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Fluorescence visualization improves the detection of oral, potentially malignant, disorders in population screening

Luciana Estevam Simonato[a], Saygo Tomo[b,*], Ricardo Scarparo Navarro[c,f], Antonio Guillermo Jose Balbin Villaverde[d,e]

[a] Dental School, University Brasil (UnivBrasil), Fenandópolis, Brazil
[b] Oral Oncology Center, São Paulo State University (UNESP), School of Dentistry, Araçatuba, Brazil
[c] School of Dentistry, University Brasil, São Paulo, Brazil
[d] Centro de Inovação, Tecnologia e Educação (CITÉ), Estrada Dr. Altino Bondesan, 500, Distrito de Eugênio de Melo, CEP 12247-016, São José dos Campos, SP, Brazil
[e] Biomedical Engineering Center, Anhembi Morumbi University (UAM), São Paulo, SP, Brazil
[f] Bioengeneering and Biomedical Engineering- Universidade Brasil- ICT Rua Carolina Fonseca 235- 08230-000 Itaquera São Paulo, SP, Brazil

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ABSTRACT

Background: Scientific literature shows the great potential of fluorescence visualization (FV) in the detection of lesions in the skin and mucosa, though its use has been intermitant. Thus, the aim of this study was to compare the detection of oral cancer and oral potentially malignant disorders (OPMD) with and without the use of fluorescence visualization in population screening.

Patients and methods: During a population screening for oral cancer and OPMD, general practice dentists (GPD) performed conventional oral examination (COE) in the first year, and in the second year the FV was inserted in the oral examination. When detecting any suspicious lesion in oral mucosa either by COE or FV, patients were referred for final diagnosis by a specialist in oral medicine. Biopsy was performed in cases of high-risk lesions to confirm the diagnosis, presence of epithelial d (ED), and oral squamous cell carcinoma (OSCC).

Results: During the oral cancer prevention campaign in the first year, benign neoplasms were the oral lesions with higher diagnosis rate (26.2%), followed by non-neoplastic proliferative processes (23.8%) and potentially malignant disorders (21.4%). During the second year, with the implementation of the use of FV, OPMD were the lesions with higher diagnosis rate (37.7%). The sensitivity, specificity and accuracy for the detection of potentially malignant disorders were respectively equal to 94.4%, 96.2% and 96.1%. The detection of lesions with epithelial dysplasia for these amounts were respectively equal to 100%, 92.4% and 92.6%.

Conclusion: FV presented high diagnostic values when used by GPD and improved the detection of OPMD in population screening. FV has potential to be used as an adjunctive method for early diagnosis of oral high-risk lesions.

1. Introduction

With the increasing incidence of oral squamous cell carcinoma (OSCC) and its low rates of cure and poor survival, methods and actions for early diagnosis of this disease are mandatory. OSCC is one of the most common human cancers and delayed diagnosis is closely related to worse prognosis [1,2].

Great efforts have been given from researchers to prevent and to diagnose OSCC earlier [3]. Screening and awareness programs within general populations from several countries in relation to the risk factors for OSCC and the importance of consulting healthcare providers are not effective enough [3]. These programs fail to reach the real population at risk for OSCC, besides the lack of ability and experience of healthcare providers to clinically detect OSCC and oral potentially malignant disorders (OPMD) [4,5].

Since 1924, when Policard [6] began to study the fluorescence applied to oncology, several studies have been performed, leading biomedical engineering to develop new techniques based on fluorescence to detect neoplastic processes. This is possible because biologic tissues reflect fluorescent light when stimulated by incident light in determined wavelength (tissue autofluorescence). Therefore, due to molecular and morphologic changes in neoplastic tissues, the affected tissue undergoes an autofluorescence loss (AFL) [7,8].

Fluorescence visualization (FV) consists on the emission of light in a determined wavelength over a biologic tissue and observation of this tissue's autofluorescence through optical filters which blocks emitted

* Corresponding author at: Oral Oncology Center, UNESP-Univ Estadual Paulista, José Bonifácio St, 1193, Araçatuba, São Paulo, 16015-050, Brazil.
E-mail address: saygotomo@hotmail.com (S. Tomo).

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light and allow the examiner to observe the reflected fluorescence. Thus, in visual examination of oral mucosa autofluorescence, the diseased tissue present as well deliniatated dark area [9,10]. This method demonstrated satisfactory efficacy, easily applicability and low costs [9,10]. Handheld devices which allow the performance of easy and fast oral mucosa examination by FV were designed [11], and are nowadays commercially available.

Although FV demonstrated high diagnostic values, there is a lack of evidence supporting its efficacy in population screening, especially when used by examiners with few experience in oral diagnosis. Therefore, the aim of this study was to evaluate the applicability of FV to detect oral lesions with malignant risk when used by general practice dentists (GPD) during a population screening program for OSCC and OPMD.

2. Materials and methods

2.1. Ethical approval

This study was carried out after approval by the ethics committee for research of the Camilo Castelo Branco University (UNICASTELO) through the protocol no.43602515.5.0000.5494.

2.2. Patients recruitment

This prospective study was carried out in the health care network of the city of Fernandópolis, Brazil, during the Oral Cancer Prevention Campaigns in the years 2014 and 2015. Recruitment of patients was carried out by mass communication (radio, newspaper, television and internet) and by alternative means (folders and banners). In total, 18 primary healthcare centers (PHCC) participated in the study. Patients were neither selected nor excluded based on social habits or medical/dental history.

2.3. Conventional oral examination

Prior to data collection, the attending GPD from each PHCC of Fernandópolis city were calibrated to perform a uniform conventional oral examination (COE) and recognize high-risk alterations of the oral mucosa. Therefore, this examination was systematically performed, observing and palpating all oral structures. Then, the examiners reported the positivity or negativity of suspicious oral lesion on patients' individual records. The COE was performed in all 18 PHCC in 2014 and 2015.

2.4. Oral examination with fluorescence visualization

In the year 2015, four of the 18 PHCC received a FV device. FV examination was performed using the handheld device EVINCE® (MMOptics, São Carlos, SP, Brazil), which emits light in 400 nm wavelength through LEDs system, and allows the observation of tissue autofluorescence through optical filter linked to the device. This examination was performed with room lights turned off. The examiners were equally calibrated for using the device and performed the examination systematically, observing the autofluorescence of all oral structures. When noticing a well demarcated area of AFL (Fig. 1), examiners reported the positivity of lesion on patients' individual records.

2.5. Final diagnosis

Patients who had any oral mucosa lesion, either by COE or by FV, were referred to a specialist in oral diagnosis and oral pathology at a second level healthcare center. This professional conducted the final diagnosis process applicable for each case. Biopsy was performed for high-risk cases (clinical suspicion of OPMD or OSCC, and in lesions detected by FV but not by COE), and the presence of epithelial dysplasia (ED) or malignancy were assessed.

2.6. Data analysis

Through descriptive analysis we performed the collection, organization and description of the data obtained. In this analysis we evaluated the following variables: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for FV and COE to detect OPMD, ED and OSCC, taking as Gold Standard the histopathologic analysis.

3. Results

3.1. Oral lesions diagnosed in the oral cancer prevention campaign in the year 2014

During the oral cancer prevention campaign in 2014, 1003 patients underwent COE in 18 PHCC. Of these, 94 (9.4%) were referred for specialized care due to the presence of oral lesion, but only 54 (5.4%) attended for final diagnosis. Of the 54 patients reassessed, 56 oral alterations were diagnosed, including 13 (23.2%) normality variations, 42 (75.0%) benign lesions and only one (1.8%) malignant lesion (Table 1). One patient presented more than one lesion simultaneously.

Among the 13 normality variations diagnosed, the highest prevalence was five (38.5%) for lingual varicosity, followed by three (23.1%) cases of geographical tongue. Table 2 shows the frequency of the benign lesions diagnosed in this campaign. Of the 42 benign lesions diagnosed, the most frequent were benign mesenchimal neoplasms (26.2%), followed by non-neoplastic proliferative processes (23.8%). The only malignant lesion diagnosed during the oral cancer prevention campaign in the year 2014 was diagnosed as OSCC.

3.2. Oral lesions diagnosed in the oral cancer prevention campaign in the year 2015

During the oral cancer prevention campaign in 2015, 762 patients underwent COE in 18 PHCC. Ninety-six of these (12.6%) were referred for specialized care due to the presence of any alteration in oral mucosa, but only 72 (9.4%) attended for final diagnosis. Of the 72 reassessed patients, 81 oral lesions were diagnosed, including 19 (23.4%) normality variations, 61 (75.3%) benign lesions and only one (1.3%) malignant lesion (Table 1). One patient presented more than one lesion simultaneously.

Among the 19 normality variations diagnosed in the oral cancer prevention campaign in 2015, the highest prevalence was five (26.3%) for geographic tongue, followed by four (21.0%) cases of racial melanin pigmentation. Table 2 shows the frequency of benign lesions diagnosed in this campaign. The most frequent lesions were the OPMLs (37.7%), followed by benign neoplasms (24.6%). The only malignant lesion detected during the oral cancer prevention campaign in the year 2015 was diagnosed as OSCC.

3.3. Comparative analysis between two years of the campaign with and without fluorescence visualization

During the oral cancer prevention campaign in 2014, the patients were examined exclusively by COE in all PHCC. In 2015, 4 PHCC were selected to receive the FV device.

In the 4 PHCC where the FV would be inserted in 2015, during the campaign of 2014, 359 patients were screened. Of these, 36 (10.0%) were referred for specialized care due to the presence of an alteration in oral mucosa (Table 3). In 2015, 283 patients underwent COE followed by FV examination, and 33 (11.7%) were referred for specialized care due to the presence of an oral mucosa alteration detected either by COE or by FV (Table 3).

Of the total of 36 patients reassessed in 2014, 38 oral lesions were

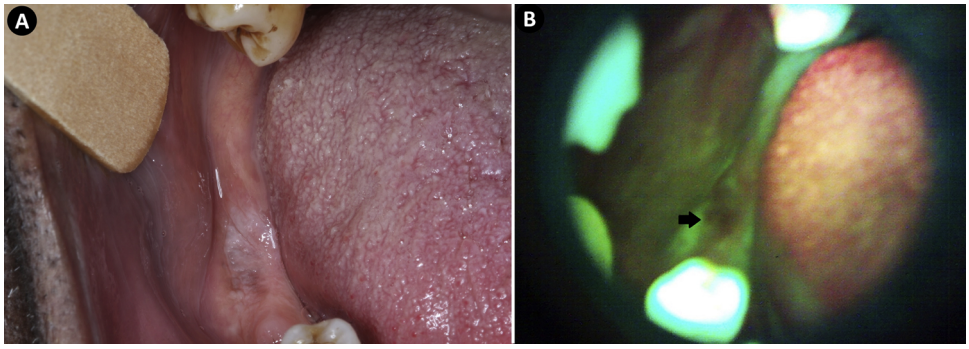

Fig. 1. Oral potentially malignant lesion (oral leukoplakia) under COE (A) and FV (B).

Table 1
Oral alterations diagnosed in the 2014 and 2015 oral cancer prevention campaigns.

Oral mucosa alterations	2014		2015	
	n	%	n	%
Normality variations	13	23.2	19	26.4
Benign lesions	42[a]	75.0	61[a]	84.7
Malignant lesions	1	1.8	1	1.4
Total	**56**	**100**	**81**	**100**

[a] One patient had more than one oral alteration.

Table 2
Frequency of oral benign lesions diagnosed in the 2014 and 2015 oral cancer prevention campaigns.

Benign lesions	2014		2015	
	n	%	n	%
Benign neoplasia	11	26.2	15	24.6
Non-neoplastic proliferative	10	23.8	7	11.5
OPMD	9	21.4	23	37.7
Infectious	7	16.7	9	14.8
Traumatic	3	7.1	3	4.9
Pigmented	2	4.8	4	6.5
Total	**42**	**100**	**61**	**100**

OPMD = Oral potentially malignant disroders.

Table 3
Frequency of patients assessed in population screening and reassessed for final diagnosis during the oral cancer prevention campaigns in the years 2014 and 2015 in the PHCCs with FV.

PHCC	2014				2015			
	Assessed		Reassessed		Assessed		Reassessed	
	n	%	n	%	n	%	n	%
I	95	26.5	8	22.2	104	36.8	7	21.2
II	70	19.4	14	38.9	75	26.5	10	30.3
III	157	43.8	13	36.1	73	25.8	14	42.4
IV	37	10.3	1	2.8	31	10.9	2	6.1
Total	**359**	**100**	**36**	**100**	**283**	**100**	**33**	**100**

PHCC = Primary healthcare center.

diagnosed: eight (21.0%) normality variations and 30 (79.0%) benign lesions (Table 4). No patient was diagnosed with OSCC. Of 33 patients reassessed in 2015, 31 oral lesions were diagnosed: three (9.7%) normality variations, 27 (87.1%) benign lesions and one (3.2%) malignant lesion (Table 4). Two patients did not have any diagnosis and none had concomitant oral lesions.

Table 4 shows the frequency of lesions diagnosed in oral cancer prevention campaigns in the years 2014 and 2015 in the four PHCC with FV device. Benign neoplasia was the most frequent in 2014 (33.3%), whereas in 2015, after the insertion of FV, the most frequent referred lesions were OPMLs (64.3%).

Table 4
Frequency of oral lesions diagnosed in oral cancer prevention campaigns in the years 2014 and 2015 in the PHCC that used FV.

Oral mucosa alterations	2014		2015	
	n	%	n	%
Normality variation	8	21.0	3	9.7
Benign lesions	30[a]	79.0	27	87.1
Malignant lesions	0	0.0	1	3.2
Total	**38**	**100**	**31**	**100**

[a] One patient had more than one oral mucosa alteration.

Of the 28 lesions diagnosed in the oral cancer prevention campaign of 2015, six had ED on histologic analysis, 18 were OPMD (oral leukoplakia, oral erythroplakia, oral lichen planus or actinic cheilitis), and one was a moderately differentiated OSCC (Table 5).

3.4. Diagnostic values for fluorescence visualization and conventional oral examination

The FV demonstrated 94.4% sensitivity and 96.2% specificity to detect OPMD, whereas for the COE, 83.3% sensitivity and 95.1% specificity was observed to detect OPMD (Table 6). FV demonstrated 100% sensitivity and 92.4% specificity to detect lesions with ED, while for COE a sensitivity of 66.7% and a specificity of 91.3% to detect ED was observed (Table 6). For the use of FV, a sensitivity of 100% and a specificity of 90.8% were observed to detect OSCC, whereas for the COE a sensitivity of 100% and a specificity of 90.4% to detect these lesions were observed (Table 6).

Table 5
Frequency of oral lesions diagnosed in oral cancer prevention campaigns in the years 2014 and 2015 in the PHCC with FV in 2015 (excluding normality variations).

Oral mucosa lesions	2014		2015	
	n	%	n	%
OPMD	6	20.0	18	64.3
Benign neoplasia	10	33.3	4	14.3
Infectious	5	16.7	2	7.1
Pigmented	2	6.7	2	7.1
Non-neoplastic proliferative	7	23.3	1	3.6
Malignant	–	–	1	3.6
Total	**30**	**100**	**28**	**100**

PHCC = Primary healthcare centers; FV = Fluorescence visualization; OPMD = Oral potentially malignant disorders.

Table 6
Diagnostic values of FV and COE to detect OPMD, ED and OSCC in population screening (during the oral cancer prevention campaign in 2015, Fernandópolis, Brazil).

Diagnostic values	OPMD		ED		OSCC	
	FV	COE	FV	COE	FV	COE
Sensitivity (%)	94.4	83.3	100	66.7	100	100
Specificity (%)	96.2	95.1	92,4	91.3	90.8	90.4
PPV (%)	63.0	53.6	22,2	14.3	3.7	3.6
NPV (%)	99.6	98.8	100	99.2	100	100
Accuracy (%)	96.1	94.3	92,6	90.8	90.8	90.4

OPMD = Oral potentially malignant disorders; ED = Epithelial dysplasia; OSCC = Oral squamous cell carcinoma; FV = Fluorescence visualization; COE = Conventional oral examination; PPV = Positive predictive value; NPV = Negative predictive value.

4. Discussion

In the present study, we analyze the results of two years of the oral cancer prevention campaign in the city of Fernandópolis, Brazil, in order to verify the impact of the insertion of FV in population screening for OSCC and OPMD. When the FV was inserted an increase in the detection of OPMD was observed. In the 2014 campaign, the benign lesions most frequently detected were benign neoplasms, (26.2%) and non-neoplastic proliferative processes (23.8%), whereas in the year 2015, with the FV, the most frequently benign lesions were OPMD (37.7%).

The benign neoplasms and non-neoplastic proliferative processes represent lesions of unquestionable importance for the dental practice [12]. However, the prevention of OSCC is closely related to the diagnosis and appropriate treatment for patients with OPMD [13,14]. In addition, 762 patients were screened in the 2015 campaign; while in 2014, 1003 patients were screened, although, the prevention goal was more successfully achieved with the use of FV in 2015.

Flaws in the knowledge of GPD to diagnose OSCC and OPMD remain one of the key factors for the delayed diagnosis of OSCC, including GPD in the city of Fernandópolis, Brazil [5]. Not only the number of lesions detected is influenced, but also the final number of patients reached by the program. Such failures can be observed in the present study because a large number of benign neoplasms, non-neoplastic proliferative processes and normality variations were referred to specialized care during the campaign of the year 2014 (Table 2). Although these professionals have undergone pre-training and calibration, the recognition of oral high-risk lesions is not part of their daily practice. Thus, this training may not have a great effect to consolidate the necessary knowledge to recognize oral high-risk lesions, proving to be insufficient.

Several studies evaluated the knowledge and ability of GPD to recognize malignant lesions of the oral mucosa, obtaining variable results [15–17]. Although some studies described the knowledge of these professionals regarding OSCC as satisfactory, all of them verified the necessity of continuous education on this subject, and of methods that facilitate the detection of these lesions in oral examination [18]. Because it is an easily applicable method and the detection of high-risk lesions depend on easy discernment between healthy and diseased tissue, FV has been presented as an effective method to detect oral high-risk lesions [11].

FV have been evaluated in several studies and demonstrated high sensitivity and specificity [9,11,19]. However, the use of this method in population screening has not been widely studied [19]. Therefore, there is a small number of studies that can bring sufficient evidence that support its use in this context [19,20]. Farah et al. [10] did not find high sensitivity, specificity and accuracy (30%, 63% and 55% respectively) to detect ED, concluding that without a well-conducted clinical interpretation, FV was not useful to detect oral ED. In the present study, the insertion of FV in the population screening resulted in values of sensitivity, specificity and accuracy to detect ED (100%, 92.4% and 92.6%, respectively) higher than for COE to detect ED (Table 6).

A bias that is observed in most of studies is that the examiners, both for FV and COE, are specialists in oral medicine/pathology/surgery [19]. Prior to calibrate GPD and insert the FV in population screening we carried out a pilot study to verify if unskilled examiners in oral lesions would experiment improvements in their oral examinations with FV [21]. In this pilot study we observed that the diagnostic values presented by the unskilled examiner to detect both OPMD and ED were increased with the use of FV. Thus, we suggested that the use of the FV by an examiner who is not specialist in oral medicine/pathology/surgery may favor the detection of high-risk lesions in population screening. This hypothesis was confirmed in the present study.

In 2011, Scheer et al. [22] found sensitivity and specificity for FV to detect OPMD (based on the presence of ED) of, respectively, 100% and 80%. In a systematic review, Nagi et al. [23] indicated that the use of FV showed sensitivity values ranging from 22% to 100%, while specificity values varied from 16% to 100%, concluding that more clinical studies should be conducted using different methodologies to define the real efficacy of fluorescence-based oral lesion detection methods. In this study, the sensitivity, specificity and accuracy values for the detection of OPMD in the general population screening were high (94.4%, 96.2% and 96.1%, respectively). Compared to the same values for the COE (sensitivity = 83.3%, specificity = 95.1% and accuracy = 94.3%), the FV was more effective.

In 2012, *Rana* et al. [24] observed sensitivity and specificity of 100% and 74%, respectively, to detect ED by FV, but only patients diagnosed with OPMD were included in the study, not characterizing a population screening. Furthermore, in the same study, oral examination with FV was performed by specialists in oral surgery. The authors suggested that if used by unskilled examiners in oral medicine/pathology/surgery, FV could lead to high false-positive results due to misinterpretation of the test [24]. In addition, Amirchaghmaghi et al. [25] stated that this method could not be used in screenings for dysplastic or malignant lesions in PHCCs, and that, due to the high probability of false-positive results, it may lead to high unnecessary referral rates or unnecessary biopsies. In the present study, as well as in our pilot study [21,26], examiners with few experience in the diagnosis of oral lesions reached high values of sensitivity and specificity to detect ED and OPMD after basic training for the use of FV device.

The sensitivity of FV to detect OSCC was 100% in this population screening. However, the same value was observed for the COE. Specificity and accuracy also did not undergo major changes. OSCC manifests specific and evident clinical features and hardly ever pass unnoticed in COE, although frequently they are misdiagnosed as clinically diagnosed as other diseases (traumatic, autoimmune or infectious) [27].

In recent systematic review Tiwari et al. discussed the bias found within studies evaluating the FV to detect OPML, ED and OSCC. Among those, unclear description of inclusion and exclusion criteria and small sample size were avoided in this study. First because we performed this study in a clinical screening, thus all patients who presented for the screening were included and examined. Furthermore, the lesions diagnosed during the campaign (benign, malignant and with or without ED) were described. Secondly, by performing this study in a well stablished oral cancer screening program, we were able to reach a satisfactory sample size, and 283 patients underwent oral examination with FV.

Considering the limits of this study, the following conclusions can be drawn. FV presented high diagnostic values when used by GPD and improved the detection of OPMD and ED in population screening. This method has potential to be adopted as an auxiliary method to COE in population screening. Nevertheless, future research must be performed evaluating FV along with COE, and not separately. Researchers and clinicians must be aware that the FV does not dispenses the COE and

biopsy as diagnostic gold standards for oral high-risk lesions.

Conflict of interest

The authors declare there are no potential conflict of interest regarding this work.

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