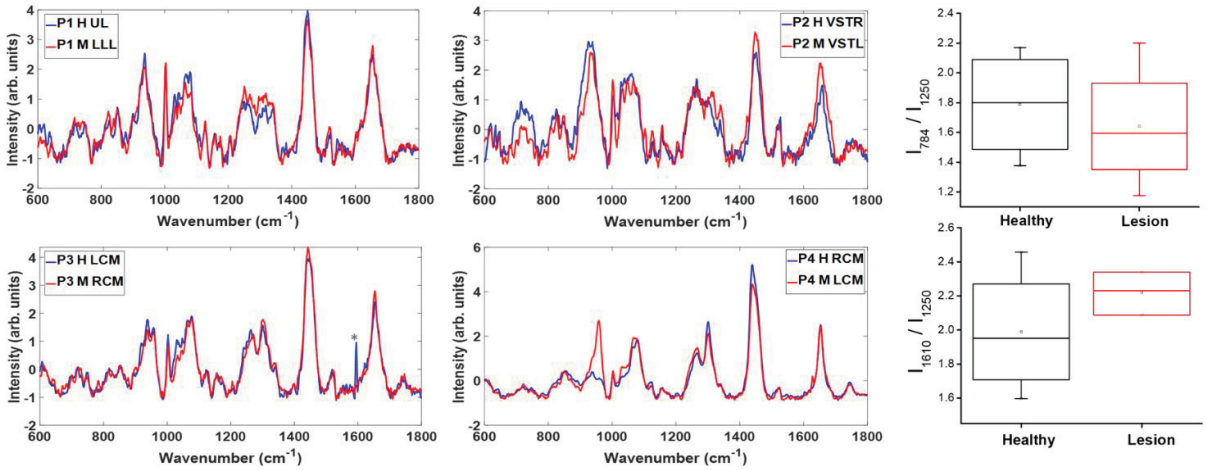

Figure 3: Left: Preliminary representative *in vivo* Raman results from four participants having lesion in the oral cavity at different locations. Red represent malignant tissue and blue represents contralateral healthy tissue in the same participant. Right: Box plot showing relative peak ratio for DNA/Protein and Blood/ protein

4. CONCLUSION

This study aims to detect biochemical changes in saliva and tissue through Raman spectroscopy and surface enhanced Raman spectroscopy during cancer progression. SERS analysis represents change in lipid, glycogen and amide I in saliva with the development of malignancy. This change can also be confirmed with the ratio of DNA to protein and blood to protein the *in vivo* tissue data.

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