A survey paper on development of screening device for oral cancer detection

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Abstract—*Oral cancer is the most significant and growing concern worldwide. It ranks as 3rd in India and 8th largest prevalent form of cancer in world. Oral cancer is often diagnosed, only after reached to an untreatable stage. Early detection and prevention are the major objectives to control the oral cancer. Histopathology analysis of biopsied lesion followed by visual examination is the current clinical procedure. This procedure is invasive and requires a waiting period for the diagnostic results. Thus, there is a need to develop a non-invasive screening device for oral cancer detection. Optical imaging has emerged as effective tool for detecting malignant changes associated with oral cancer and also effective in assisting with the detection of oral mucosal abnormalities. Hence, this paper focuses on development of non-invasive, real-time diagnostic tool based on optical imaging technique in which involves - fluorescence emission and diffuse reflectance imaging modalities for screening of oral cancer.*

Keywords—***Early diagnosis, non-invasive, Optical Imaging, fluorescence emission, diffuse reflectance imaging modality.***

I. INTRODUCTION

World Health Organization (WHO) has estimated that the oral cancer deaths in India are projected to increase to 12, 00,000 by 2015 [1]. Oral and pharyngeal cancers (OPC) are considered an important part of the global burden of cancer, mainly due to the widespread use of tobacco and alcohol [2].Cancer can develop from different types of lesions into histopathological defined ones, throughout different lesions and stages. Early stages are often hard to detect due to their flat appearance, unnoticed irregularities of the mucosal surface and the lack of morphological characteristics oral lesions.

The current clinical procedure for oral diagnosis remains tissue biopsy with histological examination. But this method is based on visual examination and identifying the most malignant site for the biopsy, is difficult for the clinicians. Further, this leads to multiple oral biopsies which are painful and discomfort to the patients. This process is invasive and requires a waiting period for the diagnostic results and not always accurate.

Therefore a recent advancement in oral cancer research has led to the development of potentially useful diagnostic tools at the clinical and molecular level for the early detection of oral cancer. Many researchers have developed non-invasive and real-time diagnostic tools to enhance the early detection of oral lesion.

Some of the commercially available diagnostic tools for detection of oral cancer include- Toluidine blue dye, Oral CDx brush biopsy tool, and salivary diagnostics and lastly optical imaging devices include: ViziLite, VELscope, Identafi 3000 and Oscan. All these existing products are helps the clinician in visual examination.

1) *Toluidine blue stain*

This method has been used for decades to aid in the detection of mucosal abnormalities of the cervix and the oral cavity.Toluidine blue is a dye used as a marker to differentiate oral lesions at high-risk population which helps in early diagnosis. This method is useful in identifying the carcinoma in situ and invasive Squamous cell carcinoma, but this is only an adjacent tool for clinicians. Toluidine blue has advantage in identify the sites needed for the biopsy and also delineating margins of the lesions which helps in early diagnosis for the surgical management.

Monastir J et al [3] conducted a study on toluidine blue application to identify the tumour margin. In total 56 patients were used in this study and result obtained was 100% sensitivity and 84.9% specificity. This paper concludes that toluidine blue is simple and cost-effective method and its best method to identify the smaller oral lesion than larger lesions. This method is still in use by many clinicians in India because of its cost. This method cost 60 INR per patient for one time usage.

2) Brush biopsy technique

Removal of tissue from living body to identify whether a tumour is malignant or benign is called biopsy. Brush biopsy technique involves collection of epithelial cell by brush and evenly fixing samples onto a glass slide and analysis done by microscopic via computer and followed by imaging system. This complete system is known as OralCDx. The OralCDx brush system method includes trans-epithelial sample of cells collection from mucosal lesion. This provides dentists to identify an early stage of oral cancer [4].The result of brush biopsy is highly sensitive and specific in identifying dysplastic changes in high-risk population but the accuracy is reduced when it used in low risk patients and gives more false-positive results [5].

3) SALIVA as a diagnostic tool

Saliva has been used as a diagnostic tool in oral cancer detection. It contains proteomic and genomic biomarkers, in which reflects the normal and disease states. Saliva has been used to detect caries risk, periodontitis, breast and oral cancers, disease related to salivary gland and human immune deficiency virus and hepatitis C virus.

A highly sensitive and high-throughput assay such as DNA microarray, mass spectrometry and nanoscale sensors provides the protein and RNA measurements with less concentration in saliva, thus expanding the utility of saliva as a diagnostic tool [6].

4) Chemiluminescence

Chemiluminescence is emission of light as a result of chemical reaction [7].ViziLite systems manufactured by Zila, USA is Chemiluminescence based hand-held imaging device includes disposable chemiluminiscent light stick in which emits light at wavelengths of 430,540 and 580 nm. This system is used to improve the visual examination to discriminate normal tissue and oral lesions. Normal cells absorb light and appear dark whereas dysplastic lesions appear white. This colour difference related to changes in epithelial thickness and mitochondrial matrix that reflect light in the pathological tissues [8].

ViziLite is useful in detecting dysplastic changes in high risk patients with 95.45% specificity and 84.6% were obtained in [9] and this paper concludes that this screening device is adjacent tool to identify malignant lesions and some of the limitations are early detection of oral lesion cannot be done and device cost is very high ($300).

Some of the products are available in the market are based on fluorescence imaging based.

5) VELscope system

It is manufactured by LED Medical Diagnostic Inc. It is hand-held fluorescence based visualization tool which uses Light emitting diode (LED), wavelength at 400-460nm for the visualization of tissue fluorescence. When blue light is illuminated in the oral cavity, pale green autofluroscence emitted by normal mucosa and there is decreased auto fluorescence in abnormal tissues which appears darker compared to healthy tissue [10]. 97% of sensitivity and 94% of specificity was obtained in identifying premalignant lesion a study conducted by Poh and others [11].

6) Identafi®

It is a small size, compact, dental-mirror-shape device manufactured by TrimiraTM LLC. The device uses fluorescence and reflectance techniques to enhance visualization of mucosal abnormalities. To examine the tissue reflectance Identafi technology use LEDs produce three different light wave lengths (white, violet and amber), amber light is to enhance the reflective properties of the oral mucosa, allowing a distinction between normal and abnormal tissue vasculature [12].

Schwarz RA et al [13] study conducted using the Identafi 3000 for screening of 124 subjects, result obtained was 82% sensitivity and a specificity of 87% in differentiating between neoplastic and non-neoplastic oral conditions.

7) Oscan

It is a plastic mouth positioner mounting for Smartphone’s which enables early diagnosis of the oral cavity developed by Prakash Lab at Standford University. It consists on a plastic mouth positioner with a circuit board and two rows of fluorescent blue light emitting diodes, which can be attached to any smart.

This screening approach takes advantage of built in camera of the Smartphone, which allows the operator to take a high-resolution panoramic picture of the oral cavity. Images can be wireless sent to doctors and dentist for its analysis and diagnosis [14].

All these devices have their own advantages and disadvantages in detecting oral precancers but unfortunately patients are still being diagnosed in advanced stages of oral cancer because of failure in their practical implication in the community setup, and also not popular among Indian practitioners due to their price, lacks in gathering and analyzing the image.

Hence there is need to develop a non-invasive screening device in which identifies the oral precancers in real-time. The non-invasive detection techniques can be obtained through Optical spectroscopy. The basic principle of this technique is the optical spectrum of a tissue contains information about biochemical composition that conveys diagnostic information in cancer detection.

II OPTICAL SPECTROSCOPY

It is a non-invasive method capable of measuring structural and molecular changes of oral tissues during neoplastic progression. Screening with optical imaging and spectroscopy has the potential to improve oral cancer diagnostics, while also lessening time and discomfort associated with traditional procedures.

Optical imaging system involves two types of modalities –Fluorescence emission and diffuses reflectance techniques. These modalities give morphological information of tissue which helps in cancer detection. Each of this spectroscopic technique has its physical basis and all have potential to become an adjacent method to conventional cancer detection methods. By the current researches have proved that among these optical techniques, the fluorescence emission and diffuse reflectance are best techniques for cancer diagnosis.

1) **Fluorescence technique**

It is a new method to differentiate cancerous cells from normal. Flurophores with in oral epithelium and stroma absorbs UV and Visible light and these cells re-emit some of this light at a longer wavelength in the form of fluorescence. The reflected light with long wavelength fluorescence is possible to visualize by naked eye.

Its non-invasive, gives real-time diagnosis and no dye is required. Changes in the tissue morphology in which related to development of cancers can be detected using fluorescence method also have the potential to discriminate stages of cancer development. Autofluorescence emission is produced by fluorophores present in human tissue such as collagen, FDA present in epithelial layer, NADH and elastin in stroma, porphyrin [15].

Changes in the structure i.e., cellular increase and metabolism and sub-epithelial stroma alteration during tissue transformation towards malignancy modify the way light interacts with tissue.

These changes alter the distribution of tissue fluorophores and the way they emit fluorescence after stimulation with blue excitation light in 400 to 460 nm range. This technique has many advantages such as real-time diagnosis and non-invasive, improves the effectiveness of oral exams, has been studied by many researchers.

Svistun E et al [16] observed a maximum contrast in characterization of oral tissues by observing autofluroscence spectra at 530 nm. Xenon lamp is used for illumination.SLR Canon camera with a 100-mm micro lens and a broad band (60 nm) filter is used to view the fluorescence image. The sensitivity of 91% and specificity of 86% obtained for discrimination of normal tissue from neoplasia compares favorably with the sensitivity of 75% and specificity of 43% obtained with white light illumination. This study concludes that the fluorescence based system enhances the visual examination in which helps the clinician to view by naked eye and also provides the contrast between the normal and cancerous tissues.

Catherine PF et al. presented a florescence based VELscope which uses metal halide lamp 405nm and 436nm emission peaks. VELscope enhance the visualization of neoplastic lesion. The study achieved a sensitivity of 98% and specificity of 100% from biopsies taken from 44 patients using histopathology method for discriminating normal tissue from precancerous cells [17].

Ramanujam et al [18] performed a clinical trial based on fluorescence spectroscopy to diagnose the cervical cancer. 28 patients were examined using fibre-optic probe with laser at 337nm for illumination of tissue. Result obtained was sensitivity of 92%, and a specificity of 90% in separating normal from abnormal tissues using spectral based algorithms.

Rupananda J et al [19] developed a spectral ratio reference standard (SRRS) to identify the early stages of oral cancer. The fibre-optic spectrometer with 404 nm diode laser is used to collect the fluorescence spectra in 420-720 nm spectral range from the 35 healthy patients and 44 patients with high- risk lesion in oral cavity. The mean in vivo LIAF spectra of different tissue types, normalized to the intensity of the autofluroscence peak is shown in Fig.2.These fluorescence intensity ratios were used for scotterplot to discriminate the oral normal mucosa from hyperplasia, dysplasia and from SCC. 100 sensitivity and specificity were achieved by F500/F685 intensity ratio and 1005 sensitivity and 83% specificity by F500/F635 intensity ratio.

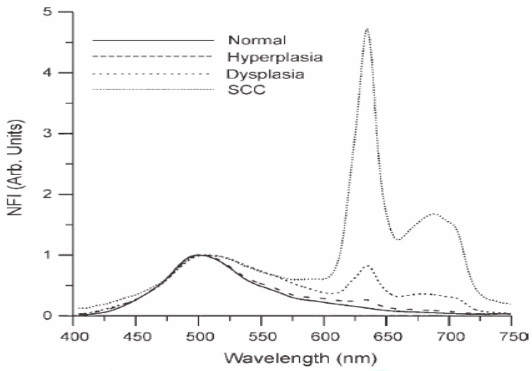

Fig.2 Laser-induced autofluroscence spectroscopy (LIAF) emission from different types of oral mucosa [19].

2) **Diffuse reflectance technique**

Among all new quantitative optical methods, diffuse reflectance system is simple, low-cost and non-invasive modality for diagnosis of tissue abnormalities. When white light entering the tissue undergoes a combination of multiple elastic scattering and observation, re-emits the diffusely reflected light.

It is analyzed to identify spectral sign of tissue which helps in identification of dysplastic transformation of tissue. Cancer detection with reflectance spectroscopy is based on optical properties, such as coefficients of absorption and scattering, tissue change as dysplastic, in which change the reflectance spectrum.

The biological tissues contain water (H2O), melanin and oxy and deoxy hemoglobin (Hb and HbO2), these are wavelength dependent and absorption coefficient are presented in Fig 1.The wavelength ranges from 600-1300 nm is called optical window used for the diagnostic purposes. The light in this region provide the better penetration.

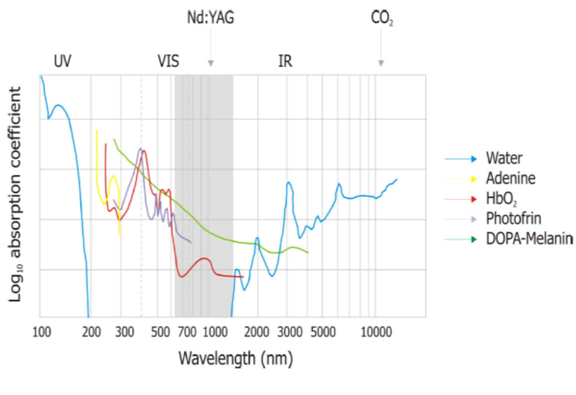

Fig.1 Absorption coefficients of biological tissue is along with the wavelength [20].

Oxygenated hemoglobin dips at 420, 545, and 574nm can be observed in this region.Therefore, this absorption gets affected by changes in blood content and oxygenation that are known to be associated with cancer due to altered tissue metabolism. Therefore the absorption features of HbO2 has been used for detecting tissue abnormality, characterization and early cancer diagnosis [20]

Several researchers have used diffuse reflectance spectroscopy to study biological tissues and in tissue characterization. Many of the instruments developed and tested both in vitro and in vivo, show promise to increase both sensitivity and specificity.

Bing Yu et al [21] developed a low cost, portable, smart optic sensor system based on diffuse reflectance spectroscopy (DRS). The system consist high power white and 850nm LEDs for tissue illumination and fiber – optic USB spectrometer for detection of DRS spectra. LabVIEW software tool is used for collecting the data and analysis processes. This paper concludes that DRS with fiber optic probe is powerful tool for quantifying the optical properties of the epithelial tissue and also helps in oral and cervical cancer detection.

Diffuse reflectance spectral features mainly depend on the absorption and scattering properties of tissues and on oxygenation levels of haemoglobin. The oxygenated haemoglobin absorption peaks at 545 and 575 nm helps in detecting tongue cancer. The sensitivity and specificity achieved are 86% and 80% to differentiate normal lesions from benign hyperplasia [22]

Dr. N. Subhash et al [23] studied clinical application of diffuse reflectance spectroscopy using a fibre-optic system. The system consist fibre-optic probe with six fibers mounted around will collects reflectance spectra in 400-600 nm range from different site of Oral cavity. It has been observed that DRS shows the Oxygenated hemoglobin absorption dips at 545,547nm and intensity ratio of 545nm and 575nm useful indiscriminating a malignant from normal mucosa. This study shows that the R545/R575 ratio for healthy tissues is less and it gradually increases with the grade of malignancy. Algorithms developed to detect and grade cancer using the DR ratio and also linear discriminant analysis (LDA) are performed. This result is compared with the histopathological report of biopsy showed that DRS technique is very effective in detecting early malignancies in various anatomical sites of the oral cavity where the laser induced autofluroscence shows poor diagnostic accuracy.

Fluorescence and diffuse reflectance in measuring spectral characteristics of an oral lesion have limitation. Imaging is very useful because it gives clinician a tool to scan the oral cavity completely. There are several recent studies focuses on optical imaging system. All these studies used different approaches in terms of wavelengths of excitation, Light sources used, diagnostic algorithms, data analysis for differentiating between normal and malignant tissues.

Chih-Yu Wang et al [24] developed an imaging system based on fluorescence technique. The system consist high power laser diode with 405nm wavelength as light source and it is guided by the fiber system to get uniform distribution of light on tissue. Telescope is used to get the oral cavity images and is connected to CCD camera to capture images. Before screening an ALA dye is applied, for locating the cancer sites and the abnormal area could be easily identified. LabVIEW software tool is used for hardware control. The authors conclude that on comparing white light based image with fluorescence image, fluorescence imaging system is potential way of identifying the cancerous cells among normal cells without subjective judge by the clinicians.

Noah Bedard et al [25] developed a portable device based on multimodal imaging spectroscopy in which records the autofluroscence and reflectance images and also spectral information. The selection of wavelength range between 471-667nm was based on autofluroscence emission peaks and reflectance features. The high power 405nm blue LED and white LED were used to provide reflectance and autofluroscence excitation of tissue. The LabVIEW program is used to control the imaging system. This study concludes that multimodal spectral imaging i.e. reflectance and autofluroscence can be used for combined spectral analysis in the oral cavity.

Manju M Stephen et al [26] developed a system based on diffuse reflectance imaging. The images of oral lesion are recorded at545nm and 575nm using EMCCD camera along with tungsten halogen lamp for white light illumination shown in Fig.3c and d.

The recorded images are sent to computer and ratio of R545/R575 nm was taken as shown in Fig 3e, and pseudo colour mapping is applied to discriminate oral lesion in which provides most malignant site. Fig 3d shows the colour palette Blue colour indicates the healthy tissue, red indicates the pre- malignant tissue and yellow indicates malignant tissue. This study provides an imaging system based on diffuse reflectance to provide a non-invasive tool for clinicians to identify the different stages in oral cancer easily.

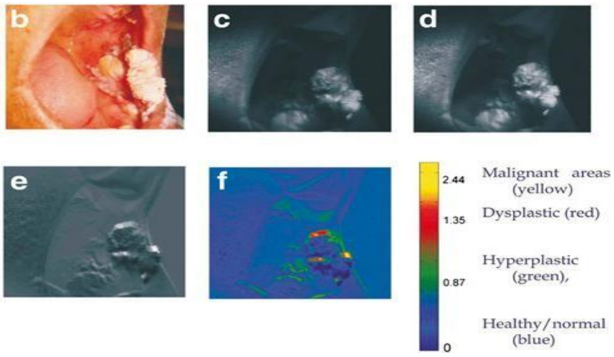

Fig.3 b) Image of oral cavity of a patient c) image recorded at 545 and (d) 575 nm, (e) computed DR ratio (R545/R575) image and (f) pseudo colour mapped ratio image [26].

Rahman et al [27] evaluated an optical imaging system to identify the oral precancers. The system uses light emitting diode (LED) to illuminate oral mucosa. A blue LED with 455nm wavelength used for fluorescence imaging and white LED with 400-700nm wavelength range used for reflectance imaging. Images were captured using CCD camera and sent to computer for image analysis. Total 61 sites in the oral cavity from 76 patients and 90 sites in the oral cavity from 33 normal volunteers were obtained to evaluate the system. Quantitative image features were used to develop classification algorithms to identify neoplastic tissue, using clinical diagnosis of expert observers as the gold standard. Result obtained were sensitivity of 90% and a specificity of 87% in differentiating the cancers tissue from normal tissue.

Carlson et al [28] developed a dual –mode reflectance and fluorescence confocal microscope (DCM). The DCM system is used to capture the fluorescence and reflectance image in which provide the information about molecular properties of tissue as well as morphological information associated with cancer progression. Total 14 patients were imaged and 33 biopsies of normal and abnormal were obtained. The mean intensity ratio of fluorescence and reflectance images is taken and this ratio values gives information about to differentiate the oral lesion from normal tissues.

III. CONCLUSION

In summary, Optical imaging system found to be a best solution to screen and detect oral pre-cancers non-invasively. The images acquired at diffuse reflectance (DR) oxygen haemoglobin bands at 545nm and 575nm are useful in identifying the cancerous from normal tissue and Auto fluorescence emission (AF) modality provides the morphological changes associated with the tissue.

Therefore developing an oral screening device based on diffuse reflectance and fluorescence imaging modalities will provide the good diagnostic accuracy, real-time image analysis and most malignant sites can be identified to avoid the multiple biopsies.

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