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History and future perspectives for the use of fluorescence visualization to detect oral squamous cell carcinoma and oral potentially malignant disorders

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ABSTRACT

The early diagnosis of oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD) is challenging. The use of fluorescence visualization (FV) has been improved as an auxiliary method to early detect alterations in the oral mucosa suggestive of malignancy or pre-malignancy. However, perhaps due to some misinterpretation regarding the clinical purpose of this method, its applicability may have been underestimated. The purpose of this review is to comment on the challenges within the prevention and early diagnosis of OSCC and OPMDs; to contextualize the use of fluorescence-based methods in the diagnosis of human cancers; and to critically analyze the methods and results of studies that evaluated the FV to detect OSCC and OPMDs, and how this method might be applicable in the clinical practice. The current evidence available in the scientific literature indicates that the FV has the potential to improve the early detection of OSCC and OPMDs. Its use in primary healthcare by general practice dentists, oral hygienists, and oral health therapists is recommended, although more research in the population screening scenario is still required.

1. Introduction

The delayed diagnosis of oral squamous cell carcinoma (OSCC) remains challenging despite the increasing scientific evidence regarding its risk factors, biological behavior in different subgroups, and advances in treatment approaches [1,2]. Huge efforts have been given to increase the rates of early diagnosis of OSCC and, consequently, the chances of longer survival [1,2]. Nevertheless, methods to enhance the early detection of this disease are still required.

The use of fluorescence both in the diagnosis and in the treatment of many types of cancer have been studied. Fluorescence-based methods to detect OSCC were developed with huge enthusiasm and demonstrated important diagnostic values (sensibility, specificity, positive predictive value, negative predictive value, and accuracy). The use of fluorescence to clinically evidence alterations in the oral mucosa may be either by administrating an exogenous fluorophore, as 5-aminolevulinic acid (ALA-5) [3] or by directly observing the tissue autofluorescence (AF), as described in the items 2.4 and 2.5 of this paper. Betz et al. [4] observed that the sensitivity and specificity values for the direct observation of the tissue autofluorescence (fluorescence visualization (FV)) were low compared to the conventional oral examination (COE). Thereafter, many studies were performed to better understand the clinical application of this technique to detect oral lesions. However, perhaps the challenges to perform studies excluding important biases to validate the application of fluorescence-based techniques in the early detection of OSCC led this method to underestimation [5,6].

Many original studies and systematic reviews were performed to validate and discuss the use of the FV to detect oral high-risk lesions. Nevertheless, there is still the need for deep critically discuss the problems behind the need for methods to help clinicians to early detect those lesions and improve the oral cancer prevention work. Moreover, for being a new and unexplored theme, we must put all the available evidence together and discuss the flaws in methodologies aiming to propose insights for future research. Hereby we present a comprehensive review of the use of the fluorescence-guided detection of OSCC, epithelial dysplasia (ED) and oral potentially malignant disorders (OPMD), aiming to clarify the real applicability of this method and to provide future perspective for the implementation of this method in the primary healthcare practice.

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2. Review of literature

For a better understanding of the need for methods to help clinicians and researchers to act within the early diagnosis and prevention of oral cancer, we briefly describe the general aspects of the epidemiology, risk factors and prognosis for OSCC and OPMD, and the challenges to early diagnose these lesions, focusing on population screening programs.

A review of studies that evaluated the FV to detect OPMD, ED and/or OSCC is presented (Table 1). A search in PubMed/MedLine database was performed and studies that evaluated the FV to evidence oral soft tissue malignant lesions or at risk for malignancy were selected and discussed. Forty studies were found in the English literature. A critical analysis of the methodology and results presented by these studies is described in item 2.5 of this paper. From this analysis, we describe the strengths and weaknesses of these studies, and the challenges faced to perform studies evaluating the FV to detect OSCC, ED and/or OPMD. Finally, we provide insights for future research that must fulfill the lacking evidence to clarify the role of the FV to early detect OPMD and OSCC. Studies that aimed to propose algorithms or more specific protocols for the FV-guided detection and/or risk assessment of oral lesions were not included in Table 1, due to high methodological discrepancies.

2.1. Oral cancer and potentially malignant disorders

Oral cancer is a major health problem worldwide. It is one of the most common cancers and one of those with lower survival expectancy [7]. Squamous cell carcinoma (SCC) is the most common type of malignant disease in the oral cavity, representing > 90% of malignancies in this location [7].

Chronic tobacco and/or alcohol consumption are the major risk factors for OSCC occurrence. Although tobacco smoking is the major risk factor for OSCC, the association with alcohol drinking increases the risk of OSCC up to 100-fold [8–10]. Other risk factors have been associated with the occurrence of oral cancer, like the development of SCC in lip vermilion due to chronic and unprotected exposure to solar radiation [11,12]; and human papillomavirus (HPV) infection, which has been associated with the occurrence of OSCC in some groups [13–16]. Since the factors capable of trigger the oral mucosal carcinogenesis are known, we can define groups of people at high-risk for OSCC [17]. Hence, people over 45-years old, smokers and/or chronic alcoholics are considered more likely to develop OSCC [1].

Oral potentially malignant disorders (OPMD), according to the World Health Organization (WHO), are benign lesions that carry a high potential for malignancy when compared to other oral benign lesions. Oral leukoplakia (OL) and oral erythroplakia (OE) represent the most relevant oral lesions at higher risk for malignant transformation. The OL stands out as the most frequent OPMDs and the OE has the highest malignant risk [18]. To predict malignant transformation for OPMDs is challenging and has been an issue for extensive research. Nevertheless, some clinicopathologic variables seem to predict a higher risk for malignancy, among which the presence of any degree of ED is the most important [19].

The rates of OPMDs malignant transformation remain variable, although only a portion of OSCC cases is diagnosed after a pre-existing OPMD [19]. It is possible that the carcinogenesis of the oral mucosa can either manifest clinical signs evident in its early stages of ED or may occur in a silent way. This may impair the early diagnosis, the verification of the risk of malignancy and, consequently, the prevention work [20].

2.2. Delayed diagnosis of oral cancer

The mortality rate of OSCC is high [21]. Despite the ease of the oral examination, most patients are diagnosed with advanced disease, when the treatment is associated with high morbidity, high cost and little success [22]. Hence, the early diagnosis of OSCC and OPMDs is mandatory to improve patients' survival and quality of life [1,18].

One of the major challenges for obtaining the early diagnosis of OSCC and OPMDs is the lack of practice and knowledge of healthcare providers [23]. There is a consensus regarding the need for continuing education programs and awareness among healthcare providers about oral cancer and the development of techniques that facilitate the identification of early neoplastic processes in the oral mucosa [24].

Another problem strongly associated with the delayed diagnosis of OSCC is the lack of awareness within the general population regarding this disease [25], which eventually leads to the resistance of the patients and the dental professionals to perform the biopsy. Therefore, the adequate and well-justified recommendation of the biopsy is essential for the good clinical practice, and for the acceptance of the patient to undergo the procedure.

Thus, the delay in the diagnosis of oral cancer is categorized into 1) patients' delay, which is the time between the patients' perception of the first sign of the disease until the first consultation with the health professional; 2) professionals' delay, which is the time between the first consultation of the patient until the final diagnosis. The overall delay in the diagnosis is the time between the appearance of the first signal and the final diagnosis of the disease [26].

The early diagnosis of oral cancer still represents a great challenge in clinical practice, even for experienced professionals [27].

2.3. Oral cancer prevention and early diagnosis

Faced with the problem of the delayed diagnosis of OSCC, healthcare networks worldwide began to discuss and implement, regionally, programs aimed at improving the index of early diagnosis of OSCC, together with the prevention work within the general population [2,25,26]. These programs are focused on the primary healthcare level, which is the most important for the detection of diseases and referral to specialized care.

Campaigns to early diagnose and prevent OSCC have been implemented more frequently in several parts of the world. Such campaigns can be carried out on specific dates or extend for weeks or months [1,28]. The campaigns are publicized through mass media (radio, television, newspaper) or by alternative means (pamphlets, folder, banner), by which the population is invited to attend the health facilities, where the clinical exams are performed, seeking for the identification of oral mucosa alterations suggestive of malignancy [29,30]. The definitive diagnosis is obtained by biopsy [31]. During the exams, the patients are advised about the risk factors for oral cancer and the signs and symptoms of the disease [25,32].

These programs have the potential to reach a large portion of the general population. However, few cases of OSCC and OPMDs have been diagnosed from them [33]. These campaigns may not be reaching the population at real risk for OSCC, which may be due to the lack of awareness within the population [34]. Hence, it is important to carry out new studies aiming to identify and propose methods for such campaigns to have relevant efficacy.

Studies analyzing the programs for the prevention of oral cancer show variable results, and some were considered effective while others did not reach its objectives [2]. However, no standard of efficacy has been described for such programs. Thus, the results presented as satisfactory may not be reliable, insofar as the verification of results was analyzed through the perspective of each author. It is evident the need to implement new methods to these programs and the evaluation of new technologies that may help in the scanning of the population in the search for early signs of oral cancer.

2.4. Principles of fluorescence in oncology

In 1924, Policard [35] began to study the use of fluorescence spectroscopy to detect neoplastic lesions. For decades it has been used as a promising method in the detection and characterization of

Table 1
Studies that evaluated the FV in the detection of OPMD, ED and/or OSCC (adapted from Tiwari et al. [5]).

Author, year	Examiner(s)	Patients characterization	Sample size	FV device and technique	COE	Sensitivity	Specificity
Onizawa et al., 1996 [57]	Oral surgery specialist	Patients with oral lesions	30	Prototype. Autofluorescence photography	Unclear	88%	94%
Betz et al., 2002 [4]	Otolaryngology specialist	Clinical diagnosis of OSCC or suspicious lesions	214	Modified short xenon lamp for in vivo tissue excitation. Subjective darker shade of green was considered positive for malignancy	Yes	COE: 99.2 FV alone: 87.8 Combined: 100	COE: 42.9 FV alone: 56.4 Combined:51.3
Lane et al., 2006 [41]	Oral medicine specialist	Biopsy confirmed of oral ED or OSCC	50	Cone of blue excitation light emitted from handheld unit prototype AFL positive for abnormality	Yes	FV alone: 98	FV alone: 100
Huff et al., 2008 [77]	General Practice Dentist	Prospective randomized. Patients that showed up for clinical oral examination in general practice clinic.	905	VELscope. Well demarcated AFL area considered positive for suspicious lesions. The incandescent light and direct tissue fluorescence examination together yielded a 1.3% prevalence of mucosal abnormalities, 83% of which were potentially premalignant.	Yes	Not reported	Not reported
Jayaprakash et al., 2009 [51]	Dental Oncology specialist	High-risk patients, with suspicious oral lesions or recently diagnosed untreated OPMD or OSCC	60	Fluorescence imaging and point spectroscopy prototype. FV classified in 3 scores: 1- No AFL; 2- Moderate AFL; 3- Significant AFL	Yes	FV + COE: 100% to pathologic high grade lesions and OSCC. FV + COE: 70% to determine OPMD and OSCC. FV alone: 38% to determine OPMD and OSCC.	Not reported
Moro et al., 2010 [63]	Oral Medicine specialist	Patients with a history of oral cancer, presence of OPMD or suspicious lesion.	32	FV device prototype. LED lamp emitting 450 nm. Non-specified parameter to consider FV examination positive for oral lesion.	Yes	FV alone: 100	FV alone: 93
Mehrota et al., 2010 [58]	Oral Medicine specialist	Patients with clinically innocuous lesions	100	VELscope. AFL considered positive for dysplasia or carcinoma	Yes	FV alone: 50	FV alone: 38.9
Awan et al., 2011 [59]	Oral medicine specialist	Patients with white, red and mixed white/red patches in oral mucosa	126	VELscope. AFL considered positive for lesion	Yes	FV alone: 87.1	FV alone: 21.4
Koch et al., 2011 [72]	Oral medicine specialist	Patients with clinically diagnosed OSCC or suspicious oral lesions	78	VELscope. Characteristics of FV determined from photographs. A low or absent FV signal, as well as red FV signal was considered positive for ED or OSCC.	Yes	COE: 96.6 FV alone: AFL parameter only: 93 Red AF only: 20 All for OSCC	COE: 95.8 F alone: AFL parameter only: 15 Red AF only: 98 All for OSCC
Paderni et al., 2011 [73]	Oral medicine specialist	Patients with clinical suspicion of OPMD or OSCC	175	VELscope. Abnormally dark on fluorescence considered positive for ED or OSCC.	Yes	FV alone: Lesions with ED vs lesions without ED: 65.5 Lesions with mild ED vs lesions without ED: 60 Lesions with moderate/ severe ED vs lesions without ED: 71.4 High risk lesions versus low risk lesions: 75	FV alone: lesions with ED vs lesions without ED: 97.4 Lesions with mild ED vs lesions Without ED: 97.4 Lesions with moderate/ severe ED vs lesions without ED: 97.4 high risk lesions versus low risk lesions: 92.3
Scheer et al., 2011 [74]	Oral and maxillofacial surgery specialist	Patients referred to rule out invasive OSCC	64	VELscope. FV analyzed by photos. AFL considered positive for ED or OSCC	Yes	FV alone: 100	FV alone: 80.8

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Table 1 (*continued*)

Author, year	Examiner(s)	Patients characterization	Sample size	FV device and technique	COE	Sensitivity	Specificity
Sweeny et al., 2011 [60]	Oral medicine specialist	Patients with history of treated head and neck cancer	17	Identafi 3000 ultra. AFL parameters not defined	Yes	WL: 50 FV: 50	WL: 98 FV: 81
Babiuch et al., 2012 [78]	Oral surgery specialist	Patients with history of lip and oral cavity cancer	18	VELscope. AFL considered positive for malignancy	Yes	FV alone: 100	FV alone: 12.5
Farah et al., 2012 [48]	Oral medicine specialist	Patients with an oral mucosal lesion (white, mixed white-red)	118	VELscope. AFL and negative diascopy was considered indicative for dysplasia/ malignancy	Yes	COE: 25 FV alone: 30 Combined: 46	COE: 82 FV alone: 63 Combined: 68
Marzouki et al., 2012 [64]	Head and neck oncology specialist	Patients with high smoking and alcohol history, with suspicious lesion, history of treated oral cancer	33	33 16 additional suspicious lesions were detected with VELscope. Lesion detection enhanced by 31%	Yes	Not reported	Not reported
McNamara et al., 2012 [79]	General practice dentists	Patients presenting for screening in dental clinic	130	VELscope. AFL considered positive for malignancy/ premalignancy Of 42 patients with oral lesion detected by FV, only one had histologic evidence of premalignancy. One patient with oral lesion detected by COE alone had ED.	Yes	Not reported	Not reported
Rana et al., 2010 [52]	Oral surgery specialist	Patients with OPMD randomly allocated into two groups	CO group: N = 166 COE + AF group: N = 123	VELscope. LAF indicated dysplasia/ malignancy. Negative diascopy also considered positive for dysplasia/malignancy	Yes	COE: 17 Combined: 100	COE: 97 Combined:74
Hanken et al., 2013 [53]	Oral medicine specialist	Patients with suspicious OPMD	120	VELscope. AFL considered indicative of underlying dysplasia/malignancy	Yes	COE: 5.9 Combined: 97.9	COE: 33.3 Combined: 41.7
Takahama-Junior et al., 2013 [54]	Oral medicine/ pathology specialist	Patients with confirmed diagnosis of AC and normal volunteers	57 with AC. 45 normal volunteers.	Homemade handheld device. Pale green fluorescence considered normal and well demarcated area of AFL considered ED. FV combined to COE increased the detection rate of ED (40.7%) from COE alone (19.5%)	Yes	COE + FV: 80.7	COE + FV: 78.3
Bhatia et al., 2014 [55]	General practice dentist	Patients presenting to a general dental clinic for general check-up	222	VELscope. AFL or negative diascopy considered positive for dysplasia/SCC. 2 week review protocol used for positive diascopy	Yes	COE alone: 44 FV alone: 64 Combined: 73.9	COE alone: 99 FV alone: 54.3 Combined: 97.9
Laronde et al., 2014 [50]	General practice dentists	Patients presenting for dental care	2.404	VELscope. AFL considered positive for oral lesion. Lesions assessed initially as IR and HR had a 2.7-fold increased risk of FVL persisting to the reassessment appointment versus the LR lesions.	Yes	Not reported	Not reported
Petruzzi et al., 2014 [65]	Oral medicine specialist	Patients with oral lesions suspicious for malignancy and who had a history of oral lesions or were at high risk for an oral lesion	56	VELscope. AFL was considered positive for ED or OSCC	Yes	FV alone: Detection of dysplasia + malignancy: 70 Detection of moderate/severe OED/ SCC (mild dysplasia considered negative): 76.47	FV alone: Detection of dysplasia + malignancy: 57.69 Detection of moderate/severe OED/ SCC (mild dysplasia considered negative): 51.28

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Table 1 (*continued*)

Author, year	Examiner(s)	Patients characterization	Sample size	FV device and technique	COE	Sensitivity	Specificity
Awan et al., 2015 [75]	Oral medicine specialist	Consecutive sample of patients with white, red and mixed white and red patches	116	VELscope. AFL indicates ED	Yes	FV alone: 84.1	FV alone: 15.3
Ayoub et al., 2015 [66]	Dental hygienist	Patients who presented for routine oral examination and were addicted to either cigarettes or a dual addiction (cigarettes plus hookah)	30	VELscope. AFL considered positive for oral high-risk lesion. No lesions were detected neither by COE nor FV	Yes	Not reported	Not reported
Sawan and Mashalah, 2015 [61]	Specialized center	No inclusion or exclusion criteria described	71	VELscope. Positive measures not defined.	Unclear	AF alone: 100	AF alone: 74.14
Lalla et al., 2015 [67]	General practice dentist	Patients presenting for general dental check	161	Identafi. LAF & partial blanching positive for dysplasia or malignancy	Yes	COE = 30.1% WL = 42.6% Violet light = 55.9%	COE = 75% WL = 84.5% Violet = 77.9%
Lalla et al., 2016 [68]	Oral medicine specialist	Patients presenting with white, red, mixed red-white lesions	233	Identafi. LAF & partial blanching positive for dysplasia or malignancy *Identafi's WL was equivalent to WL used with use of overhead LED & magnification	Yes	Not reported	Not reported
Ohnishi et al., 2016 [80]	Unclear	Patients with biopsy confirmed primary cancer of the oral region	20	VELscope. Reduction of normal pale green fluorescence considered positive for OSCC	Yes	FV alone: 91	FV alone: 100
Scheer et al., 2016 [69]	Oral surgery specialist	Post-treatment OSCC patients with undiagnosed mucosal lesions	41	VELscope. Fluorescence characteristics based on photographs. AFL indicates dysplasia or carcinoma	Yes	FV alone: 33.3	FV alone: 88.6
Burian et al., 2016 [81]	Unclear	Retrospective analysis of intraoral photographs of patients with OSCC	90	VELscope. AFL in photographs considered positive for OSCC. FV was positive in 85.6% of OSCC cases	Yes	Not reported	Not reported
Ganga et al., 2016 [70]	Oral pathology specialized center	Patients referred with undiagnosed oral lesion	200	VELscope. AFL considered positive for malignant or dysplastic change.	Yes	FV alone: 76	FV alone: 66.29
Simonato et al., 2017 [49]	Dental student followed by oral medicine specialist	Screening clinic	15	Evince. AFL considered positive for ED, OSCC or OPMD	Yes	Unskilled in detection of OED: COE: 50 FV alone: 100 Skilled clinician in detection of OED COE: 100 FV alone: 100	Unskilled in detection OED: COE: 46.15 FV alone: 46.15 Skilled clinician in detection of OED: COE: 38 FV alone: 46
Yamamoto et al., 2017 [71]	Oral medicine specialized center	Patients with clinical suspicion of oral leukoplakia or SCC of the tongue	62	VELscope. Black area of AFL was defined as lesion area for ED.	Yes	FV alone: 85.9	FV alone: 26.7%
			54		Yes		

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Table 1 (*continued*)

Author, year	Examiner(s)	Patients characterization	Sample size	FV device and technique	COE	Sensitivity	Specificity
Amirchaghmaghi et al., 2018 [56]	Oral medicine specialist	Patients presenting with soft tissue lesions needing incisional or excisional biopsies		VELscope. Regions with AFL or that seen as red/ orange were considered suspicious		Dysplastic lesions only: COE: 75 FV alone: 83 Combined: 100 Dysplasia + OSCC: COE: 81 FV alone: 90 Combined: 100 Oral Mucosal Lesions: COE: 86 FV alone: 90 Combined: 100	Dysplastic lesions only: COE: 71 FV alone: 12 Combined: 11 Dysplasia + OSCC: COE: 67 FV alone: 12 Combined: 6 Oral Mucosal Lesions: COE: 85 FV alone: 15 Combined: 12
Canjau et al., 2018 [82]	Oral surgery specialist	No inclusion or exclusion criteria described	18	VELscope. AFL considered positive for malignancy	Yes	FV alone: 94.44	FV alone: 100
Chiang et al., 2018 [62]	Oral surgery specialist	Patients with mucosal disorders and history of alcohol, tobacco and betel quid	126	Autofluorescence digital photography. Unclear parameters	Yes	FV alone: 88.89	FV alone: 43.86
Simonato et al., 2019 [76]	General practice dentists	Population screening program	283	EVINCE® AFL considered positive for OSCC, ED or OPMD	Yes	ED: FV alone: 100% COE alone: 66.7% OSCC: FV alone: 100% COE alone: 100% OPMD: FV alone: 94.4% COE alone: 83.3%	ED: FV alone: 92.4% COE alone: 91.3% OSCC: FV alone: 90.8% COE alone: 90.4% OPMD: FV alone: 96.2% COE alone: 95.1%
Morikawa et al., 2019 [83]	Specialized center in oral and maxillofacial surgery	Patients referred for final diagnosis and treatment of oral lesions	201	ORALOOK® AFL considered positive for oral lesion Subjective and objective analysis of images were performed	Unclear	Subjective analysis of FV alone for OSCC and ED: 83.3% Objective analysis of FV alone for OSCC and ED: 47.7% for luminance value, 94.7% for luminance ratio, and 100% or coefficient variation	Subjective analysis of FV alone for OSCC and ED: 75.5% Objective analysis of FV alone for OSCC and ED: 72.4% for luminance value, 79.6% for luminance ratio, and 68% for coefficient variation
Farah et al., 2019 [84]	General practice dentists and oral health therapists	Population screening program	360	VELscope AFL considered positive for OPMD. Lesion size increased and border distinctness and visibility improved with FV.	Yes	Not reported	Not reported

OSCC = oral squamous cell carcinoma; COE = conventional oral examination; FV = fluorescence visualization; ED = epithelial dysplasia; OPMD; oral potentially malignant disorders; AFL = autofluorescence loss; AF = autofluorescence; AC = actinic cheilitis; IR = intermediate risk; HR = high risk; LR = low risk; WL = white light.

neoplastic processes [36].

The method consists of the emission of light at a specific wavelength over biological tissues, aiming to identify changes in the morphology by determining the fluorescence emission spectra when excited by light. The molecules present in the lighted tissues, which react when stimulated by fluorescence emitting light at a higher wavelength (lower energy), are called endogenous fluorophores [37,38]. In other cases, exogenous fluorophores or specific endogenous fluorophores recruiting agents may be applied to the tissue [37,38]. The staining of tumor cells with ALA-5 and subsequent observation under fluorescence was initially investigated to detect oral cancer, but due to more costs and complex administration, its application in the population screening scenario is not viable [3].

Due to the presence of endogenous fluorophores, the healthy tissues are autofluorescent [22]. This autofluorescence (AF) can be detected by fluorescence spectroscopy, which consists of light irradiation over the tissue, capture of the emitted autofluorescence and transfer of that spectrum to computers. With the use of specific software, the collected spectra will be analyzed, with the presentation of data regarding the quantification of the fluorophores present in the tissue [4].

Another option to analyze the tissue AF is the fluorescence visualization (FV), which consists of the visual observation of the stimulated tissue in real-time or by images [39,40]. The use of optical filters is mandatory to prevent the visualization of the excitation light, allowing the observation of the tissue AF only [40,41].

Nowadays, many applications for the optic fluorescence imaging and direct visualization has been described not only to evidence oral soft tissue lesions but also teeth structural alterations [42]. Moreover, the medical applications of this technology include the detection of skin and genital lesions and the determination of surgical margins for tumor and necrotic tissue resections [43–47].

2.5. Fluorescence visualization to detect OSCC and OPMD

Devices were developed for the FV of the oral mucosa in the clinical practice [40,41]. The detection of OSCC and OPMDs can be done through this method due to biochemical changes in the epithelial cells, the presence of inflammatory infiltrate and the angiogenesis that occurs since the early stages of neoplastic processes [48,49]. An optimal excitation violet light at 400 nm by a light-emitting diodes (LEDs) system was validated to stimulate the oral mucosa, which, through optical filters, can be observed with an "apple-green" glow in physiologic condition [40,41]. The altered tissue will be observed as a well-demarcated dark area due to the loss of tissue autofluorescence [40,41]. For the record, the use of dental light curing units (LCUs) as an alternative to FV devices is not reported in the literature. However, due to variability in the delivered light wavelength by LCUs and light guides in beam profiles measuring 6–8 mm to focus on a single tooth, these devices are not expected to replace the FV devices with the same effectiveness.

In 2004, Svistun et al. [40] presented the prototype of an FV mechanism, which consisted of LEDs stimulating biological tissue. The AF emitted by the tissue stimulated by the LEDs was observed through an optical filter, which enabled not only the visualization but also the recording of images by cameras.

Based on this mechanism, Lane et al. [41] presented an experimental compact and easy to handle FV hand-held device. In this study, 44 patients with OSCC were examined and the authors found 98% sensitivity and 100% specificity values to detect these lesions. However, the efficacy of the device in the screening of a population in the search for early signs of cancerization was not evaluated.

Laronde et al. [50] published the results of a study conducted in an 11-months population screening with the aid of an FV device in which 2.404 patients were examined. The inclusion of the FV in the intraoral examination significantly improved the detection of lesions in the oral mucosa.

The FV proved to be an effective auxiliary method for the detection of early OSCC and OPMDs by presenting high specificity and sensitivity [5]. The sensitivity of the FV to detect either OPMDs, ED or OSCC ranges from 30% to 100%, while the specificity ranges from 12.5% to 100% (Table 1). Nevertheless, most studies fail to evaluate the association of the FV to the COE. Only 8 of 40 studies present the sensitivity values for the association of the FV with the COE to detect OPMDs, ED and/or OSCC [4,48,51–56], and 7 studies present the specificity value to the same purpose [4,48,52–56]. The sensitivity of the FV + COE to detect OPMDs, ED and/or OSCC ranges from 46% to 100%, but in 7 of these 8 studies the sensitivity values observed were > 70% (Table 1). The specificity of the FV + COE to detect OPMDs, ED and/or OSCC ranges from 41.7% to 97.9% (Table 1). For both measures, the lowest values found when associating the FV with the COE are higher than the lowest values found for the FV alone. Although this is a critical observation, we can call attention to the use of the FV as an auxiliary method in the oral examination, which does not dispense the COE and/or the biopsy for the final diagnosis. Furthermore, future research must exclude this bias and present clear results for both the FV alone and the FV + COE in the detection of OPMDs, ED and/or OSCC.

Despite the variable results, the sensitivity and specificity of the FV to detect OPMDs, ED and/or OSCC are, in general, high. However, to compare the results among studies is not possible due to methodological heterogeneities. Many studies fail to describe in detail their inclusion and exclusion criteria [50,57–62], letting unclear what lesions the FV was used to detect. Moreover, some studies focus the analysis at one specific group of lesions [4,41,48,51,55,56,63–71], while others describe the results found for OPMDs, ED and OSCC separately [49,52,53,72–76], and others present a grouped analysis of these lesions [54,77–83]. The clear description of the inclusion and exclusion criteria and the specific analysis for each group of lesions are biases that must be considered in further studies.

Of the 40 studies found in the English literature, in only 9 the examiner was represented by a general practice dentist (GPD), dental student (DS), dental hygienist (DH) or oral health therapist (OHT) [49,50,55,66,67,76,77,79,84]. Although the high diagnostic values found for the FV in most studies (Table 1), the oral examination performed by specialists in oral medicine, pathology and/or surgery might influence the results. When it comes to the prevention and early diagnosis of oral high-risk lesions, the primary healthcare level should receive more attention. Thus, there is a need to better understand the value of the FV to detect oral high-risk lesions when used by GPDs, DSs, DHs, and OHTs. Only one study compared both the FV and the COE when used by examiners that were unskilled and expert in oral diagnosis [49] and observed that the use of the FV enhanced the capacity of a DS to detect OPMDs and oral lesions more prone to be dysplastic. However, although this study was performed in the population screening scenario, it is a pilot study with a small sample [49], and thus these results must be confirmed in a broader sample.

Nine studies evaluated the FV to detect OPMDs, ED and/or OSCC in the population screening scenario [49,50,55,66,67,76,77,79,84]. The development of the FV technique required studies to validate the technique including patients with known oral lesions. Nevertheless, while the results of most of these studies demonstrate high diagnostic values for the FV to detect OPMDs, ED and/or OSCC in selected samples, the value of this technique in population screenings remains unknown. The need to perform more studies using the FV in population screenings is crucial to identify the biases that should be considered for research and for clinical application.

We observe that besides the amount of methodologic biases, we must be careful with the misinterpretation of results and the drawing of emphatic discussions and conclusions that cannot be supported by the methods used in the studies. Perhaps the concept that the FV was developed to be an auxiliary method in the early detection of oral mucosa suspicious alterations is not well established. This misunderstanding of the objective of the FV led to the interpretation that this method could

not be used in primary healthcare due to the high risk of false-positive results which would lead to the referral of benign lesions to specialized care and the performance of unnecessary biopsies [6,56]. We have recently published the results of a population screening in which the insertion of the FV improved the referral of OPMDs to specialized care for final diagnosis and decreased the referral of benign lesions [76]. This suggests that the use of FV in the primary healthcare level may help to avoid the referral of false-positive results [76]. However, the use of FV in the primary healthcare level by unskilled professionals in oral medicine/pathology/surgery is poorly explored [5,6,49].

Recently, Simonato et al. [76] and Farah et al. [84] presented results from the insertion of the FV in clinical population screenings for the detection of oral lesions. In both studies, an oral examination either by FV or COE was performed by GPDs or OHTs, who were not specialists or experienced in oral medicine, oral surgery or oral pathology. Moreover, both studies had access to large samples and reassessment by specialists for the final diagnosis of the lesions detected. Simonato [76] et al. observed that the insertion of the FV in the population screening improved the detection of OPMDs. Farah et al. [84] observed that the FV associated with the COE within a trial program to detect oral lesions was highly useful. Although the risk of false-positive results, both studies recommend the FV in the population screening as an auxiliary method to early detect OPMDs [76,84]. Future research should follow and improve the methodologies proposed by both studies [76,84].

3. Conclusion

The current evidence available in the scientific literature suggests that the FV has the potential to improve the early detection of OSCC and OPMDs. The use of the FV for this purpose in primary healthcare by GPDs, OHs, and OHTs is recommended. The underestimation of the FV to detect oral high-risk lesions is probably due to the misinterpretation of this method as a diagnostic method and not as an auxiliary method to clinically evidence lesions that may undergo unnoticed on the COE.

Future research in the population screening scenario is required and should consider the following: 1) GPDs, OHs, or OHTs should be taken as primary examiners; 2) Patients with previously diagnosed oral lesions should be excluded, or used as positive controls when applicable; 3) The COE must be performed and the diagnostic values must be presented for the FV and the COE alone and together; 4) A specialized care service (oral medicine, oral pathology and/or oral surgery) must be included at a secondary level to obtain the final diagnosis of the lesions detected; 5) Larger samples must be reached to characterize populational screenings. Besides, the methodologies and discussions must consider and describe the healthcare network in which the study was performed, due to the high variability of the healthcare systems between countries.

Declaration of Competing Interest

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

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