Diagnostic applications of optical spectrometric techniques in oral precancer and cancer detection: A 5-year PubMed literature review.

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Abstract:

Oral cancer is the sixth most common cancer globally, where almost one-third of the total burden is contributed by India, thus ranking second in having the highest number of oral cancer cases. Most of the oral cancer patients do not show early symptoms with diagnosis being done at advanced stage of the disease, contributing to a low 5-year survival rate. Early detection may be imperative to reduce mortality in oral cancer. Hence, there is a need to employ a cost-effective and non-invasive technique to diagnose and differentiate these malignancies at various stages. Optical Spectrometry may provide a solution appropriate to facilitate the above due to its advantages over traditional methods such as painlessness, speed, sensitivity, objectivity, cost, and ease-of use in clinical setting. This review aims to provide a comprehensive overview of optical spectrometry in biological fluids and tissues for oral precancer and cancer diagnosis. A literature review was carried out in PubMed database, using keywords "Optical Spectroscopy", “Oral precancer” “Oral Cancer” and “Early Detection”. Research and review articles dealing with diagnosis of oral cancer using optical spectroscopy were considered and summarised according to the Year, technique used, their sensitivities and specificities.

Key Words: Optical Spectrometry, Oral Precancer, Oral Cancer.

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INTRODUCTION:

Spectroscopy refers to "The broad area of science dealing with the absorption, emission, or scattering of electromagnetic radiation by molecules, ions, atoms, or nuclei." Spectrometric methods refer to "The measurement of the intensity of radiation with a photoelectric transducer or other types of electronic device." Today, spectroscopic techniques are widely used analytical methods, which are useful in determining the identity and concentration of unknown substances in solution. It is widely based on the principle of interaction between matter and ultraviolet, visible, infrared, or Xray radiation.[1]

Cancer is a global health problem, with oral cancer being most common in the Indian scenario.[2] Cancer refers to "uncontrolled growth of cells, invading the nearby tissues via blood and lymphatic system".[3] Oral cancers are often preceded by clinically visible mucosal alterations termed "precancer stages." Early diagnosis is thus beneficial to improve cancer control and survival outcomes. Hence, these limitations can be overcome by spectroscopic tools, which provide real time, non-invasive, and rapid, bedside analysis of structural and biochemical changes in cancerous tissues.[2] Spectroscopic techniques collect the spectral signatures generated by endogenous fluorophore molecules in abnormal and healthy tissues upon excitation with a suitable wavelength and thus used as diagnostic tools.[4] When light interacts with matter, a a plethora of optical phenomena such as reflection, scattering, absorption, and fluorescence take place. These optical properties of the biological matter can be analysed using spectroscopy, to provide information about their physical, chemical and metabolic state.[2] Optical spectroscopic techniques such as Raman spectroscopy (RS), fluorescence spectroscopy (FS) and diffuse reflectance spectroscopy (DRS) have been widely used as adjuvants in oral cancer screening[2,3]. This review aims to provide an overview of use of the above spectrometric methods in biological fluids and tissues in oral precancer and cancer diagnosis revealed through clinical studies in PUBMED database. It concludes with the note on future developments from a clinical view point.

Table 1: Comparison of general characteristics of RS, FS and DRS [4,5,6,7]

	Raman spectroscopy (RS)	**Diffuse Reflectance Spectroscopy (DRS)**	**Fluorescent spectroscopy (FS)**
Principle	The Raman shift effect caused due to inelastic scattering of light provides information on the composition of the sample.	Multiple back scattering of light inside the specimen due to change in the size, shape, cellular density, refractive index, and absorption in the sample.	Excitation of fluorophores in sample causing change in vibrational energy, thus emitting the difference in the energies in the form of visible fluorescence.
Incident light	*UV, Visible, *NIR	Visible, *NIR	*UV, Visible
Phenomenon	Scattering	Absorption and Scattering	Photoluminescence effect
Suitable for ex vivo/in vivo	Yes	Yes	Yes
Suitable for biological specimen	Yes	Yes	Yes
Suitable for blood & Saliva	Yes	Only highly scattering specimen	Yes
Specificity	High	Moderate	Moderate
Sensitivity	Low	High	High
Instrumentation	Measures significant changes in Raman the signals	Analyses concentrations of absorbing tissue chromophores in the sample	Rapid detection of fluorescence and autofluorescence intensities.
Drawbacks	Strong background fluorescence, weak signals	Diagnostic accuracy may be low.	May show misdiagnosis due to low specificity.

Significance in Cancer Research	RS helps identify specific chemicals produced from in the body during malignancies.	Helps identify cancerous changes in tissue such as epithelium thickness, collagen content, size of nucleus and the vascularity.	Helps identify spectral differences in *FAD, *NADH and tryptophan in cancer and normal tissues.

***UV – Ultraviolet** ***NIR- Near Infra-red**

*** NADH - Nicotinamide adenine dinucleotide + H^+** ***FAD - Flavin Adenine Dinucleotide**

Table 2: Comparison of Optical spectrometry with various diagnostic methods[8-15]

Properties	**Optical spectrometry**	**Other methods (*H/P, Imaging, Vital staining, Molecular and genetic methods)**
In Vivo application	√	X (except Imaging technique)
Non-Invasive	√	X (except Imaging and PCR technique)
Real time	√	X (except Imaging and PCR technique)
Time required	Instant	Mins - Days
Portability	√	X (except other light-based detection methods)
Detection accuracy	Medium	Med – Very high
Cost effectiveness	Low cost	Low – Expensive
Expertise	Not required	Required
Automation	√	X

***H/P - Histopathology**

Table 3: Clinical studies showing sensitivities and specificities in oral cancer diagnosis using RS, DRS and FS[16-28].

Author & Year	Type of Spectroscopy & Objective of study	Pathology	Conclusion	Sensitivity	Specificity
Sahu A et. Al, 2017	**RS** Use of RS coupled with cytopathology in differentiating oral cancer and precancer	Oral Precancer	RS coupled with cytopathology could be considered a useful adjunct in screening and monitoring of oral precancerous lesions	83%	-
Tan Y et. Al, 2017	***SERS of Sera** To use surface enhanced Raman spectroscopy (SERS) in combination with other techniques in serum samples of oral cancer patients to develop new diagnostic technique.	Oral Cancer	*SERS combined PCA-LDA was successful in Diagnosis of OSCC through the serum sample.	80.7%	87.1%
Malik A et. Al, 2017	**RS** Utility of RS in predicting recurrences in oral precancer and cancer.	Oral precancer and Cancer	RS was able to identify sites which has higher propensity to progress to cancer.	80%	29.7%
Yan YJ et. Al, 2017	**FS** To develop a portable LED-induced autofluorescence (LIAF) imager for screening of oral cancer	Oral cancer	FS spectroscopy was capable of ex vivo diagnosis in oral cancer.	84%	76%
Kumar P et. Al, 2018	**FS** To test diagnostic ability of saliva in Oral precancers and cancers using FS and *SS	Oral precancer and Cancer	*SS spectroscopy makes using saliva makes a better diagnostic tool for oral precancer.	100% 94% 94%	97% 100% 94%

	spectroscopy				
Xue et. al, 2018	**RS** Use of SERS in detecting the clinical and histologic staging using serum samples in oral cancer.	Oral Cancer	SERS of blood serum had the ability to predict the occurrence of OSCC.	-	> 85% (Mentioned as Accuracy)
Brouwer de Koning SG, 2018	**DRS** To develop a technology that can assess tumour margins during resection in oral surgery.	Oral Cancer	DRS showed high sensitivity in differentiating normal and tumour tissue with a distance as small as 1 mm ex vivo.	89%	82%
Madathil GC et. al, 2019	**RS** Testing of a novel SERS catheter device for rapid detection, classification, and grading premalignant, and malignant tissues	Oral cancer and precancer	SERS catheter device can be used for accurate detection and grading of solid tumors.	-	97.24% (Mentioned as Accuracy)
Jeng MJ et. al, 2019	**RS** To study the utility of RS in detecting normal tissue from oral cancer using different classification model studies.	Oral Cancer	Found differences in protein biomolecules to be useful markers for detecting oral cancer	90.90%	83.33%
Jeng MJ et. Al, 2020	**RS** To use combination of VELScope and RS technique to increase accuracy of detection of oral cancer in screening programs	Oral Cancer	Combination of two spectroscopic methods greatly enhance the sensitivity and specificity.	100%	94.3%

***SS- Stoke shift spectroscopy** ***SERS- Surface enhanced RS**

LIMITATIONS & FUTURE PERSPECTIVES:

Optical spectrometry methods show instrumental limitation and lack of diagnostic validation and hence cannot still be conventionally used in clinical diagnosis. Thus, there is need for improvise on instrumentation, analysis approach and standardisation. However, It can provide an excellent tool for mass screening as it does not require expertise. Trace elemental detection is an upcoming field in cancer detection where various spectrometric methods such as atomic absorption spectroscopy (AAS), atomic emission spectroscopy (AES), Proton induced X-ray Emission (PIXE) etc. are being used. Use of multimodal approaches and combination techniques could possibly overcome the limitations of independent techniques.

CONCLUSION:

Biomedical optical spectrometry provides real-time diagnostic information which is non-invasive, cost-effective, and painless with less expertise and higher sensitivity and specificity qualities. It can be used as an adjuvant to biopsy or in cases where biopsy is not feasible in potentially malignant and malignant diseases of oral cavity. There is also a scope for usage of endoscope combined with spectrometry in these diseases. Body fluids like blood and saliva as well as tissues from various parts of the body have also proven their potential in diagnosis of oral cancers using spectrometric methods.

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