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Early Detection Of Premalignant And Malignant Oral Soft Lesions By Fluorescent Light - Velscope®

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Abstract:
The development of oral cancer is a multistep process that needs the buildup of multiple genetic alterations, usually preceded by detectable mucosal changes, most frequently leukoplakia and erythroplakia. The World Health Organization has identified prevention and early detection as key goals in the global fight against oral cancer. Oral cancer screening and early detection and its pre-invasive intra-epithelial phases are still largely focused on visual inspection of the mouth. But unfortunately, simple visual inspection is widely known to be limited by subjective interpretation and the possibility of dysplasia and early OSCC within patches of the normal-looking oral mucosa. As a result, several techniques are developed to boost the clinical and cytological diagnosis of oral potentially malignant lesions (OPMDs) and identify areas of dysplasia/early OSCC that are not evident to the naked eye. Toluidine blue, brush biopsy, chemiluminescence, and tissue autofluorescence are some of the techniques used. This review paper takes concern within the early detection of premalignant and malignant oral soft tissue lesions by autofluorescence technique, with special emphasis on VELscope.

Key Word: *Malignancy, Oral cancer, Tissue autofluorescence, VELscope®, Cancer screening, Autofluorescence based devices*

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I. Introduction

Oral cancer is major public health problem in the Indian subcontinent, where it ranks among the top three types of cancer in the country.[1,2] According to Dr Tedros Adhanom Ghebreyesus (Director-General, WHO), “Cancer is the second most common cause of death globally, accounting for an estimated 9.6 million deaths in

2018.The 2017 World Health Assembly requested WHO, in collaboration with IARC, to provide a global perspective on all measures that are recognized to limit the burden of cancer. The outcome of this charge – the *WHO Report on Cancer: Setting priorities, investing wisely and providing care for all* – complements the IARC *World Cancer Report* by synthesizing evidence to translate the latest knowledge into actionable policies to support governments."[3]

Worldwide, head and neck cancer is the seventh most common cancer overall (the fifth most common in men and the12th most common in women), accounting for an estimated 888,000 new cases in 2018. India (9.1) ranked 4th in age-standardized incidence rates (per 100 000) just behind Papua New Guinea (20.4), Pakistan (12.2) and Bangladesh (9.5).[3]

Head and neck cancers are further classified by theanatomical area in which they arise (Fig. 1):[3]

(i) Oral cavity: lips, front two thirds of the tongue, hard palate, mucosa inside the cheeks, gums, and floor of the mouth

(ii) Pharynx: nasopharynx (upper part), oropharynx (middle part, including the soft palate, uvula, the base of the tongue, thetonsils, tonsillar pillars, and oropharyngeal wall), and hypopharynx (lower part)

(iii) Larynx: located below the pharynx, including the supraglottic and infra-glottic areas, with the vocal cords in the middle

(iv) Nasal cavity and paranasal sinuses

(v) Salivary glands.

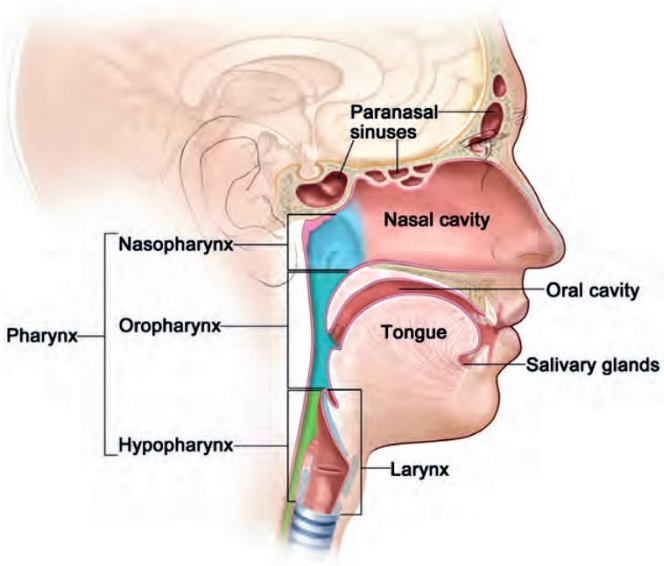

Fig. 1 Major anatomical areas of head & neck cancer in India[3]

Almost 50% of head and neck cancers arise in the oral cavity. In 2018, there were an estimated 355,000 new cases and 177,000deaths worldwide for oral cavity cancer.[3,4]In 2018, India was the country with the highest burden, with 120,000 new cases. As a result, oral cancer has become one of the most concerning malignant tumors in the Indian subcontinent, and its prevention is of utmost importance in recent times.

Fig. 2 Distribution of oral cancer across India[5]

RISK FACTORS:[3]

1) **Human Papilloma Virus -**In the past 15 years, strong evidence has accumulated that infection with certain human papilloma viruses (HPVs) is etiologically involved in a subset of head and neck cancers, particularly oropharyngeal cancer.[6] But, unlike squamous cell carcinomas of the cervix (almost all of which are believed to be HPV driven) [7] oral cancers commonly develop as a result of multifactorial etiology. To accurately classify a tumor as HPV-driven, it is crucial toinclude other markers related to HPVinduced carcinogenesis, such asp16^{INK4a} and messenger RNA (mRNA) of the viral oncoproteins E6 and E7.HPV-related cases of head and neck cancer arise more often in the oropharynx (for which 30.8% of cases are HPV-related), and particularly in the tonsils. There is a greater predominance of HPV16 in head and neck cancers compared with other HPV-related cancers. Globally, 84.9% of HPVrelated head and neck cancers are attributable to HPV16/18; forHPV6/11/16/18/31/33/45/52/58, the proportion is 89.7%.[8]

2) **Tobacco & Betel Quid use -**Tobacco is one of the major risk factors of oral cancers in the world, as well as in India. The relationship between smoking and oral cancer has been established firmly by epidemiological studies.[9,10] The most important carcinogens in tobacco smoke are the aromatic hydrocarbons benz-pyrene and the tobacco-specific nitrosamines (TSNs) namely 4-(nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN). Some commonly used forms of tobacco are -

(i) Smoke - Cigarettes, Biri, Cigar & Pipes etc.

(ii) Smokeless tobacco - Chewing tobacco (loose leaf, plug, or twist)[11]

- Snuff (moist, dry, or in packets)[11]
- Dissolvables (lozenges, sticks, strips, orbs)[12]

3) **Alcohol -**IARC has classified alcohol consumption as carcinogenic to humans, and the WCRF/AICR Continuous Update Project concluded that there is convincing evidence that consumption of alcoholic beverages increases cancer risk.[3] Alcohol consumption mainly acts synergistically with tobacco in the increased risk of development of oral cancer. However, few studies have found independent role of alcohol to be a risk factor of potentially malignant lesions. In one such study, alcohol has been found to be an independent risk factor for oral leukoplakia in an Indian population.[9,13]

4) **Diet and Nutrition -** The relationship between diet and nutrition to the risk of cancer development has been established by several epidemiological and laboratory studies.[9,14] The working group of International Agency for Research on Cancer (IARC) has affirmed that low intake of fruits and vegetables predisposes to increased risk of cancer development.[9]

5) **Others -** other factors like hereditary causes, viral & fungal infections, immunocompromisation, radiation etc. Are also believed to contribute in the increased incidences of oral cancers in India.

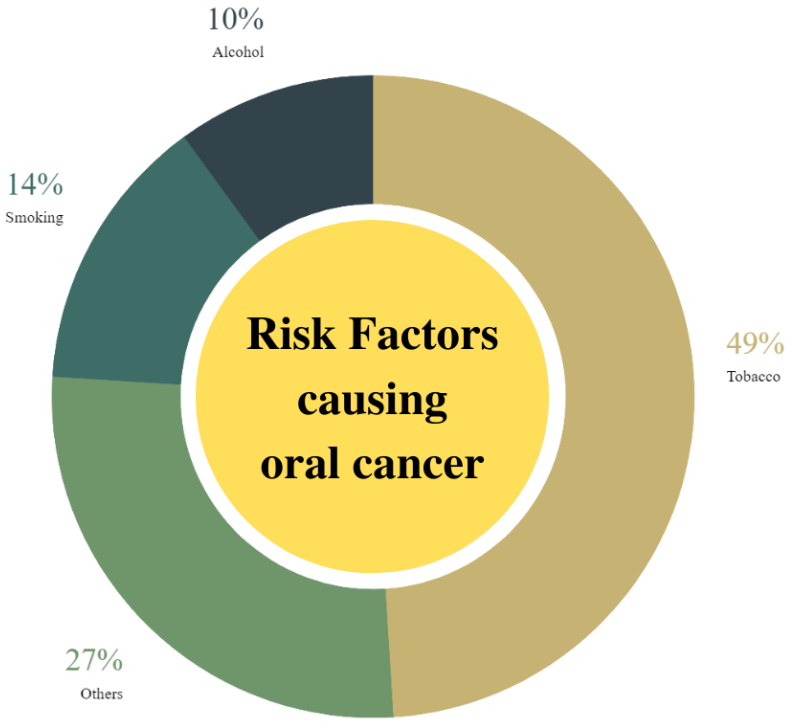

Fig. 3 Distribution of various factors responsible for oral cancer in Maharashtra[5]

II. Importance of early detection of oral cancer

Malignancies of the oropharynx region most often develop from potentially malignant lesions and de-novo. Despite easy access to the oral cavity, there has been significant mortality associated with oral cancer as they are often diagnosed at very later stages. The 5-year survival for oral squamous cell carcinoma (OSCC) associated with tobacco and alcohol use has remained consistently poor in recent times.Prognosis is further complicated by the high rate of second primary tumours in these patients, which is thought to be the result of 'field cancerisation' in the upper aerodigestive tract.[15,16]Early detection of neoplastic changes in the oral cavity is the best method to improve patient survival rates.[15,17]If cancer is detected in the initial stage, the potential for remission is 80%.[18] But, the prevailing early diagnostic methods in India rely heavily on patient awareness and

visual methods, which is highly subjective, and often lead to ignorance from the subject, thereby leading to delay in diagnosis.

The most common OPMDs include leukoplakia, erythroplakia, oral lichen planus, and actinic cheilitis. Early detection of these lesions can be carried out by spreading mass awareness and encouraging the population to undergo routine checkup at regular intervals.

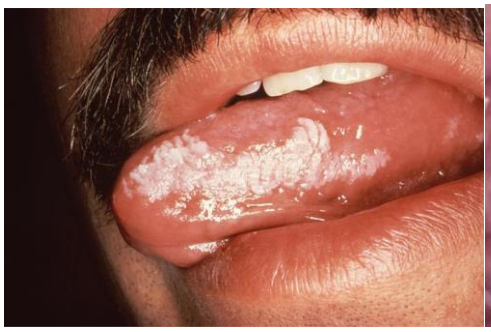

Fig. 4 Leukoplakia[19]

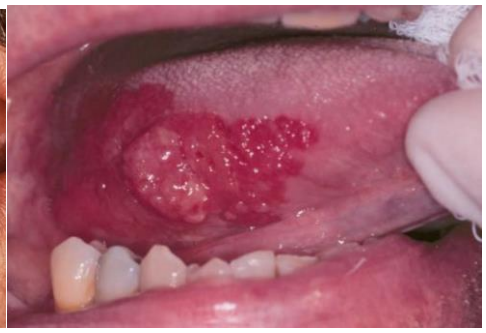

Fig. 5 Erythroplakia[20]

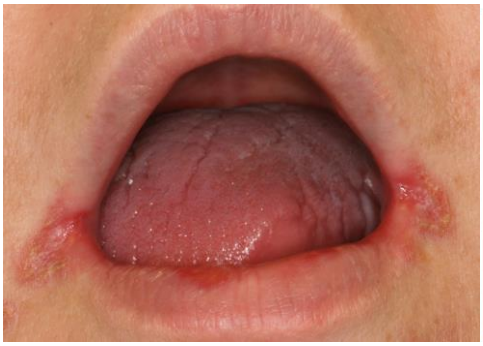

Fig. 6 Angular cheilitis[21]

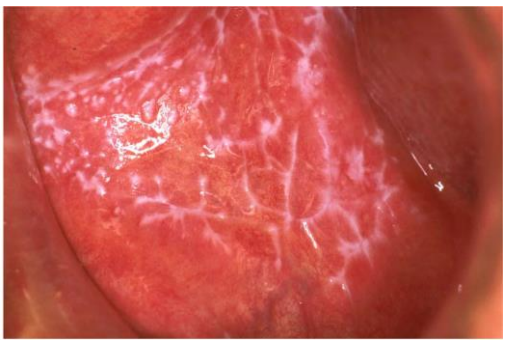

Fig. 7 Oral lichen planus[22]

III. Methods of detection of oral potentially malignant lesions (OPMDs)

The present standard method of diagnosing oral potentially malignant lesions takes place via a thorough histopathological analysis following surgical biopsy. But, major disadvantages like, it being an invasive procedure, needs a lot of time and has chances of post-procedural infections, along with it being quite technique sensitive, paves the way for the introduction of non-invasive procedures. Various non-invasive procedures are:

1) Conventional Oral Examination (COE)
1) Brush Biopsy
1) Vital Tissue Staining
1) Chemiluminescence
1) Tissue Autofluorescence
1) Confocal in-vivo Microscopy
1) Tissue Fluorescence Spectroscopy
1) Salivary Biomarkers
1) Optical Coherence Tomography
1) Positron Emission Tomography etc.

IV. Concept of Autofluorescence

Autofluorescence (AF) is defined as natural fluorescence emission of tissue arising from endogenous fluorophores after exposureand activation by radiation of a suitable wavelength.[23] In its resting state, a fluorophore is at a stable energy level at which it does not fluoresce. When a fluorophore is illuminated, its electrons are promoted to a higher energy level. In this excited state,the fluorophore is unstable and will quickly revert to a slightly more stable lower energy level by releasing heat. To return to its baseline the fluorophore emits light. Since some energy has already been released as heat, the emitted light is of lower energy and longer wavelength than that of the illuminating light.[23,24]

The naturally occurring fluorophores are collagen, tryptophan, elastin, keratin hemoglobin, NADH, FAD, porphyrin etc.Potentially malignant disorders and cancerous conditions cause a change in the concentration of these fluorophores.[25,26]

The degree of autofluorescence depends upon the anatomic location and the type of lesion that occurs on it. In normal mucosa, fluorescence in the ultraviolet (UV) and visible region of the spectrum is predominantly due to tissue collagen. The epithelium always shows weak autofluorescence due to the mitochondrial NADH and FAD present in the basal cells of the epithelium. Neoplasia causes loss of stromal collagen, which leads to **loss of autofluorescence**. Epithelial dysplasia, on the other hand, increases mitochondrial fluorescence of the epithelium. Besides, Loss of both epithelial and stromal autofluorescence is observed in inflammatory lesions.

Thus, through various properties like these, a clinician can take the concept of autofluorescence into consideration and can evaluate various dysplastic changes in the oral mucosa.

V. Visual Autofluorescence - Visually Enhanced Lesion Scope (VELscope®)

VELscope® (LED Medical Diagnostics, White Rock, BC, Canada) is a hand-held non-magnifying device for direct visualization of oral mucosa autofluorescence that became commercially available after FDA approval in 2006.[27,28]The VELscope® relies on two key components – an LED ring that emits a specific wavelength of blue light (400-460nm) and an eyepiece with an integrated optical filter. The combination of shining light into the oral cavity and viewing the patient's oral mucosa via an optical filter are what allows clinicians to observe cellular and structural tissue changes and, therefore, visualize areas that warrant further investigation.[29]

Working principle of the VELscope®:

When utilizing the VELscope®, normal fluorescence patterns typically appear as a bright apple-green color, indicating that the fluorophores in the tissues of the oral mucosa are responding normally when exposed to blue light. Normal fluorescence patterns can also show a lack of fluorescence: lymphoid aggregates, the fungiform papillae on the tongue and the heavily vascularized anterior tonsillar pillars are good examples of this. Abnormal fluorescence patterns allow clinicians to observe unhealthy areas of the mucosa, which may be overlooked with the naked eye during a typical white-light reflectance examination.

Abnormal fluorescence patterns typically arise from:

- An increase in metabolic activity in the epithelium.
- A breakdown of the fluorescent collagen cross-links in the connective tissue layer beneath the basement membrane.
- An increase in tissue blood content, either from inflammation or angiogenesis.
- The presence of pigments (eg. melanin or amalgam particles) which absorb light.

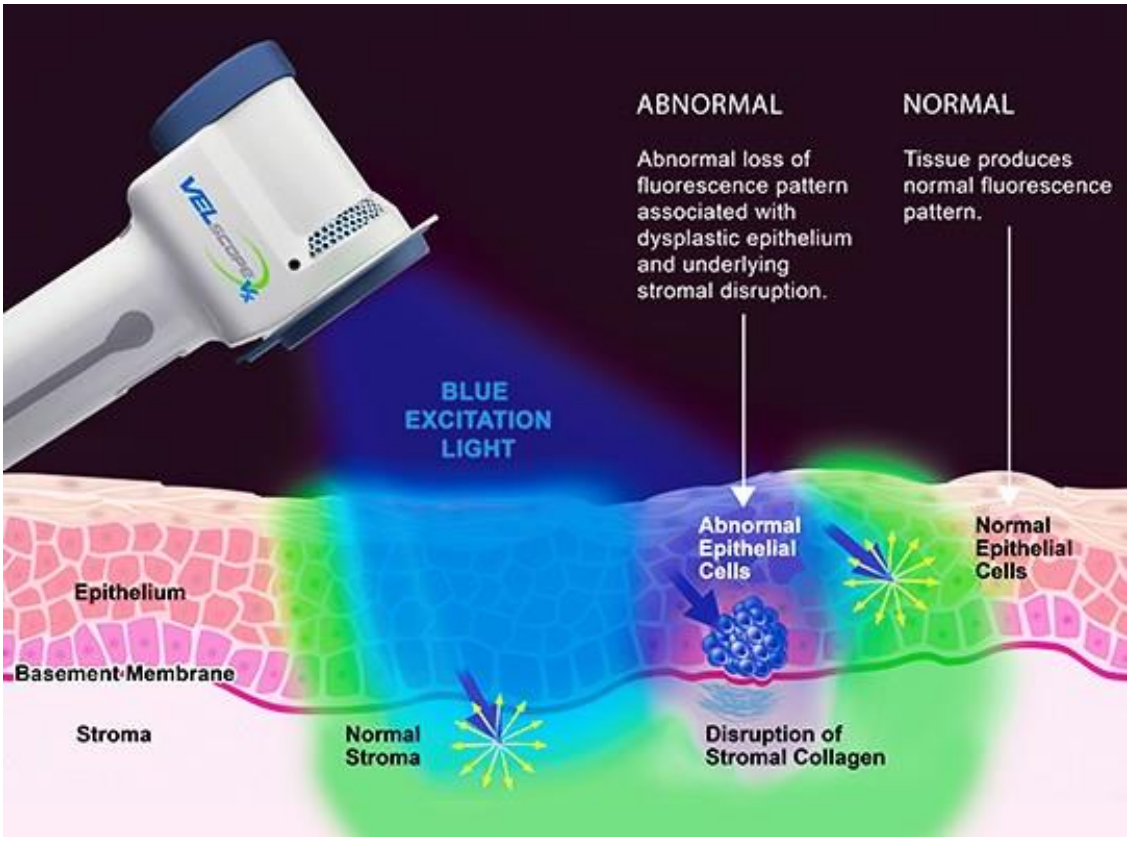

Fig 8. Working principle of VELscope®

Clinical Images using the VELscope®:

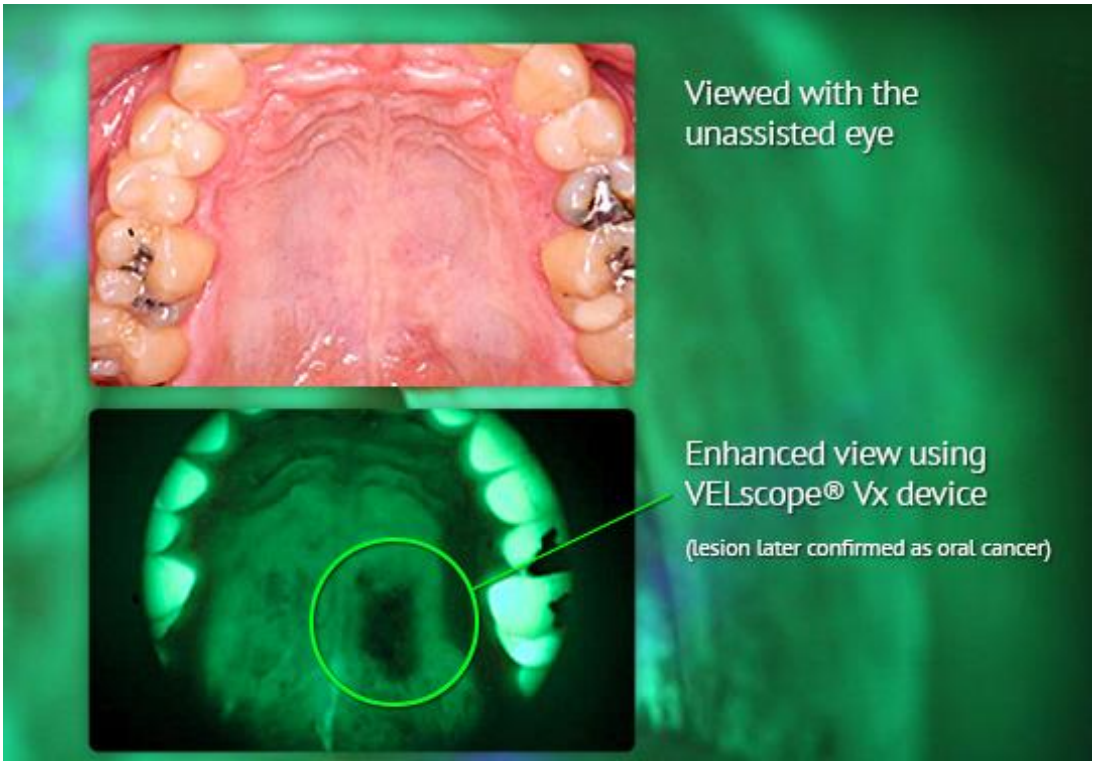

Fig 9. Clinical image courtesy Dr. Samson Ng

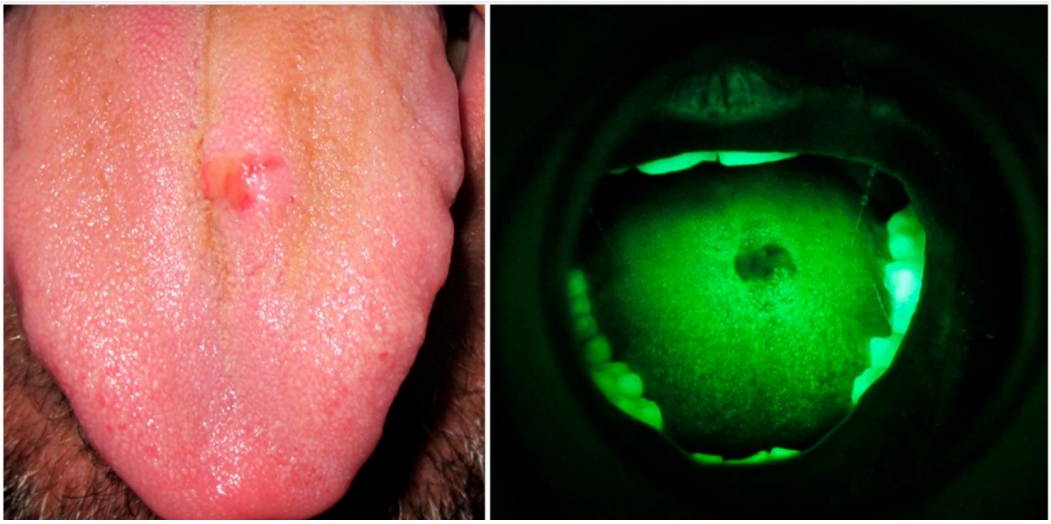

Fig 10. VELscope® results before a tongue biopsy. COE vs. VELscope®. For gentle concession of Prof. L. Laino.[30]

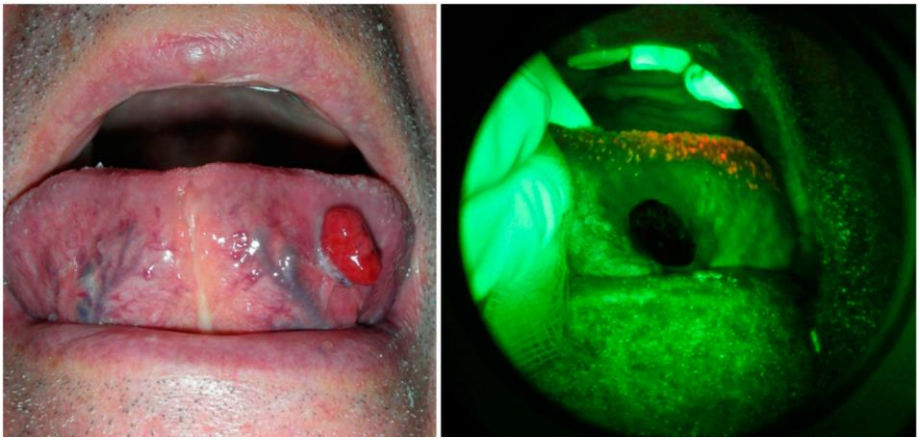

Fig 11. VELscope® results before a tongue biopsy. COE vs. VELscope®. For gentle concession of Prof. L. Laino.[30]

Clinical trials held with the VELscope® :[31]

Author	Year	Study Design	Sample Size	Selection Criteria	Sensitivity	Specificity
Sharwani A et al.[32]	2006	Cross-sectional study	79	Clinically suspicious oral leukoplakia	83-90%	79-89%
Lane et al.[33]	2006	Cross-sectional study	44	Oral leukoplakia patients	98%	100%
Mehrotra et al.[34]	2010	Cross-sectional study	156	Oral mucosal white lesions	50%	38.9%
Awan KH et al.[35]	2011	Prospective study	126	Patients with OPMD	84.1%	15.3%
Koch et al.[36]	2011	Prospective blinded clinical trial	78	OSCC or suspicious epithelial lesions	93%	16%
Pardeni et al.[37]	2011	Cross-sectional study	175	Patients with atleast one clinical oral lesion	OSCC:96.4% Dysplasia:71%	NA
Scheer et al.[38]	2011	Prospective study	64	Patients at risk of OSCC and prior history of OSCC	100%	80.8%
Babiuch et al.[39]	2012	Pilot study	50	Patients with OSCC and lip cancer	100%	12.5%
Farah CS et al.[40]	2012	Prospective study	112	Patients with OPMDs	30%	63%
Marzouki et al.[41]	2012	Prospective single blind study	85	History of smoking, alcohol use or previous head and neck cancer	92%	77%
Mc Namara K et al.[42]	2012	Cross-sectional study	130	Consecutive recruitment for routine dental care	NA	NA
Rana et al.[43]	2012	Cross-sectional study	123	Patients with OPMD	100%	74%
Hanken H et al.[44]	2013	Single blinded study	120	Patients with OPMD	22%	8.4%
Sawan et al.[45]	2015	Prospective study	748	Consecutive recruitment for routine dental care	74.1%	96.3%
Salas et al.[46]	2015	Pilot study	30	Patients with mucosal pathology	40%	80%

Ganga et al.[31]	2017	Prospective study	200	Patients with mucosal pathology	76%	66.29%

Advantages of the VELscope®:

- The combination of COE and VELscope® examination in patients with oral lesions could provide a significative diagnostic yield(Marzouki et al., 2012; Rana et al., 2012; Hanken et al., 2013).[27]
- VELscope is not much technique sensitive. A comprehensive training can be more than enough to operate the device.
- As scanning with a VELscope® requires less than 2 minutes, so, it can be a very useful tool in screening large population groups.
- VELscope weighs less than 1kg, and is a portable device, and hence, is pretty easy to handle.

Disdvantages of the VELscope®:

- As seen from the available published clinical samples, VELscope® produces good results only when it is used in congregation with COE. It has not performed very great while used independently, according to the available reports.
- Though easy to use, VELscope® is not commercially available in India at present. Hence, effective cost of using the device in India may not be feasible in current times.
- The device's use is limited to screening purpose only. To confirm a diagnosis, histopathological examination following surgical biopsy, still remains the gold standard of examination.

Other non-invasive diagnostic devices:[27]

Besides VELscope®, there are many other non-invasive devices for early screening of oral cancer and OPMDs.

- **Vizilite®** - ViziLite® (Zila Pharmaceuticals, Phoenix, AZ, United States) is a chemiluminescence-based detection device designed to facilitate the early identification of PMD and OSCC. In 2002 ViziLite® became the first device approved by FDA for this purpose.[47]This is a disposable capsule formed by an outer shell of flexible plastic containing acetyl salicylic acid and an inner glass vial containing hydrogen peroxide. To activate it, the capsule is bent to break the inner glass vial, triggering the reaction of the chemicals contained in the two compartments. Consequently, a bluish-white light (430–580 nm) is produced, lasting for 10 min.[48]The altered epithelial cells, due to higher nuclear/cytoplasmic ratio, reflect the light and cause the appearance of an "aceto-white" lesion, whereas normal cells appear blue.[49]Although, ViziLite® facilitates the identification of hyperkeratotic areas and may increase the visibility of mucosal lesions, but the main limitation is currently the high proportion of false positive and false negative tests, regarding the identification of dysplastic areas rather than hyperkeratosis.[50]
- **Identafi®** - Identafi®(StarDental - DentalEZ, Lancaster, PA, United States) is a probe-like device designed for multispectral screening of OPMDs, approved by FDA in 2009 as oral screening device.[51]It has three light sources of different wavelengths: white, violet (405 nm), and green-amber (545 nm) lights, that can be sequentially used in oral examination. White light provides classical visualization of oral mucosa, violet light excites endogen fluorophores, enabling the assessment of mucosa autofluorescence andgreen-amber light, through the reflectance spectroscopy, excites hemoglobin molecules in the blood, with the aim to visualize the vasculature.[52] A mirror is attached to the probe to help visualize relatively obscure areas in oral cavity. The use of Identafi provides the clinician with more data than COE. Unfortunately, the results interpretation requires high level of experience and clinical training in oral pathology, suggesting that its usage should be limited to reference centres for oral pathology.[53]

- **Microlux/DL™** - Microlux/DL™(AdDent Inc., Danbury, CT, United States) is a chemiluminescence-based device which became commercially available after FDA approval in 2005. It has a diffused blue-white LED light source and a fibre optic light guide.[54] The device uses similar principles to that of ViziLite®. Althoughthe device is not effective to distinguish between benign and malignant lesions, it seems to be a promising screening test for oral lesions.[55]
- **Goccles®** - Goccles® is a medical device (Pierrel S.p.A, Italy) approved by FDA in 2015. This is a low cost and easy-to-use device consisting in a pair of glasses equipped with special optical filters that allows autofluorescence detection. Indeed, Goccles® was created to provide an easy and low cost mean of identification of autofluorescence abnormalities in oral cavity with the use of any dental curing light.[56]
- Sapphire® Plus LD (DenMat Holdings, Lompoc, CA, United States), DentLight DOE™ Oral Exam System (DentLight, Richardson, TX, United States), and OralID™ 2.0 (Forward Science Technologies, Stafford, TX, United States) are other tissue autofluorescencebased devices developed in order to detect oral lesions.[57]

VI. Future Prospects

VELscope®, as found through various reports work quite efficiently. But, a major limitation of the instrument is that it cannot distinguish between malignant or benign lesions, or even a simple inflammation. Hence, clinical correlation becomes mandatory during the use of this device.

Although recent advancements in the field of diagnosing oral cancers have shown great promise in screening oral lesions, the gradually increasing incidences in oral cancers, especially in the subcontinent calls for the introduction of more efficient devices and methods, that can be implemented in large scale population. Besides, extensive use of these devices, unfortunately have been hindered due to several factors like:

(i) The available data don't demonstrate the clear superiority of those methods compared toCOE.
(ii) There remains the necessity for well-designed multi-center prospectivestudies.
(iii) These devices exhibit a not-negligible inter-observer variability, limiting their use to clinicians with significant experience in Oral Pathology.

Further researches in the current field should be conducted without delay to ensure a quality living, thereby improving the general health of the society.

VII. Conclusion

The current evidences suggest that these devices can be useful in -

i. Assessing lesion margins that has to be biopsied and, therefore, is also useful in surgicalmanagement.
ii. Investigating biological aspects of oral carcinogenesis, resulting in more accurate methods for interpreting data from light-based detection systems.
iii. Engaging greater awareness for oral lesions among both patients and general dentalpractitioners, allowing successively to market a culture of carcinomaprevention.

Hence, it is conclusive that in spite of having a great scope for improvements, autofluorescence based devices are gaining its importance in today's world due to its excellent screening capabilities. It can be used in supplementary with conventional oral examination in large populations, and has its importance in both rural and urban setup.

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