

Role of Direct Fluorescence Visualization for Screening of Oral Cancer and its Impact on Raising Awareness

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Abstract

Background: Oral cancer accounts 3% of all cancers worldwide with an increase in rates for both sexes and rising trends in young men. As survival rate increases when diagnosed at early stages, systematic visual inspection is recommended at the beginning of dental treatment of patients. However, diagnosis of oral cancer by visual oral examination may be challenging sometimes and, determining the malignant transformation of clinically visible potentially malignant disorder is not possible. Public awareness of OC has been reported to be very low, causing delay in referral and treatment. This study is aimed to assess a light based screening instrument as a diagnostic adjunct in oral cancer risk group and non-risk group patients. Additional aim was to evaluate the awareness of patients on oral cancer and their confidence with an adjunct visualization tool.

Methods: Oral visual examination that is followed by light based screening was performed on 150 patients who admitted to oral surgery department for routine oral surgical procedures. A hand-held device VELscope[®] which permits direct fluorescence visualization of oral mucosa was used as a light based screening device. Incisional biopsies were obtained from the areas either with clinical suspicious appearance or with loss of autofluorescence that may indicate a neoplastic change in 39 patients. Awareness and knowledge of patients on oral cancer, and their reliability on an adjunct aid in the diagnosis of oral cancer were evaluated by a written questionnaire.

Results: A total of 39 biopsies were made from suspicious lesions in both groups detected by oral visual examination and/or by VELscope[®] examination. Among those biopsies that were detected both by visual examination and by VELscope[®] examination, 2 were reported as malignant. Five suspicious lesions detected only by visual examination were reported as potentially malignant. Awareness of patients on oral cancer was found to be low. Patients reported screening with VELscope[®] more reliable than screening with unaided eye.

Conclusion: Direct fluorescence visualization has not proven effective as a diagnostic adjunct for screening of oral cancer but found very reliable by patients in this study.

Keywords: Oral Cancer; Screening; Visual Oral Examination; Direct Fluorescence Visualization; Early Detection

Introduction

Oral cancer (OC) has been reported to have one of the highest mortality ratios amongst all malignancies, with five-year relative survival rate less than 50% [1,2]. Five-year survival rate is 81% when diagnosed in Stage 1, drops to 40% when diagnosed in Stage 4 [3].

Several risk factors have been found to be associated with oral cancer including tobacco and alcohol consumption as major risk factors, and also age and sex, oral conditions, family history, occupational exposures, diet, infections, exposure to UV radiation, ionizing radiation, lifestyle and environmental factors [4]. Besides, oral lesions like leukoplakia, erythroplakia, and lichen planus are considered as potentially malignant disorders with varying rates of malignant transformation [5-7]. The annual malignant transformation rate of leukoplakia is 1% that corresponds to 20 in 100,000 cases and, very high for erythroplakia though the exact rate has not been calculated [8]. Retrospective studies of patients with oral lichen planus revealed 3.7% and 5.32% malignant transformation rate at the site of OLP. [6-8].

Awareness of oral cancer, the key factor for avoiding the risk factors and motivation for regular appointments for oral examination was found unfortunately very low among dental patients [9].

Although oral visual and tactile examination is still the conventional and effective method for detecting oral cancer at early stages of development [10], several detection methods and procedures are studied as an adjunct. High sensitivity (100%) has been reported VELscope and suggested as a useful device for detection of oral cancer [11].

The aim of the study is two-fold; comparing the visual oral examination findings by direct fluorescent visualization findings when used for oral cancer screening in randomly selected high risk and non-risk patients for oral cancer and to evaluate awareness of patients on oral cancer.

Methods

Opportunistic visual oral examination and screening by direct fluorescent visualization using VELscope® (LED Dental, Inc., White Rock, BC, Canada) was performed on 150 patients who admitted to oral surgery department for routine oral surgical procedures. The protocol set conformed to the provisions of the Declaration of Helsinki.

Patients were divided into 2 groups; Group 1 consisted of 100 patients positive for one or more risk factors for oral cancer that were revealed during anamnesis. The risk factors included were, being at age of 40 years or over, history of smoking, alcohol consumption, poor nutrition, extensive exposure to

sunlight and/or having poor oral hygiene. Group 2 consisted of 50 patients as controls that reported no risk factors for oral cancer.

Informed consent was obtained from subjects prior to the oral examination. Patients in both groups were examined by the same, experienced PhD students calibrated for oral mucosal examination and VELscope® use. Oral screening of patients including the lower lip was performed initially by visual oral mucosal examination under a light source and, any irregularities, suspicious lesions or color changes were recorded. Following visual examination, oral mucosal examination was done by direct fluorescent visualization using the hand-held device VELscope® in every patient. It is used in an aim to visualize tissue autofluorescence in the mucosa of the oral cavity. When oral tissues are exposed to intense blue excitation light (400-460 nm) by this device, certain biofluorophores present within the normal tissue become fluorescent on excitation and appear green, while abnormal/diseased tissues appear dark due to the disrupted distribution of biofluorophores.

Incisional biopsy was made, from the suspicious lesions on visual oral examination or if any dark area indicating loss of autofluorescence was observed by direct fluorescent visualization to confirm possible malignancy. Findings recorded in oral mucosal screening by both techniques were compared with each other and matched with the results of biopsies.

Awareness and knowledge of patients on oral cancer, and their reliability on an adjunctive aid in the diagnosis of oral cancer were evaluated by a 17-item self-administrated questionnaire. Student t test was used to analyze awareness of patients.

Results

There were 49 females and 51 males in the risk group; 35 females and 15 males in the control group. Mean age of patients was 46.3 years in the risk group and, 25.9 in the control group. Socio demographic characteristics of patients are shown in Table 1.

The visual oral examination and VELscope® examination findings of Group 1 are shown in Table 2. Visual oral mucosal examination and direct fluorescence visualization did not reveal any abnormal appearance or loss of fluorescence in 64 patients consisting of 34 females (53%) and 30 males (47%) with a mean age of 45-years.

Table 1. Socio demographic characteristics of patients.

		Frequency	Percentage
Age	18-39 years	73	49%
	40 + years	77	51%
Gender	Female	87	58%
	Male	63	42%
Marital status	Married	103	69%
	Single	47	42%
Education	Elementary school	43	29%
	High school	51	34%
	University	56	37%

Table 2. Visual oral examination and VELscope® examination findings of Group 1.

# of patients	Visual oral examination	V E L - scope® examination	Biopsy
64	negative	negative	No biopsies were made
19	positive	positive	14 benign 3 potentially malignant* 2 malign lesions**
16	positive	negative	2 potentially malignant* 14 benign lesions
1	negative	positive	Normal oral mucosa
100	35	20	7

*Moderately differentiated squamous cell carcinoma (1), malign melanoma (1)

** Lichen planus (1) slight dysplasia (4).

Visual oral examination revealed suspicious oral lesions in 19 patients in which direct fluorescent visualization also showed somewhat loss of fluorescence. Of those 19 patients, 6 were female (32%) and 13 were male (68%) with a mean age of 48.3. Among those 19 lesions, 11 were pigmented lesions (58%), 2 were white lesions (11%), 1 was exophytic lesion and 5 were ulcerated lesions (26%). Biopsies were performed from all these suspicious lesions. Histopathological evaluation revealed 14 lesions being benign in nature whereas 5 as malignant or potentially malignant; reported as 1 moderately differentiated squamous cell carcinoma, 1 malignant melanoma, 1 lichen pla-

nus and 2 slight dysplasia.

In 16 patients suspicious oral lesions were detected by visual oral examination but not by direct fluorescent visualization. No dark areas were revealed by VelScope® examination. Among those 16 patients, 9 were females (56%) and 7 were males (44%). The suspicious lesions detected were, pigmented lesions in 7 patients (44%), mucosal keratinization in 5 patients (31%) and exophytic lesions in 4 patients (25%). Biopsies were obtained from all these lesions. Histopathological examination of the specimens was reported as benign in 14 cases and as slight dysplasia in 2 cases.

In 1 patient, visualization by VELscope® showed somewhat loss of fluorescence on hard and soft palate region. However, visual oral examination did not reveal any suspicious lesion on oral and palatal mucosa. Histologic examination of the biopsy was reported as normal mucosa.

The visual oral examination and VELscope® examination findings of Group 2 are shown in Table 3. Visual oral mucosal examination and direct fluorescence visualization did not reveal any abnormal appearance or loss of fluorescence in 47 patients that were comprised of 35 females (75%) and 12 males (25%) with a mean age of 25, 7. In the same group, oral visual examination revealed pigmentation in 1 patient and oral ulceration in 2 patients. No loss of fluorescence has been detected by VELscope® examination. Those 3 patients were males with a mean age of 29, 3. Histopathological examination of biopsy specimens did not show malignancy.

Table 3. Visual oral examination and VELscope® examination findings of Group 2.

# of patients	Visual oral examination	VELscope® examination	Biopsy
47	Negative	Negative	No biopsies were made
3	Positive	Negative	All benign
50	3	-	3

The known risk factors for oral cancer reported by patients were smoking (29%), being male (25%), being elderly (18%), alcohol consumption (17%), poor oral hygiene (7%), poor nutrition (3%) and ultraviolet radiation (1%) while low socioeconomic status and HPV has not been reported by any patient.

Answers to the questionnaire on oral cancer awareness given by patients are shown in Table 4. Patients reported that they would seek assistance if they have a sore (72%), red or white lesion (75%) in their mouth. However, only 39% of patients have visited dentist for oral-mucosal examination apart from dental treatment.

Table 4. Answers of patients to the questionnaire on oral cancer awareness.

Would you seek assistance from your dentist if you notice a sore in your mouth?			
	Yes	n:108	72%
	No	n: 42	28%
Would you seek assistance from your dentist if you notice red or white lesions in your mouth?			
	Yes	n:113	75%
	No	n:37	25%
Do you have an idea if oral cancer spread to any part of the body?			
	Yes	n:69	46%
	No	n:81	54%
Apart from dental treatments have you ever visited your dentist for oral-mucosal examination?			
	Yes	n:59	39%
	No	n:91	61%

Specificity was found 95%, and sensitivity was found 67% for VELscope® in our study.

Table 5. Patients' reported level of confidences with oral visual examination and VELscope® for early detection of oral cancer.

Level of confidence with oral visual examination		Frequency	Percentage (%)
	Never feel confident	32	21
	Feel somewhat not confident	19	13
	Feel somewhat confident	48	32
	Feel absolutely confident	51	34
Level of confidence with an instrument			
	Never feel confident	10	7
	Feel somewhat not confident	4	3
	Feel somewhat confident	50	33
	Feel absolutely confident	86	57

Patients rated their level of confidence with oral visual examination and VELscope® for early detection of oral cancer

(Table 5). Patients stated that they will never feel confident by visual oral examination (21%) or examination using an instrument (7%) for early detection of oral cancer. Contrarily, patients stated that they will feel absolutely confident when examined visually (34%) or by VELscope® (57%).

Discussion

Low level of awareness both among dental practitioners and patients, variances in detection methods are among reasons of late detection. Oral health care providers bear very important role in the early detection of oral cancers and should keep current with reliable and valid diagnostic technologies [12].

Visual examination of oral cavity under a good source of light, palpation of the lymph nodes still remain as conventional screening procedure for detection of oral cancer and precancerous lesions. However, lesions at early stage are often asymptomatic and, differential diagnosis with other benign or premalignant lesions is challenging on visual examination. Furthermore, it may not be noticed either by the patient or by the clinician during routine dental examination. It was found that oral cancer being overlooked at the initial presentation with an initial decision of not to refer or follow-up significantly increased tumor related death and, it caused 1 extra death for every 3 such patients [13].

More advanced screening techniques including toluidine blue staining, brush biopsy and, fluorescence imaging have been attempted for early detection of oral cancer. Benefits and limitations of oral cancer screening and the use of adjunctive screening aids to visualize and detect oral cancer have been critically evaluated focusing on the role, specificity and sensitivity of adjunctive screening aids concluding the lack of sufficient evidence to suggest other screening methods [10].

To contribute the literature, efficacy of direct fluorescent visualization compared to visual examination for screening oral mucosa in a group of patients and, patient's knowledge and awareness about oral cancer was evaluated in this study. In a group of 100 risk-group patients 2 lesions were determined as potentially malignant both by visual oral examination and examination by VELscope® and also were confirmed malign by histopathology. In the same group of patients 16 suspicious lesions observed by visual oral examination did not exhibit dark area by VELscope® examination. However, 2 biopsy results out of those suspicious lesions were reported as potentially malignant. If the clinician would use only VELscope® for screening, then would overlook the lesion and would not obtain biopsy. However, dysplasia has been confirmed by histopathology in 39.13% of all types of leukoplakia, in 67.21% of clinically diagnosed cases of speckled leukoplakia revealing the importance of obtaining biopsy at the initial appointment [5].

In the control group consisting of 50 patients only 3 suspicious

lesions were detected by visual oral examination that has not shown a malignant or potentially malignant character by histopathology. Examination by VELscope® did not reveal any suspicious lesions in this group of patients.

Tobacco use, alcoholic beverage consumption, ultraviolet radiation are included among risk factors with epidemiologic evidence for oral cancer in Ontario report series [14]. The International Agency for Research on Cancer also states alcoholic beverages, tobacco smoking, smokeless tobacco, X-radiation, Epstein-Barr virus as risk factors with "sufficient" or "convincing" evidence for oral cancer [15]. Systematic review and meta-analysis demonstrate a significant association with oral cancer risk and low socioeconomic status related to lifestyle risk factors [16,17].

The first 3 known risk factors of oral cancers by patients were smoking (29%), gender (25%) and getting older (18%). Patients' awareness of ultraviolet radiation as a risk factor was very low; HPV and low socio-economic status were not known as risk factors.

More than 70% of patients have stated that they would refer to dentist if they have a sore, red or white lesion in their mouth. However, only 39% of patients have visited their dentists for oral-mucosal examination apart from the dental treatments. Thirty-four % of patients stated that they would feel absolutely confident, while 21% stated they will never feel confident if their dentists make oral visual examination for early detection of oral cancer. Ratio of patients stating that they would feel absolutely confident strikingly increased to 57% and decreased to 7% when asked if they would feel confident if their dentists make oral cancer screening with an instrument. Although visual oral examination still recognized as a gold standard for early detection of oral cancer, patients do not have the idea of this fact.

Direct fluorescence visualization has not proven effective as a diagnostic adjunct for screening of oral cancer in this study. However, it proved to be reliable by patients and provided to be an effective adjunct in increasing awareness of patients on oral cancer. Although the specificity of direct fluorescence visualization has been found low, it may demonstrate higher specificity and sensitivity in larger population studies.

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