Review Article

Fluorescence diagnostics: A forthcoming non invasive screening adjunct in oral cancer

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DOI: 10.5455/jrmds.2016421

ABSTRACT

Oral cancer is amongst the common malignancies worldwide, hence early detection and treatment is essential. Detection of oral cancer at an early stage improves the results of treatment. One of the upcoming technologies is the use of non-invasive imaging technique to capture the molecular changes in order to improve the detection capability of early stage disease. This review highlights the Fluorescence technology and its use in early detection of malignant oral tumours.

***Key words*:** Oral Cancer, Fluorescence, non-invasive technique.

NTRODUCTION

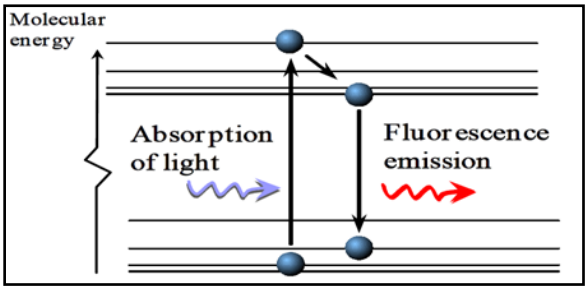
The word cancer came from a Greek word karkinos to describe carcinoma tumours by a physician Hippocrates (460–370 BC), but was not the first to discover this disease. Some of the earliest evidence of bone cancer was seen in Egypt found in mummies around 1600 BC [1]. Oral cancer is cancer starting in the oral cavity and is one of the ten leading cancers in the world. Most common site of involvement is the tongue, the floor of the mouth, buccal mucosa, gingiva and lips. In many Asian countries, like India, chewing betel, paan and Areca are known to be risk factors for developing oral cancer. If detected at an early stage, it improves the outcome of treatment. Accurate detection of early neoplasms followed by efficient treatment can significantly increase the survival rates of oral cancer patients.

If the disease is diagnosed at an early stage, the oral cancer' s survival rate of five year is 80%-85% and if found late, oral cancer's five-year survival rate is only about 50%. Unfortunately, it is often discovered at later stages when the prognosis is not good. One of the budding diagnostic methods is an optical method also known as optical biopsy [2]. One of the favourable optical biopsy method is fluorescence technique.

Flourescence

When cell interact with the light of particular wavelength, it become excited and re-emit light of varying wavelength (colour), which is called as fluorescence. The wavelength of the emitted light being longer than that of the absorbed light. (**Fig-1**)

Figure 1: Fluorescence of light



Principle of Fluorescence

This diagnostic method is based on a quite selective accumulation of porphyrins in tumour tissue [3]. Autofluorescence is produced by fluorophores that naturally occur in human tissues. The naturally present fluorophores being collagen, tryptophan, elastin, keratin, haemoglobin and NADH etc. Potentially malignant disorders causes a change in the concentration of these fluorophores and alterations in naturally light scattering.

Fluorophore enriched tumour tissue irradiation with the appropriate wavelength of light leads to the emission of pink-red fluorescence. This principle is called fluorescence diagnostics (FD). Fluorescence Diagnostics is a noninvasive technique for the real time characterization of superficial tissue layers [4].

This method is based on the differences in the fluorescence emission from various types of tissues. The fluorescence from a normal tissue, near 400 nm, is higher than the tumour in the range 450–550 nm, but lower in the range 600–700 nm, [5] and by taking the ratio of red intensity (600–700 nm) over the blue / green intensity (450–550 nm)

the contrast between tumour and the adjacent normal tissue is intensified significantly.[6] The potentially malignant disorders show an intensive fluorescence in the red part of the spectrum. Exogenous sensitizers at times may be administered along to enhance tumour demarcation [7,8].

Table 1: Review of literature on auto-flourescence imaging on oral cancer

Author	Tissue examined	Result
Onizawa et al [9]	Benign and malignant lesions	Orange fluorescence was observed in most of the benign and malignant lesions
Onizawa et al [10]	Carcinomas, epithelial dysplasias and benign lesions	Autofluorescence of malignant lesions tends to shift from yellow to orange
Betz et al [11]	Malignant and healthy oral mucosa	Autofluorescence imaging in the green spectral range identifies malignant lesions
Kulapaditharom et al [12]	Normal, inflammations, granuloma	Red to brown florescence indicates malignancy. 100% sensitivity, 73% specificity.
Paczona et al [13]	Precancerous and cancerous lesions of head and neck	Precancerous lesions showed diminished green fluorescence.
Robylar et al [14]	Normal dysplatic cancerous mucosa	Obtained a sensitivity of 100% and specificity of 91.4%.
Rahman et al [15]	Normal and cancerous mucosa	Sensitivity 90% and specificity 87%

VEL Scope (Visually Enhanced Lesion Scope)

The VEL scope is a handheld device that emits a visible blue light which is safe and excites the oral tissue and causes it to fluoresce. The oral cavity can then be examined in real time, enhancing the practitioner's ability to quickly identify suspicious tissue that may require further investigation.

VEL scope is a chair side diagnostic modality now marketed to a general dentist.

It usually consists of a handheld device or scope which illuminates the mucosa with a fluorescent light of wavelength 400 – 460nm.

Normal mucosa emits a green autofluorescence and abnormal mucosa appears dark.

VEL scope improves the contrast between normal and lesional area.

Numerous studies have been conducted using VEL scope for the detection of premalignant disorders. (**Table 1**)

Facts regarding VEL Scope:

Is the only dental device, among 8 other commercial devices endorsed by the World Health Organisation. Is now used by more than 13,000 dentists in 23 countries. US FDA approved.

The technology, which has been backed by over $50 million in research funded by the National Institutes of Health (NIH).

Applications of Fluorescence diagnostics:

Fluorescence imaging can facilitate guided biopsies in the clinic, thereby reducing the number of biopsies taken.

It provides visualization of tumor margins during surgical procedures.

Numerous studies show fluorescence can provide improved specificity [16].

Used for early detection of primary and recurrent malignant oral tumours, except melanoma [2].

Exact demarcation of tumor margins.

Helps in the detection of epithelial hyperkeratosis (EH) or epithelial dysplasia (ED) and lesions in oral submucous fibrosis.

Advantages:

- Non Invasive, no rinses or dyes.
- Cost effective
- Comfortable to the patient
- Minimizes need for unnecessary biopsies.
- Can be performed on medically compromised patients who are contraindicated for biopsies

However, the major **disadvantages** of fluorescence imaging are:

- High background noise from autofluorescence from endogenous molecules e.g, haemoglobin & cytochromes.
- Photodamage to biological materials.
- Fluorophores have low photostability [17].

DISCUSSION

Screening of oral cancer mainly deals with searching for potentially malignant disorders, before the symptoms appear. Early detection of oral cancer improves the treatment modality thereby

reducing the morbidity and mortality of the patient. Since majority of these lesions are benign they cannot be differentiated clinically weather they are potentially malignant or benign. Early detection therefore aims to create awareness amongst general public and improving oral health services for all.

Luminescence is the term for the emission of radiation by an object and is stimulation and emission of radiation by impact of higher energy. The fluorescence ceases almost immediately when the excitation is removed. An inherent fluorescence of many naturally occurring substances in the human tissue is termed as Primary Fluorescence or Autofluorescence. Fluorescence induced by fluorescent marker dyes is called Secondary Fluorescence [18]. Various studies have been conducted to show its potential to act as a promising diagnostic modality in the screening of oral cancer. Ebihara et al in 2003 conducted a study on cheek pouch in 18 hamsters to detect cancer using fluorescence and concluded that fluorescence hot spots were evident in severe dysplasia. Rana et al 2011 conducted a study on 289 patients divided into two groups in which white light was used for the detection of premalignant disorders in group 1 and in group 2 VELScope was used and reported a higher sensitivity rate which proved VELScope to be a promising diagnostic device.

Further studies have to be conducted to validate the correlation between fluorescence and histological patterns that would assist in discrimination of penetrating from non-penetrating malignancies.

CONCLUSION

Oral cancer is one of the leading causes of death associated with the use of tobacco. Carcinogens present in high concentration in tobacco are the main culprits in causing all forms of cancer. Screening and early detection may significantly decrease the morbidity and mortality associated with the oral cancer. With instrumentation standardization and emergence of diagnostic algorithms, fluorescence diagnostics has an immense potential for acting as an assessment tool for early detection of primary and recurrent malignant oral tumours. Thus, proving itself to be a screening adjunct in oral cancer.

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Date of Submission: 03/04/2016
Date of Acceptance: 22/05/2016