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Review Article

Vast scope of raman spectroscopy in oral cancers and head & neck regions: A review

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ABSTRACT

Higher rates of local recurrences and second primaries, ascribable to field cancerization, are known problems in oral cancers. The present review explored utility of identification of potential recurrences by Raman spectroscopy, which has been shown to identify oral precancers, cancers, and field cancerization in humans and micro-sized mechanical irritation-induced tumours in animals. There is an urgent need for improved techniques for disease detection. The focus here, in vivo Raman spectroscopy (RS), measures inelastic light scattering with the vibrational and rotational modes of molecular bonds in cells/tissue. The Raman 'signature' can be used to assess physiological and/or altered pathological statuses. This information can supplement existing diagnostic techniques for screening and diagnosis, in interventional guidance for identifying disease margins, and in monitoring treatment responses. Using fiberoptic-based light delivery and collection, RS is performed on accessible tissue surfaces, either on the skin, in hollow organs or intraoperatively. The strength of RS lies in the high biochemical information content of the spectra, that show an array of narrow peaks associated with specific chemical bonds. This results in high sensitivity and specificity, e.g., to distinguish malignant/premalignant from normal tissues. An issue with Raman signal is that it is often weak, limiting clinical use to point-by-point measurements. Recent advances in instrumentation and spectral analysis have improved the feasibility of RS, so that it is now being investigated with increased success in cancer types, locations and for non-oncological conditions. This review covers recent advances and continuing challenges, with emphasis on clinical translation.

1. Introduction

The oral cavity is the primary component of aerodigestive tract and is made up of several distinct anatomic subsites. The oral cavity is primarily composed of the buccal mucosa, the upper and lower alveolar ridges with their connected gingiva, the lips, the retromolar trigone, the hard palate, the floor of the mouth and the anterior two thirds of the tongue. Any of these anatomic subsites can develop oral cancer. Oral cancer is one of the most prevalent malignancies in the world, as well as the sixth most common malignancy, and is strongly related to activities such as smoking, drinking alcohol, chewing tobacco, and ingesting betel quid. Oral cancer are a key cause of several health burden in under developed nations such as India, where they account for more than 30% of all malignancies, with 80,000 new case recorded each year.[1]

Typically, every disease that leads to oral cancer is preceded by a series of clinically apparent mucosal tissue

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abnormality are known as precancerous phase. These precancer phases might relate to the existence of a benign lesion or morphologically changed tissue with a greatly increased chance of malignant development. Leukoplakia, Erythroplakia, Oral Submucous Fibrosis (OSMF), tobacco pouch keratosis, and lichen planus are some examples of oral precancer or premalignant lesions. The excision of moderate to severe dysplastic lesions is recommended, whilst those with mild dysplasia are regularly monitored for evidence of reversal or progression. Surgical therapy, radiation, and chemotherapy are all therapeutic options for oral cancer; surgery, when paired with chemotherapy and radiotherapy, considerably increases the patient's overall survival rate. Squamous cell carcinoma is the most prevalent histology of mouth cancer (SCC).[2] Oral squamous cell carcinoma (OSCC), together with other head and neck cancers such as oropharyngeal cancer, is clearly the sixth most common malignant tumour worldwide. This neoplasm appears to be more common in men, with a male: female ratio of 1.5:1.[3] Oral squamous cell carcinoma (OSCC) is frequently identified at later stages, resulting in a five-year survival rate of only 50%.[4]The fundamental objective of oncological surgery is to remove all malignant tissues. In practise, however, this aim is frequently unmet.[5] Effective tumour positive resection margins are a key stumbling block in oral cancer surgery. Oral malignancies have higher incidence of local recurrences and second primaries due to field cancerization.[6] Inadequate surgery (tumour positive (one millimetre) or close resection margins (more than one and five millimetres) for oral cavity squamous cell carcinomas (OSCC) ranges between 30 and 85%. This suggests that current intraoperative procedures, such as eye inspection and/or tissue probing by the surgeon, are insufficient for adequately defining tumour margins.[7] Biopsies are the gold standard in the diagnosis of any oral cancer. They are intrusive and hence uncomfortable, necessitating an incision in the suspicious tissue. Because biopsies are both time -consuming and invasive, practitioners are increasingly preferring non-invasive procedures such as vital staining, light-based detection, and other optical diagnostic technologies. During surgery, frozen tissue slices are frequently collected to determine whether the margins are tumour-free. Although cutting-edge, this approach has many drawbacks, including being time-consuming and allowing only a small proportion (1-5%) of the resection margin to be examined successfully.[8] Water content in cells was reported as a potential measure for discriminating between tumour and healthy tissue as early as 1971. Following then, tissue water content has been extensively studied using a variety of methods, including magnetic resonance imaging (MRI).[9] Biomedical imaging technologies such as magnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT) have advanced greatly in their application in identifying tumours in recent decades. However, these traditional techniques have significant disadvantages, notably in terms of intraoperative efficacy. Optical imaging technologies, which may give quick, real-time tissue assessment with a better degree of spatial resolution, have recently been discovered to be critical in improving cancer diagnosis and therapy.[10]Infrared spectroscopy has been used effectively in the identification of head and neck tumours, along with other optical methods such as elastic scattering spectroscopy, differential path length spectroscopy, fluorescence techniques, and optical coherence tomography.[11] Raman spectroscopy (RS) is a rapid and simple optical method. Raman spectroscopy, a vibrational spectroscopy approach based on light's inelastic scattering property, offers a molecular fingerprint of the sample under examination.[12]

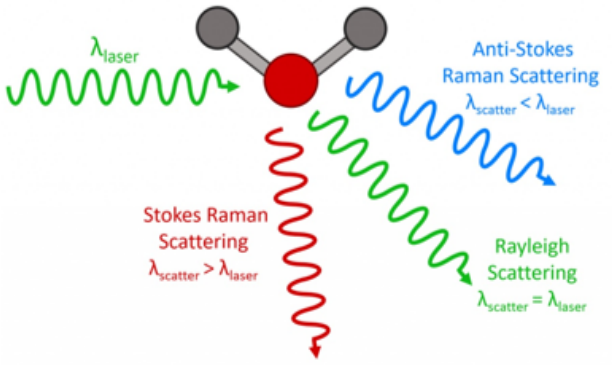

Fig. 1: All three different ways light can be re-emitted: (a) Rayleigh scatter (b) Stokes Raman scatter (c) Anti-Stokes Raman scatter.

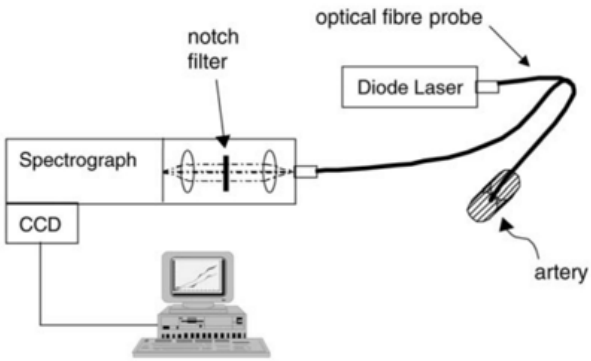

Fig. 2: Clinicalraman system

1.1. Raman spectroscopy (RS) for disease detection

As the name implies, it was discovered in 1928 by Indian Nobel Laureate C V Raman. However, it was not until 1970 that the phenomenon was documented for its use in the field of biomedicine (Lord and Yu 1970). Sir C. V. Raman discovered the property of inelastic scattering of light, popularly known as the Raman effect, following his pioneering investigations on the phenomena of scattering.[12] Raman spectroscopy has two key oncological applications: (A) biopsy guiding/early diagnosis and (B) surgical guidance. Light absorption, scattering, and reflection occur when any material is exposed to strong monochromatic light. The majority of photons that scatter have the same frequency as the incoming light (Rayleigh scattering), whereas a very tiny fraction (one in ten million) are inelastically scattered, i.e., with a frequency different from the incident photons; this phenomenon is known as the Raman effect.[13] In any tissue, only one out of every few million photons experiences inelastic scattering due to an exchange of energy with the vibrational or rotational modes of the molecular connections.[14] The laser photons that contact with the molecules finally excite the electrons within them. The energized electrons are inherently unstable. As these electrons lose energy and revert to their native ground state, photons are emitted in return. There are three possibilities for how light can be reemitted after an electron has exchanged energy: Because an electron returns to its original ground state with no energy change, a photon of identical wavelength to the energy released by the same electron is re-emitted. This is known as Rayleigh scattering. An electron that has been stimulated by incoming light falls to a vibrational level rather than the ground level. This signifies that the molecule absorbed energy throughout the operation, resulting in photons with a longer ger wavelength than the input light. This form of Raman scattering is known as "Stokes". When an electron is stimulated again from a vibrational level, it advances to a higher energy virtual level. When an electron from a higher energy level descends to the ground level, the emitted photon has more energy than the original photon, resulting in a shorter wavelength. This form of Raman scattering is known as "Anti-Stokes."

In all cases of Raman scattering, the energy change is inversely proportional to the wavelength of the photons, which may be observed spectroscopically as a colour change and is unique to each material under investigation. A Raman Spectrum is the outcome of Stokes and Anti-Stokes scatter measurements. (Figure 1) However, the Raman signal is relatively faint, making detection of Raman-scattered light difficult, especially against a substantial background of elastic scattering, fluorescence, and phosphorescence originating from the tissue.[15] As a result, advanced apparatus such as a strong excitation source, a high throughput spectrograph, and sensitive detecting systems are essential. The Raman spectrometer is typically comprised of the following components: (I) a source of excitation, (ii) an optical system, (iii) a spectrograph, and (iv) a detection and computer control/processing system. It is normally more convenient to provide the light to the tissue and collect the RS light using a specially built fibre probe, however various alternative probe designs for point-based measurements in contact with tissue have also been documented.[16] The probe normally consists of one central illumination fibre surrounded by several detector fibres, with a lens on the tip to enhance Raman signal collection. One of the most difficult difficulties in probe design is minimizing the detection of tissue fluorescence and Raman-scattered light created in the probe itself, such as silica-Raman of glass-fiber cores and fluorescence-Raman from the fiber buffer. These background signals can be created in both the light supply and collecting fibers, except if the light that is elastically dispersed by the tissue is prevented. It is especially challenging to incorporate properly tailored filters into the probe. Contact probes, endoscopic probes, and needle-based probes are some of the probe designs that have been refined for specific therapeutic uses.[17]

1. Light steering systems direct and choose laser wavelength for specimen excitation in the optical system.
2. The most important component of the Raman system is the Rayleigh rejection system, which prevents elastically scattered light from being incident on the spectrograph and detector. It facilitates the rejection of any Rayleigh scattered light and the effective detection of any comparatively weaker Raman scattered light.
3. The spectrograph will separate light into its constituent wavelengths.
4. In recent years, CCDs have been the most extensively used detectors for RS. (Figure 2)

Raman microscopy and imaging, resonance RS, surface-enhanced RS (SERS),[18] drop coating deposition Raman (DCDR),[19] and coherent anti-Stokes RS are some of the specialized forms of RS used for specific purposes (CARS).[20]

2. Applications

RS has been widely used in the domains of chemistry, biology, geology, pharmacology, forensics, pharmaceuticals, and material sciences because of characteristics like sensitivity, high information content, and non-destructive nature. Raman Spectroscopy can detect these changes quickly and help with illness diagnosis. This is the foundation for all Raman spectroscopic diagnosis of numerous illnesses, including cancer detection. Raman spectroscopy has a wide range of clinical uses, including surgical guiding and screening, as well as histopathological diagnosis. It is increasingly being employed in tissue

characterisation, thanks to recent technical and analytical advances. Many firms, such as Verisante (Canada) for skin cancer, ODS Medical (Canada) for brain cancer, and Endofotonics (Singapore) for endoscopic cancer detection, have already created an in vivo system for the clinical use of Raman Spectroscopy.

Raman spectroscopy is also being used to diagnose illnesses by measuring numerous fluids in the body such as blood, saliva, and urine, with several businesses producing toolkitsand microscopes for the same goal, such as RiverD. (The Netherlands). While a few single center studies have been undertaken on Raman technology and its human applications, there have been very few prospective studies, no blinded clinical trials, and no multicenter studies to evaluate its therapeutic impact. Furthermore, with the exception of Verisante for skin lesion diagnostics (Canada and Europe) and Raman Spectroscopy equipment, none of the businesses have gained regulatory permission (eg CE Mark in Europe, FDA in the United States) for the use of Raman-based devices in any clinical practise (ProTrusTech Co., Ltd., Taiwan).[13,21]

2.1. Oral cavity tissue

Oral and pharyngeal cancer cumulatively sums up as the sixth most common cancer in the world, out of which 50% of diagnosed cases are mortal.[22] Squamous cell carcinoma (OCSCC) is one of the most common form of cancer involving both the head and neck regions. Raman probe for cancer detection can be easily done in a clinical setup. Oral cancers commonly include lesions of the tongue, buccal mucosa, hard and soft palate along with the floor of the mouth. Clinico-epidemiological studies revealed that the biological characteristics of buccal mucosa and tongue cancers may differ these projects clinical manifestation in the prognosis, aggressiveness, metastasis to lymph nodes and overall survival. Surgical margins can have impact on disease control and survival for cancers in head and neck regions. Different biological markers such as the size of tumour, oncogene mutation expression, and apoptotic signals have been detected for buccal and tongue tumours on qualitative and quantitative estimation.[23] Under three categories, namely (a) diagnosis, (b) surgical margin detection and (c) prediction of treatment response the applications in oral cancer are summarized. Based on the characteristic Raman signal of adenine at 735 cm^{-1} Dai et al. performed Surface-Enhanced Raman Scattering (SERS) to differentiate human oral cancer cells from normal fibroblast cells in vitro.[24] Malini and colleagues (2006) studied the ability of Raman spectroscopy to insight 216 cases of pre-malignant, malignant, inflammatory and normal tissue samples from the oral cavity.[25] Sahu et al. carried out Raman spectral analysis of serum from oral cancer patients and also from healthy subjects revealed that Raman bands of beta-carotene and DNA content could be used for oral cancer diagnosis.[26,27] Hu et al. acquired spectra from 66 human oral mucosa tissues (43 normal and 23 malignant) using confocal Raman micro spectroscopy in 2008. After pre-processing these spectra using wavelet based analysis, PCA along with the calculation of these areas under the bands 1004, 1156, 1360, 1587 and 1660/cm were carried out for discrimination of the normal and malignant oral mucosa tissue samples.[28] Shifted excitation Raman difference spectroscopy study (SERDS) on 12 oral squamous cell carcinoma (OSCC) tissues could differentiate between malignant and benign areas with sensitivity of 86% and specificity of 94%.[29] Keratin used as a marker for OSCC identification using RS was recently demonstrated on 24 tissues samples with a sensitivity and specificity rate of 77–92% and 100%, respectively.[30] Rapid detection of oral cancer using 24 normal and 32 oral tumour sections on Ag TiO2 nanostructured SERS substrate has been recently shown to achieve 100% sensitivity and 95.83% specificity.[31]

Guze et al. carried out the first in vivo Raman spectroscopic study on humans for identifying site wise variations in the oral cavity. In this study, the feasibility of spectral acquisition from oral cavity, reproducibility of Raman spectroscopic signature of normal oral mucosa among different anatomical oral sites was evaluated on 51 subjects of different clan (Asian and Caucasian) and genders.[32] Li et al. demonstrated the use of near-infrared Fourier transform infrared (FTIR) spectroscopy in tandem with support vector machines for classifying oral squamous cell carcinomas (OSCC), oral leukoplakia (OLK) and normal tissues. Using FTIR and support vector machines (SVM), Li et al. were able to achieve a high level of sensitivity, specificity and accuracy hence, Raman spectroscopy may also have the potential to provide similar results.[33] In 2014, Krishna et al. created an in vivo multi-fibre Raman probe system and scaled a total of 28 healthy volunteers and 171 patients with oral lesions. Spectra were explained, based on histology or by clinical assessment, as oral squamous cell carcinoma (OSCC), oral submucosa fibrosis (OSMF), oral leukoplakia (OLK) and normal mucosa. Each group (OSCC, OSMF, OLK and normal) was correctly classified, when applying the developed diagnostic algorithm, in 89%, 85%, 82% and 85% of the cases, respectively.[34] In 2015, Guze et al. conducted an in vivo pilot study on 18 patients with a Raman probe to measure oral diseases. Benign and malignant oral lesions were classified correctly with sensitivity of 100% and specificity of 77% using a multi-fibre Raman probe.[35]

2.2. Raman applications in head & neck surgery

Multimodality treatment consist of surgery, radiation and/or chemo/biotherapy. Immunotherapy was added as a promising option according to a recent study. Surgery is often used to remove the bulk of the tumour before

chemotherapy or radiotherapy. This treatment is associated with high morbidity, as large surgical margins.[36] Achieving adequate resection margins is quite challenging. The lack of reliable intraoperative guidance and the proximity of tumours to vital structures are common reason for inadequate tumour resection. Barroso et al. investigated how the water concentration changes across the border between the tumour and healthy surrounding tissue on ex vivo specimens from patients who underwent surgery for squamous cell carcinoma in the oral cavity prior. Measurements were performed on 20 patients using a confocal Raman microscope system. The results revealed consistent amount of changes in the water concentration across the tumour border. The H&E sections performed as routine histopathological work-up revealed all the measured locations, tissue without degeneration and without any damages. For the majority of cases the water content of SCC was higher than that of normal tissue.[37] The definition of safety margin resection should consider several factors about the tumour and oral site, and the three-dimensional aspects of tumour extension and pathological factors such as the pattern of invasion should be analyzed.[38] Evidence suggests that an occult disease often extends beyond the extent of the visible tumour and is responsible for the high rate of recurrence of carcinoma at the primary site (10–30%).[39] In another study by Cals et al. Raman imaging of normal and tissue sections from 10 oral cancer patients was carried out and 127 pseudo colour Raman images were generated from it. These images were combined with the histopathological evaluation of same sections, and spectra were interpreted based on histopathological findings. LDA (linear discriminant analysis) was used to build models for tumour and surrounding healthy tissue. Thus, RS could successfully differentiate tumour and surrounding healthy tissues. As Raman measurements are fast and can be carried out on freshly excised tissue without any preparation, the development of an intraoperative tool for guiding tumour resection may improve the patient outcome.[40]

3. Discussion

Raman spectra shows correlation with molecular and cellular changes associated with disease, including cancer. Hence Raman specta can be used for monitoring treatment response associated with oral cancers. The Raman Effect is a fundamental 2-photon process in which energy is exchanged between light and matter, which is then measured in the form of inelastically scattered radiation. Raman applications in recent times is one of the most active research projects for cancer diagnosis and screening and a large number of studies have already been reported. There are several topical reviews covering different aspects of Raman applications in cancers.[41] Raman spectroscopy has shown potential changes in detection of both oral and cutaneous SCCs, along with melanoma and basal cell carcinomas. Raman spectroscopy studies associated with oral cancers have successfully demonstrated its utility in classification of normal, premalignant, and malignant lesions in the oral cavity.[42,43] Real-time in vivo Raman spectroscopy can provide rapid screening of the oral mucosa during follow-up and serve as a useful clinical adjunct to detect field changes.

4. Conclusions

Oral cancers are often associated with poor disease along with free survival rates. Improvements in screening, diagnostic, and monitoring can lead to improvement in treatment outcomes. A wide study of Raman spectroscopic applications in oral cancer have been carried out in recent times. Promising in vivo results indicate the ability to overcome the technical issues which are being faced during the use of RS in real clinical setup and motivate the need for any future advances. Fluorescence spectroscopy is a non-invasive method that must be further explored as a tool for the detection of surgical margins. The accuracy of this technique for detecting positive margins and field cancerization should be investigated in a larger number of patients.

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None.

6. Conflict of Interest

None.

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