



Efficacy of Autofluorescence Imaging as an Adjunctive Technique for Examination and Detection of Oral Potentially Malignant Disorders: A Systematic Review

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ABSTRACT

Background: Oral cancer is a serious global issue and early diagnosis of oral cancer is the key in reducing the high mortality rate. Autofluorescence properties of oral mucosa have been gaining interest in the field of early diagnosis of oral premalignant lesions.

Objective: The aim of the study was to evaluate the clinical usefulness of an autofluorescence based imaging system to detect oral premalignant and malignant lesions.

Materials and methods: A systematic review of the English-language literature to evaluate the effectiveness of visually enhanced lesion scope (VELscope) published between 1966 and March, 2014 was undertaken. Data relating to study design, sampling and characteristics of the study group, interventions, and reported outcomes and diagnostic value of VELscope were abstracted from articles meeting inclusion and exclusion criteria.

Results: Eleven articles that met the inclusion criteria were included. In nine studies, all the lesions underwent histological assessment, whereas the remaining four studies only performed histological assessment on suspicious lesions. Visually enhanced lesion scope showed high sensitivity values in detecting oral premalignant and malignant lesions. However, most of the studies reported it inability in discriminating dysplasia cases from nondysplasia cases.

Conclusion: There is insufficient evidence to support the use of VELscope in primary care setting, however, they may be useful in hands of a specialist.

Keywords: Diagnostic tools, Oral cancer, Systematic review, VELscope.

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INTRODUCTION

Oral cancer is the sixth most common cancer globally, however, the prevalence is much higher in some countries including Pakistan, India, Bangladesh and Sri Lanka.¹ In addition, despite better understanding of the disease process and numerous advancements in the treatment options, the 5-year survival rate of oral cancer has remained approximately 50%.² This poor prognosis is mainly attributed to the diagnosis of the disease in the late stages as a result of poor symptom recognition or missed diagnosis.^{3,4} Early diagnosis of oral cancer is, therefore, crucial to not only improve the patient's survival rate but also improve their quality of life post malignancy.

A systematic visual examination has long been the standard method for the detection of oral mucosal abnormalities including oral cancer and has shown sensitivities and specificities in the range of 60 to 97% and 74 to 94% respectively.⁵ However, only a small proportion of the population have oral mucosal abnormalities at one given time, and even fewer of them possess the characteristics of oral potentially malignant disorders (OPMD), thereby making it difficult for the healthcare

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professionals to identify and refer them with confidence. Fortunately, there is a dramatic increase in the potential oral cancer diagnostic or adjunctive tools that have the aptitude to identify OPMD, enhance visualization and assist in the selection of biopsy site.⁶⁻⁸

Autofluorescence imaging is one potential technique that has gained a growing interest in clinical practice for noninvasive imaging of the oral mucosa. It works on the principle that certain biofluorophores present within the tissue become fluorescent on excitation by a light source of suitable wavelength. On the contrary, the diseased tissues exhibit decreased levels of normal autofluorescence and appear dark due to disruption in the distribution of these biofluorophores. Visually enhanced lesion scope (VELscope); LED Dental, White Rock, British Columbia, Canada) is a reusable light source that emits a blue light (400–460 nm), which is then used to examine the oral cavity. The oral mucosa can be visualized directly through a narrow-band filter embedded within the viewing hand piece, providing direct fluorescent visualization. According to the manufacturer, the mucosal tissues suspected of oral epithelial dysplasia (OED) and/or oral squamous cell carcinoma (OSCC) show loss of fluorescence (LOF) and appear dark, whereas normal healthy oral mucosa shows apple green fluorescence.

A number of reviews have been published and reported a lack of evidence to support the use of autofluorescence as a diagnostic tool for the detection of OPMD and OSCC.⁹⁻¹⁴ However, since the last review¹¹ several more studies have been published requiring a reanalysis of the diagnostic value of autofluorescence. Therefore, the aim of the present study was to systematically review the clinical usefulness and efficacy of VELscope (an autofluorescence based imaging device) in identifying OPMD and OSCC and to formulate recommendations for its use in primary care setting and by a specialist.

MATERIALS AND METHODS

We formulated a key question 'What is the clinical effectiveness of VELscope in detecting oral potentially malignant disorders?' to address the role of autofluorescence imaging in early detection of oral cancer among adults during routine oral examination.

To address the question, we conducted detailed automated searches of MEDLINE OVID electronic database and PubMed to access relevant articles published between Jan 1, 1966 through March 17, 2014 using various combinations of the following keywords: 'autofluorescence', 'VELscope', 'oral precancers', 'early detection'. Review articles were also searched for additional articles missed in the automated searches.

We included studies that reported histological confirmation of the OPMD identified by VELscope and studies that specifically presented data on the accuracy of the test in comparison to the gold standard of histological assessment. The abstracts of the articles identified by the database search were screened to exclude irrelevant studies and those that were found relevant were read in full to determine if they fitted the eligibility criteria for the review. We excluded experimental studies, review articles, letters to the editor, unpublished data and articles not published in English. Studies on indirect visualization methods were also excluded; indirect visualization is based on capturing the fluorescent reflection with special spectrometers.

The initial search yielded 41 studies of which 30 studies that did not abide by our eligibility criteria and were excluded. In total, 11 studies were included. Since a limited number of studies addressed our focused question, pattern of the present study was customized to primarily summarize the pertinent information.

RESULTS

A total of 11 studies that evaluated VELscope and met the inclusion criteria were included (Table 1). Four studies were conducted in Germany,^{16,19,21,24} two in Canada,^{15,18} and one study each was conducted in UK,⁶ USA,¹⁷ Australia,²⁰ Italy²² and India.²³ Figure 1 shows an overview of the article selection process. In eight studies, patients were recruited after referral to specialists due to a primary diagnosis of suspicious lesions.^{6,16,18-22,24} Two studies recruited dental clinic patients who consulted the clinic for routine dental care,^{17,23} and the last study recruited individuals from the general population through public invitation.¹⁵ Conventional oral examination (COE) and

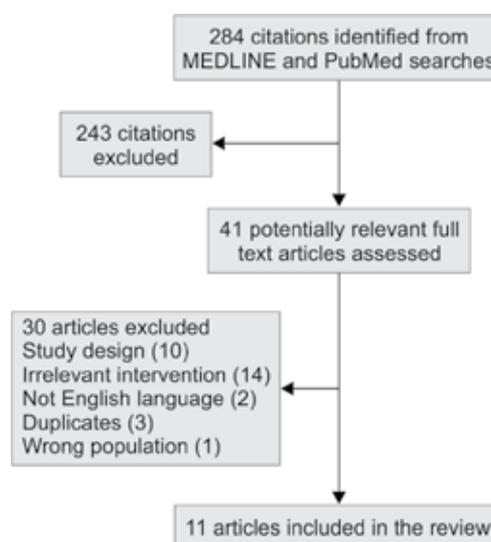


Fig. 1: Selection of the included studies

Table 1: Characteristics of the included studies

<i>Authors</i>	<i>Study design</i>	<i>Population</i>	<i>Intervention</i>	<i>Comparator</i>	<i>Clinical diagnostic criteria</i>	<i>Outcomes</i>
Laronde et al 2014 ¹⁵	Diagnostic study	Patients attending GDPs* in Vancouver, Canada was invited. A total of 2404 patients were screened with a standard protocol of medical history, head, neck and oral exam, followed by VELscope examination.	Oral examination with VELscope. Based on fluorescence visualization, lesions were classified; – FV** negative – normal green fluorescence – FV positive – reduction of loss of green fluorescence – FV equivocal – when the lesions could not be classified in one of the previous categories	COE† with incandescent light. Based on this, lesions were classified; – Low-risk – obvious trauma, aphthous ulcers, candidiasis, geographic tongue – High-risk – red and white patches, non-healing ulcers	Clinical appearance with fluorescence visualization loss	Inclusion of VELscope in the screening protocol of OPMD‡ significantly improves it.
Hanken et al 2013 ¹⁶	Prospective single blinded study	Patients attending the oral and maxillofacial surgery department at University Medical Centre, Hamburg, Germany. A total of 120 patients with suspicious oral premalignant lesions were included.	COE and VELscope examination n = 60 All lesions were biopsied and histologically examined	COE with white light n = 60	Clinical appearance with fluorescence visualization loss	VELscope may help the experienced clinician to identify OPMD and selection of biopsy site.
McNamara et al 2012 ¹⁷	Diagnostic study	Patients attending a university dental clinic at The Ohio State University for routine dental care. A total of 130 patients were included.	Oral examination with VELscope n = 130 Ninty-five lesions were clinically identified, of which 59 showed FVL and 32 underwent biopsy.	Oral examination with incandescent light n = 130	Clinical appearance with fluorescence visualization loss	VELscope does not provide any additional diagnostic benefit to COE for the detection of OPMD.
Marzouki et al 2012 ¹⁸	Diagnostic study	Patients with strong history of smoking and alcohol attending the oncology clinic at the McGill University Health Centre, Canada. A total of 85 patients with suspicious oral lesions were included.	VELscope following COE. The examiner was blinded to the results of the COE All suspicious lesions detected by COE and/or VELscope were biopsied and analyzed by an experienced pathologist.	Comprehensive clinical examination of the head and neck and the oral cavity	Clinical appearance with fluorescence visualization loss	VELscope may be an adjunct to COE in high risk patients
Rana et al 2012 ¹⁹	Randomized trial	Patients attending the Department of Craniomaxillofacial Surgery at Hannover Medical School, Germany. A total of 289 patients with oral premalignant lesions were included.	COE and VELscope examination n = 123 All suspicious lesions were biopsied (n = 52). A 2 week recall visit was arranged for lesions of acute inflammatory origin.	COE with white light n = 166	Clinical appearance with fluorescence visualization loss	VELscope is a useful diagnostic tool and may play a major role in prevention of oral cancer.
Farah et al 2012 ²⁰	Diagnostic study	Patients attending an oral medicine specialist unit at the University of Queensland, Australia. A total of 112 patients with oral suspicious lesions were included.	Oral examination with VELscope n = 112 A total of 118 lesions were identified and all underwent biopsy and histological assessment.	Oral examination with incandescent light n = 112	Clinical appearance with fluorescence visualization loss	VELscope may help in visualization of oral suspicious lesions but was unable to accurately differentiate high-risk lesions from low-risk.

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Authors	Study design	Population	Intervention	Comparator	Clinical diagnostic criteria	Outcomes
Scheer et al 2011 ²¹	Diagnostic study	Patients referred to the Department of Oral and Craniomaxillofacial Surgery at University of Cologne, Germany. A total of 64 patients with suspicious oral lesions were included.	Oral examination with VELscope n = 64 All lesions were biopsied and histologically examined.	Oral examination with incandescent light n = 64	Clinical appearance with fluorescence visualization loss	VELscope may help in detection of premalignant and malignant oral lesions in high risk patients but could not differentiate OPMD from benign lesions.
Awan et al 2011 ⁶	Diagnostic study	Patients attending the oral medicine clinic at King's College London, UK. A total of 126 patients with suspicious oral lesions were included.	Oral examination with VELscope n = 126 All lesions were biopsied and histologically examined.	Oral examination with incandescent light n = 126	Clinical appearance with fluorescence visualization loss	VELscope was useful in identifying oral mucosal disorders but failed to distinguish between high risk and low risk lesions.
Panderni et al 2011 ²²	Diagnostic study	Patients attending the oral sciences department at a university in Italy. A total of 175 patients were included.	Oral examination with VELscope n = 175 All lesions were biopsied and histologically examined.	Oral examination with incandescent light n = 175	Clinical appearance with fluorescence visualization loss	VELscope may act as a complementary device to the COE and histopathological assessment.
Mehrotra et al 2010 ²³	Cross-sectional study	Patients attending the outpatient department of a District Hospital in Madhya Pradesh, India. A total of 258 patients with clinically innocuous lesions were included.	Oral examination with VELscope n = 156 All lesions were biopsied and histologically examined.	Oral examination with incandescent light n = 156	Clinical appearance with fluorescence visualization loss	VELscope did not add any benefits to COE.
Koch et al 2010 ²⁴	Diagnostic study	Patients attending the Oral & Maxillofacial clinic at a university clinic in Germany. A total of 78 patients were included in the study.	Oral examination with VELscope n = 78 All lesions were biopsied and histologically examined.	Oral examination with incandescent light n = 78	Clinical appearance with fluorescence visualization loss	VELscope was not able to differentiate between benign and malignant lesions. The red fluorescence lesions should be used as an indication for biopsy.

*GDPs: General dental practitioners; **FV: Fluorescence visualization; †COE: Conventional oral examination; ‡OPMD: Oral potentially malignant disorders

histopathological assessment were the comparator tests in all the studies, however, biopsies or histopathology was conducted for all included patients in seven studies,^{6,16,20-24} and the other four trials conducted the histopathology only for suspicious lesions based on COE and/or VELscope examination.^{15,17-19}

Table 2 summarizes the diagnostic values of VELscope reported by the studies. Nine studies reported the diagnostic values of VELscope,^{6,16,18-24} with sensitivity and specificity ranged from 30 to 100% and 15 to 92.3% respectively. Six studies^{6,20-24} reported the positive and negative predictive values, that ranged from 6.4 to 58.1% and 57.1 to 100% respectively. The study of Laronde et al¹⁵ did not provide information on how many additional cases were detected by VELscope when compared with the standard methods. Similarly, study

by McNamara et al¹⁷ had the histopathology evaluation missing for 10 patients, and therefore, the diagnostic values could not be calculated.

DISCUSSION

As early as in 1924, it was observed that the autofluorescence of tissues could potentially be used for cancer detection.²⁵ Since then there has been considerable interests in the technologies of both fluorescence imaging and spectroscopy in cancer screening for a number of anatomic sites including the oral cavity. Fluorescence imaging works on the principle that certain molecules called biofluorophores are present within the cells and tissue matrix that produce fluorescence on excitation by a suitable wavelength light source. These biofluorophores include collagen, elastin, keratin, flavin

Table 2: Evidence of effectiveness of VELscope for detection of oral potentially malignant disorders

Authors	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Laronde et al 2014 ¹⁵	—	—	—	—
Hanken et al 2013 ¹⁶	97.9	41.7	—	—
McNamara et al 2012 ¹⁷	—	—	—	—
Marzouki et al 2012 ¹⁸	92	77	—	—
Rana et al 2012 ¹⁹	100	74	—	—
Farah et al 2012 ²⁰	30	63	19	75
Scheer et al 2011 ²¹	100	80.8	54.5	100
Awan et al 2011 ⁶	84.1	15.3	58.1	57.1
Paderni et al 2011 ²²	75	92.3	54.5	97
Mehrotra et al 2010 ²³	50	38.9	6.4	90.3
Koch et al 2010 ²⁴	93	15	41	78

adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NADH) that show green fluorescence when excited by light between 375 and 440 nm.²⁶

Visually enhanced lesion scope is a hand-held device that is based on the direct visualization of tissue fluorescence and the changes in fluorescence that occurs when abnormalities are present. The VELscope handpiece emits a safe blue light (400–460nm) into the oral cavity, which excites the tissue from the surface of the epithelium through to the basement membrane and into the stroma beneath, causing it to fluoresce. The clinician is then able to immediately view the different fluorescence responses and the manufacturer claims that this tool helps to differentiate between normal and abnormal tissue. Typically, healthy tissue appears as a bright apple-green glow while suspicious regions are identified by a loss of fluorescence, which thus appear dark.

In the current literature, nine studies reported the diagnostic values of VELscope in detecting OPMDs and OSCC. Higher sensitivities were observed in most of the studies, for example, 100%,^{19,21} 97.9%,¹⁶ 93%²⁴ and 92%.¹⁸ In the study by Rana et al¹⁹ VELscope in comparison to COE markedly increased the sensitivity of detecting oral epithelial dysplasia (sensitivity—17–100%). However, these findings should be interpreted with caution, as majority of the lesions did not undergo histopathological assessment to confirm the presence or absence of dysplasia.

In another study, the authors reported that 84.1% of the dysplasia cases by detected positively by the VEL scope device. These results notably demonstrate the ability of the device to detect high-risk lesions. However, cases of low-grade dysplasia (mild dysplasia = 5; moderate dysplasia = 2) showed negative test results. In addition, majority of other benign lesions showed loss of fluorescence (positive-test result) under VELscope examination. Inability of VELscope to distinguish between dysplastic and non-dysplastic lesions have been reported in another study where only half of the dysplasia cases were not detected by the device.²³

For the device to be utilized as a screening tool, it should demonstrate the ability to accurately detect occult cases of OSCC and OPMD. In two studies,^{18,20} the device was able to detect clinically missed lesions, some of which had dysplasia. In the study by Marzouki et al¹⁸ the device was able to detect four dysplastic lesions which were not detected by the clinical examination alone. This may demonstrate the ability of VELscope as a screening tool, however, one dysplastic lesion that was detected by clinical examination instead of VELscope may undermine this aptitude.

In a community based follow-up study, Laronde et al¹⁵ used a logistic approach to reexamine the lesions after 3 weeks of the initial assessment. Reexamination of the lesions resulted in 60% reduction in the referral of lesions that had resolved, suggesting that many lesions might be non-specific and/or inflammatory in nature. The authors suggested that this approach is critical for improving the specificity of VELscope. However, the re-examination did not improve the specificity of the device as 29% of the re-examined lesions that showed loss of fluorescence regressed in the clinical examination. Furthermore, this would not be possible in a clinical setting to keep the patients this long without a diagnostic biopsy.

A number of studies suggested other approaches to improve the specificity rates. Koch et al²⁴ reported that lesions showing red color fluorescence under VELscope examination were more likely to be malignant (specificity 98%). Other studies recommended the use of tissue blanching to reduce the false positive test results among the inflammatory lesions (diascopic fluorescence).^{17,20} In the study by Farah et al²⁰ diascopic fluorescence was observed in 10 cases of dysplasia and one case of OSCC, resulting in false negative test results. It is important to mention that the ideal pressure and appropriate tool used for diascopic fluorescence has not been standardized in these studies, thereby making the results subjective.



The performance of a diagnostic test is based on the assessment of its sensitivity and specificity values. A recent Cochrane review,²⁶ assessed COE as a potential screening tool for OPMD and oral cancer and reported a variable degree of sensitivity (>70% in six of the 10 studies) and a consistently high specificity value (>90% in all eight studies). Data in this review do not indicate any improvement in the sensitivity and specificity values by the additional use of autofluorescence.

CONCLUSION

There is insufficient evidence in the literature to show that direct tissue fluorescence visualization has the capability to be used as an oral cancer-screening tool. However, it has been shown in various studies that it can detect OPMD, but its ability to distinguish precancerous or cancerous occult lesions from benign lesions is still questionable. Also, intra- and interoperator agreement in the interpretation of test results has not been verified. Further studies need to be performed to answer these questions.

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