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REVIEW ARTICLE

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The efficacy of direct tissue fluorescence visualization in screening for oral premalignant lesions in general practice: an update

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Abstract: *Objective:* The aim of this communication is to revise papers published on autofluorescence imaging, a non-invasive technique that is used to identify neoplastic oral cavity lesions. *Methods:* A literature search was performed, using the PubMed database and the key words 'autofluorescence' and 'Velscope', limiting the search to papers in English or Spanish published from 2002 to June 2009. *Results:* The Velscope® system has a sensitivity of 98–100% and specificity of 94–100%. Autofluoresence is a supplementary tool used in the diagnosis of oral cancer, although other more reliable and robust studies are needed for confirmation. *Conclusions:* There is insufficient evidence to demonstrate that its use as an adjunct to conventional oral screening provides additional benefit to conventional oral cancer screening alone.

Key words: autofluorescence; oral cancer; Velscope

Introduction

Head and neck cancer, including the oral cavity, is the sixth most frequent cancer. Approximately 30 000 patients per year are diagnosed with oral cavity or oropharyngeal squamous cell carcinoma (OSCC) in the United States. The baseline annual risk is approximately 1/10 000 of the total adult USA population. While 84% of patients with oropharyngeal cancers will survive at least 1 year following diagnosis, overall, 40% of newly diagnosed patients will die within 5 years (1, 2).

The Oral Cancer Prevention Programme recommends systematic and standardized examination, including the medical records, habits (tobacco and alcohol), clinical examination (extraoral and intraoral) and inspection of the lesion (2, 3).

Screening and early detection in populations at risk have been proposed to decrease both the morbidity and mortality associated with oral cancer. However, the visual detection of premalignant oral lesions has remained a problem throughout the world. One explanation for this is that early lesions of oral cancer and precancer are often slight and rarely demonstrate the clinical characteristics observed in advanced cases: ulceration, induration, pain or associated cervical lymphadenopathy. Besides their clinical subtlety, premalignant lesions are highly

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heterogeneous in their presentation and may mimic a variety of common benign or reactive conditions. Furthermore, there is a growing realization that some premalignant and early cancerous lesions are not readily detectable to the naked eye. As such, additional screening aids for oral cancer are 'desperately' needed (1–7). Recent years have seen the development of visual tools for helping in the diagnosis of oral cancer, to which luminous detection systems have been recently added (chemoluminescence and tissue fluorescence techniques) with the aim of improving detection and increasing our capacity to identify potentially malignant lesions (1–12).

Tissue autofluorescence has been used in the screening and diagnosis of precancers and early cancer of the lung, uterine cervix, skin and, more recently, of the oral cavity Approximately 30 years ago, it was observed that tissue fluorescence could potentially be used for cancer detection (1, 2). Changes in fluorescence reflect a complex interplay of alterations to fluorophores in tissue and structural changes in tissue morphology. The endogenous fluorophores that are most relevant for optical screening and the diagnosis of precancer and cancer are those that excite in the spectrum from visible violet/blue (400–450 nm) to UV-A (315–400 nm) and which have properties that have been spectroscopically correlated with disease. The concept behind tissue autoflorescence is that changes in the structure (e.g. hyperkeratosis, hyperchromatin and increased cellular/nuclear pleomorphism) and metabolism (e.g. concentration of flavin adenine dinucleotide and nicotinamide adenine dinucleotide of the epithelium, as well as changes of the subepithelial stroma (e.g. composition of the collagen matrix and elastin), alter their interaction with light (5–9). More specifically, these epithelial and stromal changes can alter the distribution of tissue fluorophores and, as a consequence, the way they fluoresce after stimulation with intense blue excitation (400–460 nm) light, a process defined as autoflorescence. The autoflorescence signal is finally visualized directly by a human observer.

Autofluorescence imaging is non-invasive and rapid technique for inspecting the oral mucosa and identifying oral cavity lesions developed by LED Medical Diagnostics (White Rock, BC, Canada) using the Velscope® system (12). Given the potential advantages of the technique, it is important to decide whether it can be applied for screening purposes, for which reason we have made a revision of studies published on autofluorescence (Velscope®).

Material and methods

A literature search was conducted in the PubMed database using as search words autofluorescence and 'Velscope' and limiting the search to papers in English or Spanish published between 2002 and June 2009. Other studies were selected from references cited by the articles found in the literature search. Inclusion criteria for the analysis were for the article to specify: Velscope or autofluorescence oral cancer. Laser-induced fluorescence spectroscopy and chemiluminescence were excluded. We found seven articles with the key word 'Velscope' and 71 articles with the key words 'autofluorescence' oral cancer. Six articles fulfilled both inclusion criteria.

Results

Six (13–18) were selected for the evaluation of this system. Their main characteristics are shown in Table 1. Reported sensitivity values ranged from 97% to 98% and specificity from 94% to 100% (13–18). The Velscope® is a portable device that permits the direct visualization of the oral cavity and is sold for use in the screening of oral cancer. It has a blue light cone of 400–460 nm wavelength which permits lesions to be detected by their fluorescence (visualization by light). The cells of the mucosa epithelium absorb light energy and re-emit it in the form of fluorescence, which can be visualized directly by the human eye. The tonality for interpretation purposes is straightforward: pale green for healthy tissue and dark green, brown or black (loss of fluorescence) for a pathological situation. The Velscope® is intended to be used by a dentist or health-care provider as an adjunct to traditional oral examination by incandescent light to enhance the visualization of oral mucosal abnormalities that may not be apparent or visible to the naked eye, such as oral cancer or premalignant dysplasia (10). Velscope® is further intended to be used by a surgeon to help identify diseased tissue around a clinically apparent lesion and thus aid in determining the appropriate margin for surgical excision. Optical changes (specifically, loss of fluorescence) in the epithelium in and around oral cancers has been used to map the 'field of cancerization'. Correlation with histopathological features and specific genetic alterations indicate that fluorescence visualization is far superior to clinical judgment alone in gauging the size, extent and distribution of the cancer field.

Discussion

Velscope®: supporters of this system affirm that it may help to detect cases that would otherwise go unnoticed, although it cannot ensure that the clinical decision concerning the potential for malignant transformation is correct. Using this system, Kois and Truelove (13) of the University of Washington detected new lesions in three subjects during a follow-up of patients with previous oral dysplasia or carcinoma *in situ*, who were subsequently biopsied. Poh *et al.* (14), from the Dentistry Faculty of the University of Columbia, in a pilot study of patients with a history of oral dysplasia or carcinoma *in situ* and examined by direct visualization under autofluorescent light, found three patients with occult lesions. Subsequent biopsy identified one primary dysplasia, one primary cancer and one recurrent cancer. Sensitivity was 98% and specificity 100%. A second study by Poh *et al.* (15) investigated the ability of the Velscope® to identify cancerous tissue in patients with known cancers and also to identify the margins of abnormal tissue around the known lesion. Twenty patients were consecutively recruited as they were being assessed prior to removal of a known cancer. The Velscope® was used to assess the cancer and its margins. Biopsies of tissue with abnormal and

Table 1. **The summary of studies citing Velscope® (10, 17)**

Citation	Study design	Outcome	Results	Critique
Poh *et al.* (14)	Case study	Detection of oral premalignant and malignant lesions	Direct fluorescence visualization was effectively used to detect a new lesion in three patients during follow-up	All cases were people whom the investigators knew had a history of oral dysplasia or carcinoma *in situ*
Poh *et al.* (15)	Observational (cross-sectional) study	Detection of the extent of visibly identified premalignant or cancerous oral lesions	102 margins established Sensitivity = 97% Specificity = 94%	Pilot study Spectrum and test-referral bias participants limited to those already known to have had cancer; results in overestimate of Velscope's sensitivity and specificity No blinding of investigators
Lane *et al.* (16)	Observational (cross-sectional) study	Normal tissue; abnormal tissue severe dysplasia carcinoma *in situ*, squamous cell carcinoma	50 lesions detected Sensitivity = 98% Specificity = 100%	Pilot study shows that device may be able to distinguish between normal and abnormal tissue, but not necessarily between oral cancer and other forms of abnormal oral tissues Participants limited to those already known to have had cancer; results in overestimate of Velscope's No blinding of investigators
Kois and Truelove (13)	Case study	Detection of oral premalignant lesion	Direct fluorescence visualization was effectively used to detect a new lesion in three patients during follow-up	All cases were people whom the investigators knew had a history of oral dysplasia or carcinoma *in situ*
Huber (17)	Observational	Detection of oral premalignant lesion	Ten suspicious lesions were identified by conventional examination. No lesions identified using Velscope's	
Huff *et al.* (18)	Observational	Detection of oral premalignant lesion Lower-risk populations	1.3% prevalence of mucosal abnormalities; 83% of these were potentially premalignant epithelial dysplasia	

normal fluorescence were then taken for histopathology. All tumours showed a loss of fluorescence and this extended outside the normal visual margin for all tumours except one. When the fluorescing and non-fluorescing tissue was analysed, 32 of the 36 non-fluorescing tissue samples were found to be histologically abnormal, whereas of the 66 fluorescing samples only one was histologically abnormal. Using an arbitrary resection margin of 10 mm around the tumour would have left 6/20 cases with cancerous or highly abnormal tissue remaining, making recurrence a high probability. This study demonstrates that the Velscope® is useful for identifying abnormal tissue that may appear normal under regular lighting.

Lane *et al.* (16) in a small pilot study evaluated the use of the device in 44 patients with a history of biopsy-confirmed oral dysplasia or carcinoma recruited from the Oral Health Study at the British Columbia Cancer Agency. During each visit, an assessment of the oral mucosa under white light was conducted to identify new lesions or alterations to previously identified lesions. After turning off the room light, the oral cavity was viewed by direct fluorescence visualization (FV). The clinicians then decided whether the lesions required biopsy based on standard clinical features (patient history, clinical appearance and toluidine blue staining results) and not on the direct FV examination. Biopsied lesions were evaluated by oral pathologists and a histological diagnosis was assigned. The objective was to verify the effectiveness of the direct FV device for differentiating high-risk oral premalignant lesions and invasive SCC from normal oral mucosa. The association of direct FV changes in the oral mucosa of biopsy-confirmed sites of normal and severe dysplasia, carcinoma *in situ*, and invasive SCC was therefore assessed. Using histology as the gold standard, the device achieved a sensitivity of 98% and a specificity of 100% when discriminating normal lesions from high-risk premalignant lesions and invasive SCC. According to the authors, these preliminary results suggest that the direct FV device has potential as an adjunct to conventional white-light screening to increase the sensitivity of white-light screening alone but not reduce the specificity.

Huber (17) examined 130 patients who smoked at least one packet of cigarettes a day, comparing the clinical findings obtained by conventional examination with those obtained by Velscope® While ten suspicious lesions were identified by conventional means, none were found by Velscope®, which raises questions concerning its use for screening purposes.

Additional information on the use of Velscope® is provided by case reports (18, 19). For example, Comisi describes how a case of squamous papiloma (attributed to VPH) was discovered during a revision (19).

We should always bear in mind that in the early detection of cancer by screening (application of a test to evaluate the presence of the disease in asymptomatic subjects who apparently suffer no illness and for whom conventional visual examination represents the gold standard) and 'case detection' (application of a given procedure to patients with an identified lesion – in the case of precancer and oral cancer, biopsy) (1, 2). A Velscope® should only be used bearing in mind the patient's history and after a thorough visual examination, since it is not a diagnostic tool but a device to complement the visual and manual inspection of the head and neck by specialists/experienced professionals. It can provide information that will help such specialists decide whether or not biopsy is needed. The doctor's training is important to avoid problems related with the interpretation of the results since benign lesions also cause a loss of fluorescence (geographic tongue, aphthous ulcers, etc.).

As the revision carried out by Balevi (10) mentions, the results obtained with autofluorescence in the case of the oral cavity seem promising but most studies have included patients attending clinics specialized in the diagnosis of oral pathologies. Such a population is not representative of patients seen in general dental practice and there is therefore a risk of bias in the reference assays. However, a study of clinical cases does not intend to change clinical practice but to identify a way of helping and promoting research.

Systematic examination of the oral cavity for signs of oral cancer is recommended, especially in high-risk individuals, although there is no clear evidence that oral cancer screening programmes can detect oral cancer earlier and reduce the number of deaths from this disease. The Velscope System® has been proposed as a method to improve current oral screening methods by assisting in the identification, evaluation and monitoring of oral mucosal abnormalities.

Conclusion

There is insufficient information in the published medical literature, to demonstrate that the use of this technology as an adjunct to conventional oral screening provides additional advantages over to conventional oral cancer screening alone or that its use will result in improved health outcomes.

References

1 Lingen MW, Kalmar JR, Karrison T, Speight PM. Critical evaluation of diagnostic aids for the detection of oral cancer. *Oral Oncol* 2008; **44:** 10–22.

2 Mignogna MD, Fedele S. Oral cancer screening: 5 minutes to save a life. *Lancet* 2005; **365:** 1905–1906.

3 Trullenque-Eriksson A, Muñoz-Corcuera M, Campo-Trapero J, Cano-Sánchez J, Bascones-Martínez A. Analysis of new diagnostic methods in suspicious lesions of the oral mucosa. *Med Oral Patol Oral Cir Bucal* 2009; **14:** E210–E216.

4 Scully C, Bagan JV, Hopper C, Epstein JB. Oral cancer: current and future diagnostic techniques. *Am J Dent* 2008; **21:** 199–209.

5 Fedele S. Diagnostic aids in the screening of oral cancer. *Head Neck Oncol* 2009; **30 1:** 5.

6 Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. *J Am Dent Assoc* 2008; **139:** 896–905.

7 Onizawa K, Okamura N, Saginoya H, Yoshida H. Characterization of autofluorescence in oral squamous cell carcinoma. *Oral Oncol* 2003; **39:** 150–156.

8 Pavlova I, Williams M, El-Naggar A, Richards-Kortum R, Gillenwater A. Understanding the biological basis of autofluorescence imaging for oral cancer detection: high-resolution fluorescence microscopy in viable tissue. *Clin Cancer Res* 2008; **14:** 2396.

9 Svistun E, Alizadeh-Naderi R, El-Naggar A, Jacob R, Gillenwater A, Richards-Kortum R. Vision enhancement system for detection of oral cavity neoplasia based on autofluorescence. *Head Neck* 2004; **26:** 205–215.

10 Balevi B. Evidence-based decision making: should the general dentist adopt the use of the Velscope for routine screening for oral cancer? *J Can Dent Assoc* 2007; **73:** 603–606.

11 Westra WH, Sidransky D. Fluorescence visualization in oral neoplasia: shedding light on an old problem. *Clin Cancer Res* 2006; **12:** 6594–6597.

12 LED Dental Inc. VELscope: The Oral Cancer Screening System. [Website of LED Dental Inc., White Rock, BC], 2007. Available at: http://www.velscope.com. Accessed 30 July 2009.

13 Kois JC, Truelove E. Detecting oral cancer: a new technique and case reports. *Dent Today* 2006; **25:** 94–96.

14 Poh CF, Ng SP, Williams PM *et al.* Direct fluorescence visualization of clinically occult high-risk oral premalignant disease using a simple hand-held device. *Head Neck* 2007; **29:** 71–76.

15 Poh CF, Zhang L, Anderson DW *et al.* Fluorescence visualization detection of field alterations in tumor margins of oral cancer patients. *Clin Cancer Res* 2006; **12:** 6716–6722.

16 Lane PM, Gilhuly T, Whitehead P *et al.* Simple device for the direct visualization of oral-cavity tissue fluorescence. *J Biomed Opt* 2006; **11:** 024006.

17 Huber MA. Assessment of the VELscope as an adjunctive examination tool. *Tex Dent J* 2009; **126:** 528–535.

18 Huff K, Stark PC, Solomon LW. Sensitivity of direct tissue fluorescence visualization in screening for oral premalignant lesions in general practice. *Gen Dent* 2009; **57:** 34–38.

19 Comisi JC. Oral human papillomavirus lesion identified using VELscope instrumentation: case report. *Gen Dent* 2008; **56:** 548–550.