

Velscope guided oral cancer screening: A ray of hope in early oral cancer diagnosis

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Abstract

Context: Early oral cancer diagnosis is an important factor in reducing cancer-associated mortality and morbidity. Traditional oral cancer screening by Conventional Oral Examination (COE) is limited. A new approach in this regard is the use of “optical biopsy systems” like VELscope.

Aims: Hence, this study aimed to determine the diagnostic value of VELscope, an autofluorescence-based handheld device in detection of dysplasia and oral squamous cell carcinoma (OSCC) in general oral potentially malignant disorder.

Settings and Design: A prospective, cross-sectional study was conducted at a tertiary hospital in western Maharashtra, India.

Materials and Methods: Thirty patients with presence of clinically suspicious oral lesions were included, and for each lesion, both the COE and Autofluorescence Examination by VELscope were carried out at the same appointment by different experts. All lesions were biopsied and histopathological findings were documented and analyzed.

Statistical Analysis Used: Sensitivity, specificity, positive predictive value and negative predictive value were estimated to determine the accuracy of VELscope examination analysis outcome.

Results: The study included a total of 30 subjects including 19 (63.33%) males and 11 (26.66%) females. Autofluorescence examination by VELscope (AFV) revealed Autofluorescence Loss in 24 (80%) patients, while 6 (20%) patients showed Autofluorescence Retained. Comparison between the “high-risk lesions” (moderate/severe dysplasia and OSCC) and “low-risk lesions” (no/mild dysplasia) showed a 90.47% sensitivity but only 44.44% specificity.

Conclusions: The findings of our study indicate that although AFV cannot be a substitute for COE, it can be used as a potential complementary diagnostic aid in surveillance of the high-risk patient population.

Keywords: Autofluorescence, oral cancer, screening, VELscope

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INTRODUCTION

Oral cancer-associated mortality and morbidity has attained alarming numbers despite technological advancements in various treatment modalities. Recent studies have shown that about 60% of patients were diagnosed with stages III and IV. The recurrence rate ranges from 40% to 50% for 5 years. Only 35% of malignant lesions are detected in early stages.^[1] These numbers reflect the crisis in oral cancer detection and survival. Early cancer diagnosis has been the most important strategy and the best way to prevent and control oral cancer!^[2]

Typically, oral cancer is preceded by oral potentially malignant disorders (OPMDs), which are a recognizable group of clinically suspicious lesions that have a risk of progressing to squamous cell carcinoma (SCC).^[3]

Traditionally used conventional white light examination (COE) has inherent limitations such as observer knowledge and experience, especially while distinguishing between benign lesions and oral cancer.^[4] In addition, there is limited human eye perception, especially complicated by the moist and shiny mucosa giving a variable reflection.^[5,6]

These challenges in COE have necessitated the development of various other detection methods. A new approach in this regard is the use of “optical biopsy systems” where knowledge of light and tissue interaction is utilized. Autofluorescence uses naturally occurring fluorochromes located in epithelium and submucosa such as collagen, elastin, keratin and nicotinamide adenine dinucleotide.^[7-9]

The invoked intrinsic autofluorescence profile is altered by absorption and scattering events in the tissue before measurement. Absorption in tissue is mainly attributed to oxy- and deoxyhemoglobin, which have different absorption profiles. Scattering is due to inhomogeneities of refraction index caused by cell nuclei and cell organelles.^[7]

Applications of fluorescence-based diagnostic testing have included diseases and pathologies of skin, malignancy and upper respiratory tract among others.^[10-12] However, application of this diagnostic modality in oral mucosa is not sufficiently documented. Hence, this study aimed to determine the diagnostic value of VELscope, an autofluorescence-based handheld device in detection of dysplasia and oral SCC (OSCC) in general OPMD.

MATERIALS AND METHODS

A prospective, cross-sectional study was conducted at a tertiary hospital in western Maharashtra, India. Thirty

patients with presence of clinically suspicious oral lesions were randomly recruited from the patients referred to the specialty Department of Oral Pathology and Microbiology. All participants with history of previous diagnosis of oral cancer or undergoing active treatment for any malignancy at the time of enrollment were excluded from the study. Participants with diabetes, hypertension, collagen disorders, tuberculosis, HIV infection and patients under steroid medication were not included in the study.

The study was approved by the Institutional Ethics Committee (EC-67/OPATH-07ND/2017). It was designed according to the principles manifested in the Declaration of Helsinki and was consistent with the guidelines of Good Clinical Practice given by the International Conference on Harmonization.^[13]

After COE, autofluorescence visualization (AFV) was achieved by a handheld VELscope (C Ultra by Technomax Corporation, Pune, Maharashtra) [Figure 1].

As determined by the manufacturer’s literature, autofluorescence visualization (AFV) findings were categorized as:

1. AFL: Loss of fluorescence. [Figures 2 and 3]
2. AFR: Retained or no loss of fluorescence.

Biopsy was obtained after obtaining appropriate informed consent. The tissues were fixed in formalin routinely and embedded in paraffin for sectioning. Hematoxylin and eosin staining of tissue sections was carried out and assessed by an experienced oral pathologist who was blinded to the VELscope findings and was not involved with the clinical arm of the study. Histopathological findings were documented for all the lesions as follows:

1. No dysplasia
2. Dysplasia (mild, moderate, severe, carcinoma *in situ*)
3. Malignancy (SCC).



Figure 1: Handheld VELscope used for autofluorescence visualization examination

The findings were tabulated and statistics including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence interval (CI) were calculated to determine the diagnostic value of VELscope examination.^[14]

RESULTS

The study included a total of 30 subjects including 19 (63.33%) males and 11 (26.66%) females. The average age was 53.86 years (range: 29–80 years). On COE, the clinical diagnosis included maximum lesions of leukoplakia 19 (63.33%) followed by erythroplakia 8 (27.66%).

A comparison of the results of the VELscope examination and histopathological diagnosis was carried out. When a lesion demonstrating FVL was confirmed to be malignant or dysplastic following histopathological assessment, it was designated as a true-positive (TP) result. A false-positive (FP) result was considered when a lesion demonstrating FVL did not show any dysplastic features.

Similarly, a true-negative (TN) result was considered when FVR was noted in a lesion which on histopathological examination later did not show any dysplastic features. A false-negative (FN) result was considered when a lesion demonstrating FVR was confirmed to be dysplastic or malignant on histopathological assessment.

Autofluorescence examination by VELscope (AFV) revealed loss of fluorescence (AFL) in 24 (80%) patients, while 6 (20%) patients showed retained fluorescence (AFR). Histopathological examination revealed that in the AFL group, the number of patients with no dysplasia, mild dysplasia, moderate dysplasia, severe dysplasia and malignancy was 3 (10%), 2 (6.67%), 1 (3.33%), 6 (20%) and 12 (40%), respectively. In the AFR group, the number of patients with no dysplasia, mild dysplasia and moderate dysplasia was 1 (3.33%), 3 (10%) and 2 (6.67%), respectively. There were no cases of severe dysplasia or malignancy in the AFR group.

Thus, in our study, on comparison of the VELscope results with the histopathological diagnosis, the number of lesions with TP, FP, TN and FN values was found to be 21 (70%), 3 (10%), 1 (3.33%) and 5 (16.67%), respectively.

The sensitivity score is the indicator of the proportion of dysplastic/malignant lesions that the VELscope examination identified correctly and calculated as sensitivity = TP/(TP + FN).^[15,16]

On the other hand, the specificity score indicates the proportion of nondysplastic lesions that were correctly identified with the VELscope examination and calculated as specificity = TN/(FP + TN).^[15,16]

The sensitivity, specificity, PPV and NPV thus calculated were 77.77% (95% CI: 54.87%–90.64%), 25% (95% CI: 19.22%–30.36%), 87.5% (95% CI: 64.77%–98.84%) and 16.67% (95% CI: 10.23%–20.37%), respectively [Table 1].

The proportion of lesions with positive VELscope results that were correctly diagnosed as dysplastic/malignant on histopathological assessment gives the PPV using the formula $PPV = TP / (TP + FP)$,^[15,16] while the NPV indicates the proportion of lesions with negative VELscope results that were correctly diagnosed as nondysplastic on histopathological assessment calculated as $NPV = TN / (FN + TN)$.^[15,16] [Table 2].

On further analysis, in detection of “high-risk lesions” and “low-risk lesions” use of VELscope showed a high sensitivity of 90.47% but a low specificity of 44.44% [Table 2].

DISCUSSION

One of the most important factors in dismal mortality and morbidity figures associated with prognosis of oral cancer has been delay in detection and diagnosis. Delayed diagnosis in OSCC diagnosis has been attributed to both the patient and the practitioner factors. Cancer patients often present late in clinical practice owing to lack of knowledge of perceived symptoms and ignorance regarding the natural history of disease.^[17]

Improving patient awareness and training health-care professionals in early disease recognition are important contributors in successful preventive strategy. Although this can be challenging in general population screening, application of these strategies in high-risk groups offers a more feasible solution.^[18]

Optical techniques like autofluorescence through the use of VELscope like devices have gained popularity in oral cancer screening as they offer a rapid and noninvasive option for biopsy.^[19]

In addition, optical techniques are sensitive to tissue biochemistry. This is significant as the biochemical changes often precede visible morphological alterations making these techniques as potential screening/diagnostic tools for early cancer detection.^[19]

Table 1: Comparison of lesions showing no dysplasia with lesions with dysplasia or malignancy

	AFV		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Loss (AFL)	Retained (AFR)				
Dysplasia and malignancy	True positive 21	False negative 5	77.77	25	87.5	16.67
No dysplasia	False positive 3	True negative 1				

AFV: Autofluorescence visualization examination, AFL: Autofluorescence visualization loss, AFR: Autofluorescence visualization retained, PPV: Positive predictive value, NPV: Negative predictive value

Table 2: Comparison of “high-risk” and “low-risk” lesions

	AFV		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Loss (AFL)	Retained (AFR)				
High risk (moderate or severe dysplasia or carcinoma <i>in situ</i>)	True positive 19	False negative 2	90.47	44.44	79.16	66.67
Low risk (no or mild dysplasia)	False positive 5	True negative 4				

AFV: Autofluorescence visualization examination, AFL: Autofluorescence visualization loss, AFR: Autofluorescence visualization retained, PPV: Positive predictive value, NPV: Negative predictive value



Figure 2: Comparative images of leukoplakia in conventional white light examination and autofluorescence visualization examination



Figure 3: Comparative images of a suspected malignancy in conventional white light examination and autofluorescence visualization examination

However, over the years, a number of researchers have employed autofluorescence techniques for early cancer detection with varying results of sensitivity and specificity. A critical evaluation of these studies reveals the lack of uniformity in methodology including lack of histopathological confirmation which is the gold standard for diagnosis of oral cancer. A dissimilar study population was also included in some studies and hence the conclusions varied for the general population or only high-risk individuals.^[20] Hence, the present study was designed with inclusion of only one type of study population, namely only the patients with suspected lesions. In addition, inclusion of gold standard of histopathology for all the lesions was included in the study methodology which was a discrepancy in many of the previous such studies.

Thus, the present study assessed the oral mucosal lesions in 30 patients using COE followed by VELscope examination with further comparison with the histopathological diagnosis.

Sensitivity, specificity, PPV and NPV were estimated to determine the accuracy of VELscope examination analysis

outcome. The sensitivity and specificity of the VELscope examination were calculated to be 77.77% (95% CI: 54.87%–90.64%) and 25% (95% CI: 19.22%–30.36%), respectively, while the PPV and NPV were statistically calculated to 87.5% (95% CI: 64.77%–98.84%) and 16.67% (95% CI: 10.23%–20.37%), respectively.

In our study, we found a sensitivity of 77.77% in distinguishing dysplasia and malignancy from nondysplastic lesions. This is less compared to the study by Shia *et al.*^[21] in 2019 where they found a sensitivity of 100% in discrimination of carcinoma from oral potentially malignant disorders.

Similar higher values were documented by Koch *et al.*^[22] in their study with 97% sensitivity and 95.8% specificity for role of VELscope in diagnosing oral malignancy. Rana *et al.*^[23] in their study compared VELscope examination with COE and reported that the VELscope examination demonstrated a lower specificity (74% vs. 97%).

The poor specificity of 25% in our study also is reflective of the false positives, and this does not render well for the use of VELscope in practice where these patients would have had to undergo unnecessary biopsy. Similar poor specificity findings were noted by McNamara *et al.*^[24] in their study and hence they concluded that VELscope examination is not a suitable modality for routine oral cancer screening. Various authors have therefore recommended that in screening for early signs of oral malignancy careful, systematic visual and tactile examination of the entire oral cavity on a regular basis should remain as the gold standard.^[24-26]

In our study, the NPV of 66.66% in distinguishing high-risk and low-risk patients may suggest some role of VELscope as an adjunct in specialty clinics. It is striking to note that only 2 (6.67%) cases of moderate/severe dysplasia belonged to Group AFR, and no case of malignancy was noted in the AFR group. These values are in concurrence with the study by Ganga *et al.*^[14] who found that their VELscope examination had a similar high NPV of 95.08% (95% CI: 90.52%–97.51%).

These observations indicate that VELscope examination may be useful in screening of patients, especially to alleviate both the examiner and patient anxiety regarding a clinically suspicious oral lesion. Thus, the ability of the VELscope to rule out and exclude rather than to indicate the presence of malignant change may be of significance in contributing more to its effectiveness as an adjunct in a general practice setting. In addition, this tool can also prove to be effective in increasing patient compliance for a biopsy procedure.

Various researchers have investigated the potential causes of false-negative and false-positive observations in VELscope examination. False negatives have been attributed to operator inexperience and an inherent technical learning curve for the usage and interpretation of the autofluorescence technique^[20,27] Similarly, on the other hand, false positives which have been a major hindrance in wide-scale application of this technique in oral screening have resulted due to inflammatory lesions, pigmented lesions and vascular lesions which give similar fluorescence as the dysplastic lesions.^[20,27] A careful understanding and elimination of these possible pitfalls can help in improving the efficacy of the use of VELscope in routine oral cancer screening and can be incorporated in further studies on this subject.

A drawback of the present study may be that the data collection was specific to a tertiary care facility which would include only high-risk patients and hence the

findings may not be applicable to general population screening. Multicenter trials will help in providing validation across different demographic data and also evaluate the subjectivity via an interobserver agreement assessment. Large prospective studies including studies evaluating the genetic changes and progression rates associated with the “AFV suspicious” sites can be carried out.^[28,29]

CONCLUSIONS

Thus, the findings of our study indicate that AFV cannot be a substitute for COE. The study underscores the utility of AFV technique as a potential complementary diagnostic aid in surveillance of the high-risk patient population. Tissue biopsy and histopathology remains the gold standard for diagnosis of oral suspicious lesions.^[14] Nonetheless, autofluorescence technique-based VELscope examination is a simple, cost-effective, noninvasive easy-to-use technique. In addition, it has a wider area-imaging capability with ability to detect diffuse lesions. Furthermore, the nonrequirement of exogenous agents increases its utilization across the populations and tertiary centers.

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Conflicts of interest

There are no conflicts of interest.

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