Clinical Oral Investigations
https://doi.org/10.1007/s00784-020-03746-y

ORIGINAL ARTICLE

Diagnostic accuracy of clinical visualization and light-based tests in precancerous and cancerous lesions of the oral cavity and oropharynx: a systematic review and meta-analysis

María Rosa Buenahora[1] · Alberto Peraza-L[2] · David Díaz-Báez[3] · Jairo Bustillo[4] · Iván Santacruz[4] · Tamy Goretty Trujillo[3,5] · Gloria Inés Lafaurie[3] · Leandro Chambrone[3,6,7]

Received: 6 August 2020 / Accepted: 15 December 2020

Abstract

Objective Evaluate and compare the performance of autofluorescence, chemiluminescence, and clinical visual examination in the detection of oral potentially malignant disorders (OPMD), oral cancer (OC), and oropharyngeal cancer (OPC).

Materials and methods A systematic review with meta-analysis based on diagnostic test studies. A literature search was carried out in the MEDLINE and EMBASE databases through August 30, 2020. For this review, the quality assessment tool of diagnostic precision studies (QUADAS-2) was used. Hierarchical regression models were used to estimate pooled diagnostic precision values in a random effects model.

Results A total of 40 studies were identified for this review according to each test evaluated: 5.562 samples for autofluorescence, 1.353 samples for chemiluminescence, and 1.892 samples for clinical examination. The summary measures sensitivity and specificity of the clinical examination were 63% and 78%, respectively, AUC = 0.78 95% CI (0.74–0.81). In the autofluorescence test, these were 86% and 72%, respectively, AUC = 0.86 95% CI (0.83–0.89); and the chemiluminescent test were 67% and 48%, respectively, AUC = 0.59 95% CI (0.54–0.63)

Conclusions Autofluorescence devices displayed superior accuracy levels in the identification of premalignant lesions and early neoplastic changes compared to clinical examination and chemiluminescent test. Overall, biopsy remains the gold standard for the definitive diagnosis of OPMD, OC, and OPC.

Clinical Relevance Light-based clinical methods such as autofluorescence and chemiluminescence techniques have been used in clinical diagnosis for the differentiation of OPMD and malignant and benign lesions; although detailed visual examination appears to be effective in identifying, previous systematic reviews have not evaluated a relevant number of studies and they did not evaluate the accuracy of the clinical examination.

✉ Leandro Chambrone
leandro_chambrone@hotmail.com

María Rosa Buenahora
buenahoramaria@unbosque.edu.co

Alberto Peraza-L
aperaza@unbosque.edu.co

David Díaz-Báez
dadiazb@unbosque.edu.co

Jairo Bustillo
bustillojairo@unbosque.edu.co

Iván Santacruz
isantacruz@unbosque.edu.co

Tamy Goretty Trujillo
tgtrujilloe@gmail.com

Gloria Inés Lafaurie
institutouibo@gmail.com

[1] Unit of Oral Epidemiology Investigation-UNIECLO, School of Dentistry, Universidad El Bosque, Bogotá, Colombia

[2] School of Dentistry, Universidad El Bosque, Bogotá, Colombia

[3] Unit of Basic Oral Investigation-UIBO, School of Dentistry, Universidad El Bosque, Av. Carrera 9 No. 131 A – 02, Bogotá, Colombia

[4] Oral Pathology Department, School of Dentistry, Universidad El Bosque, Bogotá, Colombia

[5] Basque Foundation for Health Innovation and Research, BIOEF, Barakaldo, Basque Country, Spain

[6] Graduate Dentistry Program, Ibirapuera University, São Paulo, Brazil

[7] Evidence-Based Hub, Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz—Cooperativa de Ensino Superior, Caparica, Almada, Portugal

Published online: 03 January 2021

Keywords Mouth neoplasms · Sensitivity and specificity · Predictive value of tests · Diagnostic test

Introduction

Oral (OC) and oropharyngeal cancer (OPC) are pathologies of public health relevance, estimated as the sixth most common malignancies worldwide with a 5-year mortality rate of approximately 50% and 35%, respectively [1], reaching almost 700,000 cases worldwide annually [1, 2]. Tobacco, alcohol, and the persistence of human papillomavirus (HPV) infection are important risk factors for the development of OC and OPC [2, 3], as well for oral potentially malignant disorders (OPMD) [4]. OPMD have an approximate malignancy rate of 1.36% per year, and they play a preponderant role for clinical follow-up effects and prevention of cancer evolution [5–7].

It may be difficult for general dentists to detect OC and OPC in advanced stages because of limitations in their training to recognize signs and symptoms of oral pathologies [8]; however, it is their responsibility to carry out a comprehensive clinical examination, since this is the most important factor in recognizing any alterations in the oral cavity [8, 9] but only 44% of the general dentists who identify an oral lesion, consider referring the patient to a specialist [9].

Definitive diagnosis of OC and OPC is established by histological study, considering biopsies are the most reliable tests. However, it is an invasive technique and not all professionals justify their use in situations of early detection for preventive purposes of anomalies in the oral cavity [8]. Likewise, dentists are often unaware of the procedures used in this technique for the early diagnosis of oral cancer and only between 15% and 21% of general dentists have used a biopsy as a diagnostic aid to a clinical condition [10].

A biopsy is performed when, on a routine clinical examination, the dentist has the possibility of clinically identifying a benign lesion and differentiating it from ones that are potentially malignant or malignant, and the success of the definitive diagnosis lies in how quickly the biopsy is performed, or how quickly a patient with a malignant or suspected malignancy is referred, a decision that is directly related to the prognosis [8, 11]. Other clinical methods and light-based clinical tests that support diagnosis have been proposed such as autofluorescence and chemiluminescence, which facilitate the detection of suspicious lesions at risk of malignancy, which could promote their management in a timely manner [10]. Biological tissues can absorb and re-emit specific light wavelengths, detectable through spectrophotometric devices. Autofluorescence is a simple management technique that requires some training and consists of using a monochromatic light source as a complement to the visual examination [12, 13]. Chemiluminescence detects metabolic and structural changes in the mucosa tissues due to the different properties of absorption and reflectance, but it needs a dark environment, and pre-rinse with acetic acid that could increase salivary flow thus interfering with the surface reflectance of the mucosa [14, 15].

The understanding and knowledge of different operational characteristics of diagnostic tests (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)) for the detection of OPMD are fundamental and could help the healthcare professional to make better decisions [16]. A guide for evaluating the diagnostic accuracy of meta-analysis was published which includes the statistical methods for diagnostic test required to establish accuracy, correlation between the sensitivity and the specificity of a study with a summary receiver operating characteristic curve (SROC curve) [17, 18]. This guide delimits the threshold used to define positive versus negative test results, which may vary across individual primary studies and the use of sophisticated statistical methods/models, such as a bivariate model or a hierarchical mode [17, 18]. Although there is available literature and published systematic reviews with meta-analyses on diagnostic test methods for detection of OPMD, OC, and OPC; until today, no study has provided a deep quantitative analysis and those that exist did not use the analysis based on predictive values through an adjusted prevalence that allows comparison for clinical use [19–21]. Additionally, since the last complete revision of the Cochrane group by Marcey et al, in 2015 [22], there has been an increase in publications evaluating the operative characteristics of light-based tests and, in this review, the precision of the clinical examination was not analyzed. Therefore, the objective of this systematic review and meta-analysis is to compare the operational characteristics of autofluorescence and chemiluminescence with clinical visual examination to establish which of the evaluated diagnostic light tests used in the examination of OPMD, OC, and OPC have a better performance than visual examination.

Materials and methods

The protocol of this review was registered in the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (registration number CRD42018083673)

Types of Studies

Cross-sectional studies evaluating diagnostic test accuracy.

Types of participants

Studies were considered eligible for inclusion if they included the following: (a) adult patients (aged 18 years or over) with presumptive diagnosis of OPMD, OC, and OPC and (b)

comparisons between diagnostic tests: visual inspection or light-based test (autofluorescence or chemifluorescence) with biopsy of the lesions.

Main outcome(s)

Sensitivity (the proportion of true positives), specificity (the probability of correctly determining the absence of a condition), summary receiver operating characteristic (SROC) curve, PPV, and NPV.

Secondary outcome(s)

OPMD, OC, and OPC prevalence and diagnostic odds ratio (DOR).

Studied selection

In this review, the articles that met the following criteria were included: human studies, English language, studies of diagnostics test that compared one or more techniques for precancerous or cancerous lesions, without time restriction, as well as studying the accuracy characteristics. Searches were made on MEDLINE and EMBASE databases up to and including August 30, 2020. Detailed search strategies were developed for each database based on the following MeSH terms, keywords, and free terms (Supplemental Table S1).

Data extraction (selection and coding)

Two independent reviewers selected the titles, abstracts, and full texts of the articles (AP and JB) for the PUBMED search, and two independent reviewers selected the EMBASE search (MB and IS). Disagreements between the reviewers were resolved by discussion. When an agreement could not be reached, a third reviewer (DD) was consulted. When important data was missing for the review, attempts were made to contact the authors to resolve the ambiguity of the results. The following data was extracted and recorded in duplicate: publication status, year of publication, trial location, study design, characteristics of the participants, outcome measures, methodological quality of the studies, and conclusions.

The quantitative data obtained from each study was used to create a database that recorded information on sensitivity, specificity, accuracy, PPV, and NPV. Additionally, the values of true positive (VP), false positive (FP), true negative (VN), and false negative (FN) were extracted from each study.

In cases where they were not reported, an estimate was done using the following calculations: VP = Sensitivity x prevalence; FN = Prevalence - VP; VN = Specificity x (Total n - prevalence); FP = (Total n - prevalence) - VN.

Assessment of validity and data extraction

The methodological quality of all included studies was assessed by means of an instrument for the evaluation of the quality of diagnostic precision studies (QUADAS-2). The studies have been rated as high, unclear, or low according to the following qualification domains: (1) patient selection, (2) diagnostic test used, (3) baseline test, and (4) flow and times. Each domain was evaluated in terms of its risk of bias and applicability [23].

Data synthesis

The data was grouped into evidence tables and a descriptive summary of the results was created. The analyses were performed using three software packages: (a) R V 3.6.1 madauni function (R Development Core Team); (b) Stata v.12.0 (Stata Corp, College Station, TX); and (c) and RevMan software (Review Manager, version 5.3; Nordic Cochrane Center, Copenhagen, Denmark).

Since the estimation of sensitivity and specificity showed a significant correlation, a diagnostic meta-analysis was conducted, applying an approach bivariate model for studies with autofluorescence, chemiluminescence test and clinical examination which relates the precision through hierarchical methods [18], and logarithmic-type transformation in both sensitivity and specificity.

Model gave information on the SROC-curve (summary ROC). The SROC univariate approach relates to the cut-off point where sensitivity and specificity are inversely related to the precision of the test using linear regression, which is possible with the transformation of the rate of true positives and the rate of false positives. The bivariate approach, in addition to providing information on the SROC curve, which is a measure of diagnostic precision, preserves the ability to detect patients with sensitivity and identify healthy patients with the measure of specificity.

The bivariate approach was implemented to analyze the autofluorescence, chemiluminescence, and clinical evaluation tests after verification of the assumption of normal bivariate distribution between sensitivity and specificity logit based on the goodness of chi-square adjustment of Mahalanobis distances, spike plot graph and Dispersion diagrams for checking outliers using typified random effects forecasts. The summaries of the sensitivity and specificity estimates were evaluated with a 95% CI.

To facilitate comparison, all predictive values of the included articles were standardized to a total prevalence of 46% using the following formulas: Adj.PPV=Sensitivity*Prev /Sensitivity*Prev. + (1 – Specificity) *(1-Prev.) y Adj.NPV = Specificity *(1 –Prev.) /Specificity *(1- Prev.) + (1 –Sensitivity) *Prev [16, 17].

To understand the synthesis of the results of the two approaches used, it was necessary to estimate the diagnostic odds ratio (DOR) and area under the ROC curve (AUC). It is a statistical index of diagnostic accuracy and shows how often a positive result occurs in patients with the condition of interest, compared to patients without the disease. It is useful to denote the degree of intensity between the result of a test and the disease, the index is not influenced by the prevalence and is estimated as the ratio between the odds of being sick if the test is positive and the odds of not being sick if it is negative. DOR values can range from zero to infinity (the higher the DOR, the better the test result will be). If DOR = 1, that means the test is not discriminating, it is useless. If DOR ≥ 1, the test is more likely to be positive in affected patients than in healthy patients.

Results

Search results and excluded trials

Five hundred sixty-one studies potentially relevant to this review were found. Four hundred and ninety-two were excluded after cheking the title or abstract (Fig. 1). A total of 69 full-text articles obtained with the search strategy were assessed. Of these, 29 were later excluded for different reasons (for not complying with the proposed inclusion criteria and/or due to their methodological design) (Supplemental Table S2); ultimately, a total of 40 studies [6, 24–62] were included (Fig. 1). A total of 5562 samples for autofluorescence, 1353 samples for chemiluminescence, and 1892 samples for clinical examination were evaluated in this systematic review.

Characterization of the techniques used in the different groups of tests evaluated

Twenty-five studies performed the evaluation of autofluorescence techniques [6, 26, 28–31, 33, 36–38, 41, 44–47, 49, 51–59]. Thirteen studies evaluated VELscope™ [6, 30, 31, 36, 41, 46, 49, 51, 53, 56–59]. Three studies evaluated autofluorescence without mentioning the punctual method [28, 29, 37]; one study evaluated the diffuse reflectance spectrum [34] and another study evaluated EVINCE® [59]. Other studies assessed other light-based methods such as autofluorescence intensity [30], GOCCLES lenses [28], Amber Green Light [37], imaging autofluorescence (LIFE) [53], LED IMF blue and LED IMF Green [37], Protoporphyrin IX [53], Violet light [27], White light [48], and A Microlux study [45]. Fifteen studies evaluated chemiluminescence using the ViziLite technique [6, 24, 27, 32–35, 39, 40, 42, 43, 49, 50, 54, 60–62] (Table 1).

Differences in the types of oral lesions evaluated

Fourteen articles evaluated pre-malignant and malignant lesions [6, 30, 31, 34, 38, 39, 43, 45, 47–49, 51, 55, 61]; two articles evaluated benign and malignant lesions [33, 35]. One article evaluated benign, premalignant, and malignant lesions [25]. One study evaluated benign lesions and dysplasia [34]; eight articles evaluated only dysplasia [27, 31, 40, 43, 44, 56, 59, 62]; however, one of these articles performed the analysis evaluating dysplasia as positive or negative [44]. One article made the comparison between dysplasia and malignancy and at the same time normal mucosa vs benign lesions [34]. Four articles evaluated dysplasia and malignancy [24, 41, 51, 58]. Six articles evaluated only malignant lesions [24, 29, 39, 47, 58, 59]. One study evaluated leukoplakia and lichen planus specifically [26]. Ten articles evaluated only premalignant lesions [30, 32, 36, 37, 48, 56–60], two articles evaluated the tests for premalignant lesions and dysplasia [31, 49]; one article specifically evaluated squamous cell carcinoma [26].

Quality methodology of the included studies

In general, most studies had low applicability concerns; and less than 25% of the studies evaluated had any probability of risk of bias. The main risk of bias found was related to the evaluation times between tests, selection of patients and samples; as well as the blind comparison between tests (including the comparison with the reference standard).

Of the 40 studies included in this SR, five were rated as high risk [28, 33, 35, 36, 48] and eleven as unclear regarding patient selection and sample [6, 27, 31, 32, 34, 37, 38, 43, 47, 59, 60]; five studies were assessed as unclear in relation to the index test [35, 38, 42, 52, 56] and one as high risk [59]; five were classified as high risk with respect to the reference standard domain [28, 31, 37, 38, 58] and six as unclear [27, 35, 48, 56, 59, 60]. Seven studies were assessed as high risk for flow and time [27, 39, 41, 47, 48, 50, 59] and 3 as unclear [31, 45, 50] (Fig. 2).

Analysis by general estimation of sensitivity and specificity

it was observed that the most sensitive estimate was for autofluorescence with sensitivity (Se) = 0.86 95% CI (0.77–0.91), while clinical examination had the lowest grouped Se = 0.63 95% CI (0.45–0.78), although it showed the highest specificity (Ep) = 0.78 95% CI (0.65–0.87), compared to the autofluorescence test Ep = 0.72 95% CI (0.61–0.81) and chemiluminescent test Ep = 0.48 95% CI (0.28 - 0.69) (Figs. 3, 4 and 5).

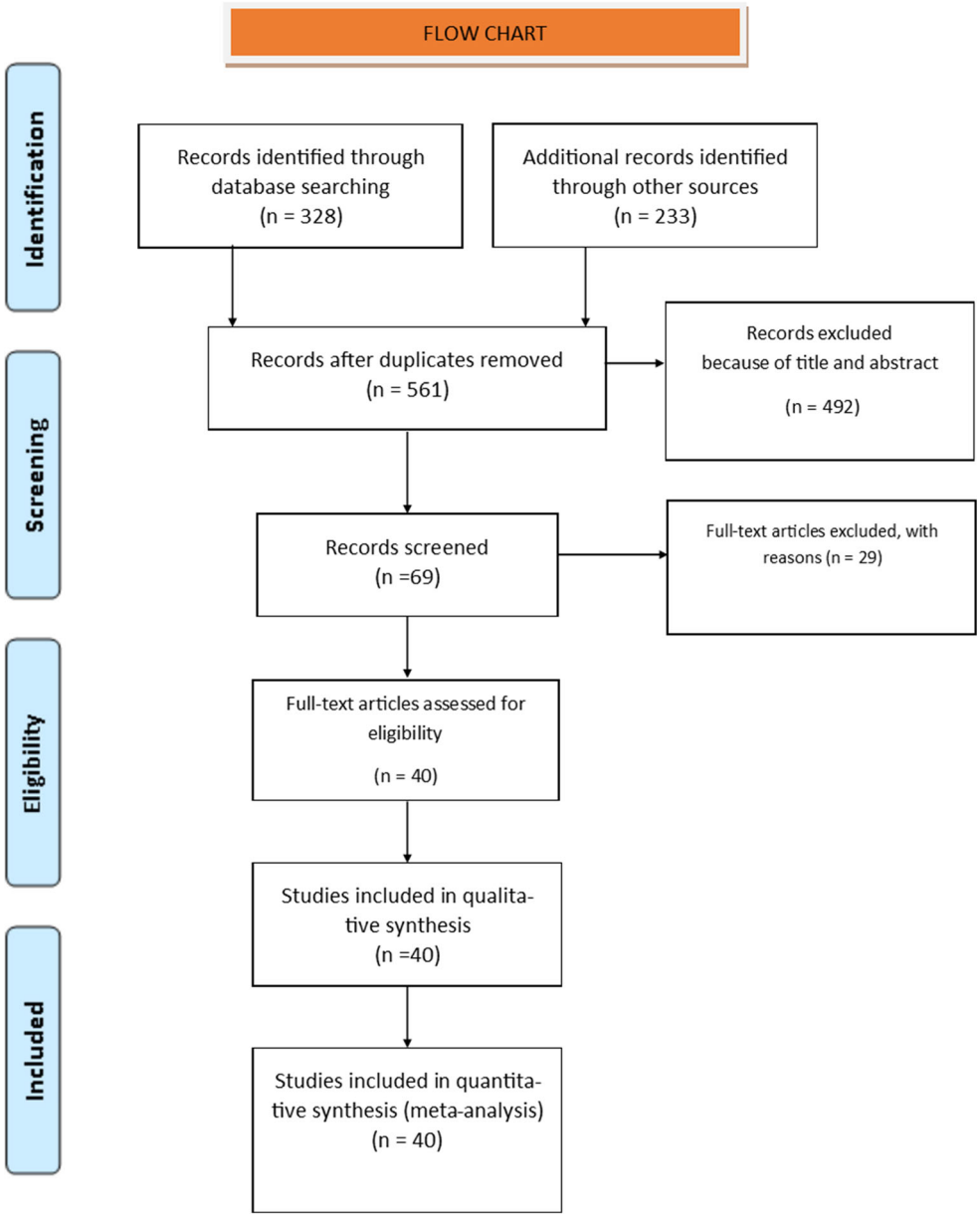

Fig. 1 Flow chart of manuscripts screened through the review process

Analysis using predictive values

The PPV and NPV values could not use for comparisons because the prevalence of the disease varies between individual studies and affects the results. For this reason, the PPV and the NPV were calculated with the total prevalence of the disease (46%) including all positives for disease in the total of the sample evaluated in the selected studies. All studies were included to compare the diagnostic accuracy of diagnostic support methods for detecting OPMD, OC, and OPC. Overall estimates at an adjusted prevalence report a better performance of PPV and NPV for autofluorescence; that is, a positive result derived from a autofluorescence test could have a greater probability of actually being an oral lesion, while a lower certainty of results was derived from the visual inspection (Table 2).

Analysis using DOR

Fluorescence test showed the highest DOR for correctly indicating diagnosis of OPMD, OC, and OPC, DOR = 15 (CI 95%: 7–33), compared to chemiluminescence test and clinical examination results DOR = 2 (95% CI: 1–5) and DOR = 6 (95% CI: 3–14), respectively.

Table 1 Characterization of patients and study samples

Author/year/country	No patients/sex/age range	Test—resultados	Se	Ep	VPP (%)	VPN (%)	VPP adj (%)	VPN adj (%)	Ref
Mashberg A. 1980/USA	n = 178 /NR	Clinical examination	0.96	0.70	74	95	40	27	[27]
Kulapaditharom B , et al. 1998/Thailand	n = 25/14–80 years	Lung imaging fluorescence endoscopy (LIFE)	1.00	0.88	88	100	31	25	[47]
		Clinical examination	0.88	0.50	63	80	50	31	
Leuning A, et al. 2000/Germany	n = 58/34–74 years	Protoporphyrin Ix fluorescence	0.99	0.60	77	97	45	26	[45]
Zheng W, et al. 2002/Singapore	F = 13; M = 15 / 31–85 years	Fluorescence IR/IG	0.90	0.900.90	87	92	30	30	[44]
		Fluorescence IR/IB	0.91	0.98	97	94	26	30	
		Fluorescence IR/IG And IR/IB	0.94		97	96	50	28	
Ram S, et al. 2005/Malaysia	F = 23; M = 17/ 35-80 years	Vizilite	1.00	0.14	80	100	68	25	[43]
Farah C 2007/Australia	F = 29; M = 26/ M = 56.8 years; F = 58.7 years	Vizilite	1.00	0.00	18	NC	45	NC	[60]
Epstein, et al. 2008/USA	F = 134; M = 534 / 49.9 - 73.1	Clinical Examination	1.00	0.00	20.6	NC	75	NC	[42]
		Chemiluminescent	1.00	0.00	20.8	NC	75	NC	
E. Allegra, et al. 2009/Italy	F = 13; M = 19/ 42-82 years	Clinical examination	0.53	0.81	84.2	46.1	35	49	[48]
Mehrotra R. 2010/India	n = ViziLite90	Vizilite	0.00	0.76	0.0	94.8	0.0	57	[49]
	n = VELscope 139 / ViziLite 39 years VELscope 41 years	VELscope	0.50	0.39	6.4	90.3	56	50	
Moro, et al. 2010/Italy	32/NR	Autofluorescence	1.00	0.95	95	93	28	25	[28]
Rahman, et al. 2010/India	109/NR	LED IMF Blue	0.92	0.84	54	98	33	29	[29]
		LED IMF Green	0.90	0.87	59	98	32	30	
Awan K.H. 2011/England	F:56, M:70/46.4 70.4 years	Autofluorescence VELscope™ (premalignant)	0.87	0.21	58.1	57.1	65	32	[58]
		Autofluorescence VELscope™ (dysplasia)	0.84	0.15	37.0	61.1	68	33	
Awan P. R, et al. 2011/England	F:158/M:147. /35–65	Vizilite (premalignant)	0.44	0.27	56.8	48.4	62	53	[50]
		Vizilite (dysplasia)	0.77	0.28	39.5	66.7	61	37	
Farah C, et al. 2011/Australia	F:66, M:46/NR	Clinical examination	0.25	0.82	30	78	34	63	[59]
		VELscope conventional oral examination	0.42	0.68	19	75	41	54	
		VELscope examination	0.30	0.63	29	82	44	60	
Güneri P, et al. 2011/Turkey	F:22, M:13/56.2 years	Clinical examination	0.92	0.43	41	92	54	29	[25]
Jayanthi JL L, et al. 2011/India	*n*: 65	Autofluorescence (normal vs benign lesions)	0.98	0.93	97	96	29	26	[26]
			0.98	0.93	97	96	29	26	
		Autofluorescence (dysplasia vs malignant)	0.98	0.92	96	96	29	26	
		Autofluorescence (benign lesions vs dysplasia)							
Scheer, et al. 2011/Germany	F:25,M:39/59.8 years	VELscope examination	1.00	0.81	54.5	100	35	25	[30]
Marzouki H, et al. 2012/Canada	F:36,M:49/23–87 years	Clinical examination	0.62	0.88	47	92.6	31	44	[36]
		VELscope	0.92	0.76	92	98	37	29	
Mojsa I, et al. 2012/Poland	F:9,M:21/NR	Clinical examination	0.99	0.0	80.5	NC	75	NC	[35]
		Chemiluminescent	0.57	0.37	79.2	17.7	57	47	
Rana M, et al. 2012/Germany	F:179,M:110/18–75 years	Clinical examination	0.17	0.97	17	97	27	67	[41]
		Clinical examination and VELscope	1.00	0.74	17	100	38	25	
Ujaoney S, et al. 2012/India	F:4,M:51/27–61 years	Chemiluminescence	0.98	0.0	17	0.0	75	NC	[39]
Rajmohan M, 2012/India	n = 66/NR	ViziLite	0.85	1.00	100	76.9	100	83.3	[62]
Hanken H, et al. 2013/Germany	F:75,M:45/38–82 years	Clinical examination	0.75	0.33	85	21	59	38	[33]
		Clinical examination And VELscope	0.98	0.42	89	81	54	26	
Bhatia N et al. 2014/Australia	F:158, M:147/35-65 years	Clinical examination	0.44	0.99	84.6	93.3	26	53	[31]
		VELscope™	0.64	0.55	15.1	92.2	48	43	
		Clinical examination and VELscope™	0.74	0.98	81	96.8	26	38	
	F:19,M:25/34–78 years	Clinical Examination	0.9	0.99	100	97.5	26	30	[34]

Table 1 (continued)

Author/year/country	No patients/sex/age range	Test—resultados	Se	Ep	VPP (%)	VPN (%)	VPP adj (%)	VPN adj (%)	Ref
Kämmerer PW, et al. 2014/Germany		Vizilite	0.99	0.3	26	100	60	26	
Petruzzi M, et al. 2014/Italy	F:22, M:27/56.7 years	Autofluorescence (mild dysplasia as positive)	0.7	0.57	65.6	62.5	47	45	[37]
		Autofluorescence (mild dysplasia as negative)	0.76	0.51	40.6	83.3	50	37	
		Toluidine Blue. (mild dysplasia as negative)							
Ibrahim S, et al. 2014/Saudi Arabia	F:149, M:450/34.8 years 450	Clinical Examination	0.99	0.29	17.2	100	61	26	[38]
		Microlux/Dl	0.99	0.32	17.9	100	56	26	
		Microlux/Dl + Tb	0.99	0.35	18.5	100	58	26	
Vashisht N, et al. 2014/India	n:60/NR	Vizilite	0.95	0.84	91.3	91.9	33	28	[40]
Awan K.H. 2015/England	F:56, M:70/51.2 years	VELscope™	0.84	0.15	37.8	61.1	68	33	[6]
		Vizilite	0.77	0.27	39.5	66.7	62	37	
Kaur j. et al. 2015/Belgium	F:39, M:41/54–76 years	VELscope™(squamous cell carcinoma)	0.67	0.62	80	46	44	42	[46]
			0.63	0.53	75	39	49	44	
		VELscope™(oral leukoplakia)	0.6	0.61	77	41	45	45	
		VELscope™(oral lichen planus)							
Moro. 2015/Italy	n = 66/> 14 years	Autofluorescence GOCCLES	0.99	0.95	95	93	28	26	[55]
N Chainani-Wu. 2015/USA	F = 56; M = 70/42–90 years	Clinical examination (dysplasia/malignant)	0.41	0.67	93	9	42	55	[24]
			0.03	0.50	41	4	50	74	
		Clinical examination (malignant)	0.18	0.83	92	8	34	66	
		Vizilite (dysplasia/malignant)	0.01	0.83	40	7	34	75	
		Vizilite (malignant)							
Scheer. 2016/Germany	F = 19; M = 22/NR	VELscope®	0.40	0.89	33.3	88.6	31	55	[56]
Chaudhry A, et al. 2016 / India	F = 26; M = 74 />18 years	Chemiluminescent Kit (Vizilite)	0.84	0.41	73.7	58.3	55	33	[32]
Lalla Y, et al. 2016/Australia	F = 49; M = 39/ M = 58.6 years; F = 62 years	Clinical examination	0.44	0.88	46	87	31	53	[54]
		Vizilite	0.13	0.85	17	81	33	69	
		Autofluorescence	0.88	0.63	88	63	44	31	
Simonato. 2017/Brazil	F = 4; M = 11/52.13 years	Fluorescence	1.0	0.5	22.2	100	50	25	[57]
Amirchaghmaghi 2017/Iran	F = 24 M = 21 / 52.3 ± 14.8 years	Clinical examination (premalignant)	0.75	0.71	64	80	40	38	[51]
		VELscope (premalignant)	0.83	0.12	40	50	69	34	
		Clinical Examination (premalignant / Malignant)	0.81	0.67	74	80	42	35	
			0.90	0.12	56	50	69	30	
		VELscope (Premalignant / Malignant)							
Shukla A, 2018/India	F = 5; M = 37/21–60 years	Vizilite	0.90	0.50	82.6	66.6	60	84	[61]
Shi L 2019/China	F = 279; M = 238/22–85 years	VELscope™ (dysplasia/malignant)	0.72	0.39	67.9	44.2	56	39	[52]
		VELscope™ (malignant)	1.0	0.35	10.5	100	58	25	
		VELscope™ (premalignant)	0.95	0.36	19.9	98.2	57	28	
Simonato 2019/Brazil	n = 54/NR	Clinical Examination (premalignant)	0.66	0.91	14.3	99.2	30	42	[53]
		Fluorescence EVINCE® (premalignant)	0.94	0.96	63.0	99.6	27	28	
			1.0	1.0	3.6	100	25	25	
		Clinical Examination (malignant)	1.0	0.92	3.7	100	29	25	
		Fluorescence EVINCE® (malignant)							

AUC evaluation

To condense the results of the meta-analysis, the area under the curve (AUC) was used as an overall measure of test performance. The test that showed greater accuracy was the autofluorescence test with an AUC = 0.86 95% CI (0.83–0.89); followed by the clinical examination test showed a smaller AUC = 0.78 95% CI (0.74–0.81), while the chemiluminescence test showed the smallest AUC = 0.59 95% CI (0.54–0.63) (Fig. 6).

When plotting the SROC curves in the same graph (Fig. 7), it was observed that the autofluorescence curve is closer to the upper left part, showing that it has high sensitivity and a low rate of false positives compared to the clinical examination curve, suggesting that autofluorescence test has higher has a greater discriminative capacity (AUC = 0.86 vs 0.78). In

Fig. 2 Methodological quality graph of included studies (Quadas-2)

addition, the clinical examination curve is closer to the upper left part compared to the chemiluminescence test curve; suggesting that the latter has the least discriminative diagnostic capacity (AUC = 0.78 vs 0.59).

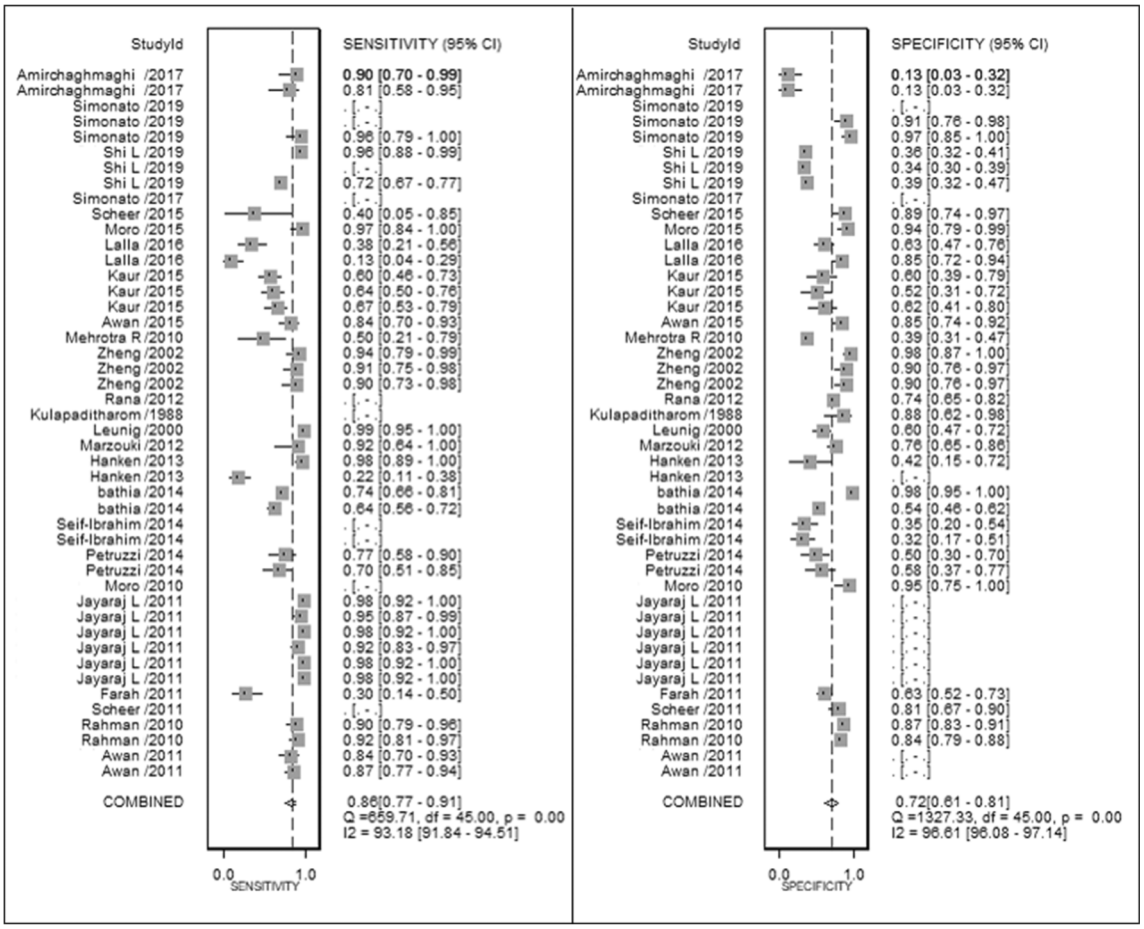

Fig. 3 Forest plot of fluorescence test

Discussion

Summary of main findings

The results of this review showed that the clinical examination was the one with the highest specificity for identifying lesions without dysplasia or without changes in the malignancy of the oral and oropharyngeal epithelium. However, the use of other diagnostic tools and techniques represents an important complement to establish a presumptive diagnosis in patients with oral mucosal lesions. The results grouped in relation to sensitivity were higher for autofluorescence in the clinical setting and its use is simpler and faster compared to other tests. Results in the primary studies showed heterogeneous results because of the different prevalence in the evaluation of each study. However, all analyses showed that the autofluorescence technique can favor the presumptive diagnosis of OPMD, OC, and OPC when used in conjunction with the clinical examination. In our study, chemiluminescence demonstrated the lowest capacity for diagnostic discrimination.

Methodological quality

The risk of bias was variable in all domains and studies. In relation to domain 1, the risk of bias was mainly rated high and unclear in terms of patient selection and sample selection. In general, it was not easy to establish whether they corresponded to consecutive or random samples. Similarly, in domain 2, some studies did not adequately describe the threshold to define the positivity or negativity of light-based tests and clinical examination; therefore, a possible risk of bias was derived. In domain 3, the risk of bias was high or unclear mainly due to the fact that it was not possible to establish whether the results of the reference test (biopsy) were analyzed without prior knowledge of the results derived from previous tests (light-based and clinical visual examination); in domain 4, although all studies applied the comparison with the reference standard to all the samples, frequently in the studies, the time interval necessary between tests and the reference test was not appropriate or was not clearly described. However, applicability concerns for all domains were low.

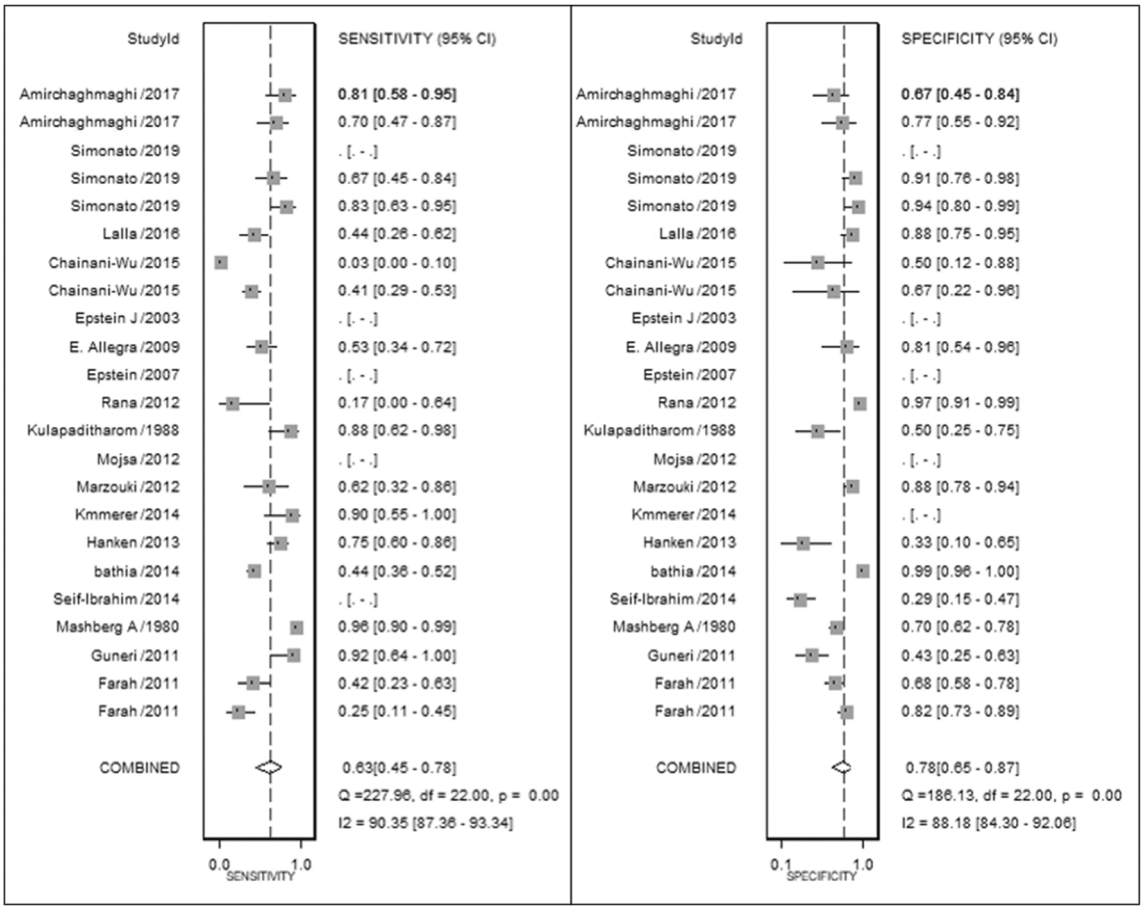

Fig. 4 Forest plot of clinical examination

Agreements and disagreements

This SR investigated and compared the sensitivity, specificity, adjusted PPV, adjusted NPV, LR+, and LR- of two diagnostic light-based tests (autofluorescence, chemiluminescence) and clinical evaluation was used to evaluate OPMD, OC, and OPC. Six systematic reviews about diagnostic accuracy for evaluation of OPMD, OC, and OPC were identified in the literature [22, 63–67]; five of them determined quantitatively the diagnostic accuracy of some methods of detecting oral lesions as summary measures of sensitivity and specificity. However, the SROC curve, which relates the sensitivity and specificity to establish the accuracy of the test was calculated only by one study [67]; likewise, none of the analyses of the previous studies determined the summary measures for each of the tests based on PPV and NPV adjusted to a standard prevalence [22, 64–67]. The results of this SR suggest that clinical examination, when performed by a well-trained professional, was the most consistent method according to the specificity for the screening of cases. This information is in line with data from Walsh 2013 study [62], and in contrast to that reported by Kim 2020 study [67]; however, the findings of this review indicate that NPV shows the lowest results compared to other tests, a condition that suggests the occurrence of a high probability/proportion of false positives.

According to Macey et al. (2015), light detection tests showed high sensitivity; Se = 0.91 (0.81–0.95 and low specificity; Ep = 0.58 (0.22–0.87) [65]. In the present review, the chemiluminescence results suggest a low probability of diagnostic accuracy, unlike the reviews by Rashid 2014 (where the results were not derived from a meta-analysis) [63] and Kim 2020 [67] (where the meta-analysis reported high sensitivity [89%].For autofluorescence techniques with more studies evaluated, the sensitivity was slightly lower, but specificity improved significantly in relation with Macey et al. (2015) [65].

Likewise, three systematic reviews evaluated diagnostic performance in light-based methods [19–21]. Cicciù et al. in 2019 in an SR of autofluorescence technique , the mean value of VELscope® for sensitivity and specificity was 70.19% and 65.95%, respectively; however, the mean value was not obtained through meta-analysis, and in this review the positive and negative predictive values were not evaluated [19]. On the other hand, Kamran & Shankargouda in 2015 did not report

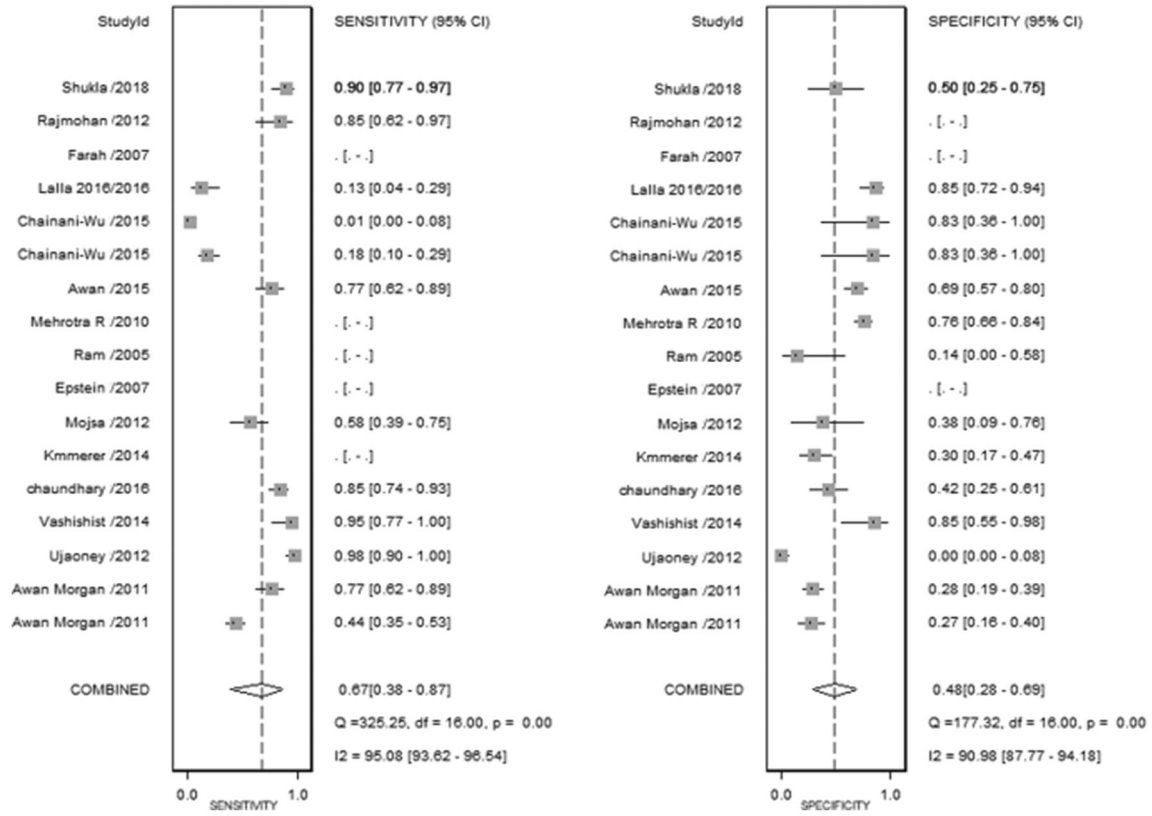

Fig. 5 Forest plot of chemiluminescent test

pooled results either for sensitivity or specificity, although they included in their analysis the information of PPV and NPV reporting for VELscope® a high sensitivity in the detection of premalignant and malignant oral lesions; however, limitations in the test were found in several studies to discriminate dysplasia cases from non-dysplasia cases [20]. Finally, the SR of Nagi in 2016 evaluated the results of 10 studies that used chemiluminescence and 10 that used autofluorescence, although no pooled results were reported by meta-analysis; the mean sensitivity of Vizilite to detect OSCC and OPMD ranged from 77.1 to 100% and the specificity was low, ranging from 0 to 27.8% [21]. In this SR we evaluated a greater number of studies: 15 of chemiluminescence and 25 of autofluorescence due to the significant increase in studies in recent years, which could influence the discrepancy in the results between these two SRs. According to Nagi in 2016, the results of VELscope suggested its high sensitivity can help the experienced clinician to find premalignant oral lesions, but it was unable to differentiate between dysplasia and benign inflammatory conditions [21]. None of these SRs evaluated performance results specifically for clinical visual examination; although the study by Kim 2020 [67] showed an approximation of pooled results of sensitivity and specificity, its analysis was developed with the information derived from only 3 studies. The current SR includes 18 articles that evaluate the diagnostic accuracy of the clinical examination, which is one of the most important results of this review.

Table 2 Grouped estimates of sensitivity, specificity, predictive values, LR +, LR- and ORD of diagnostic tests fluorescence and clinical examination)

	Se [95% CI]	Ep [95% CI]	LR+ [95% CI]	LR- [95% CI]	PPV adj	NPV adj	AUC [95% CI]
Fluorescence	0.86 [0.77–0.91]	0.72 [0.61–0.81]	3.1 [2.1–4.4]	0.20 [0.12–0.33]	0.75 [0.66–0.82]	0.84 [0.73–0.90]	0.86 [0.83–0.89]
Chemiluminescent	0.67 [0.38–0.87]	0.48 [0.28–0.69]	1.3 [0.9–1.9]	0.68 [0.34–1.35]	0.52 [0.48–0.55]	0.63 [0.59–0.67]	0.59 [0.54–0.63]
CE	0.63 [0.45–0.78]	0.78 [0.65–0.87]	2.8 [1.7–4.7]	0.48 [0.31–0.74]	0.74 [0.56–0.85]	0.68 [0.54–0.79]	0.78 [0.74–0.81]

Sensitivity (Se); specificity (Ep); positive likelihood ratio (LR+); negative likelihood ratio (LR-); positive predictive value (PPV); negative predictive value (NPV); area under the ROC curve (AUC)

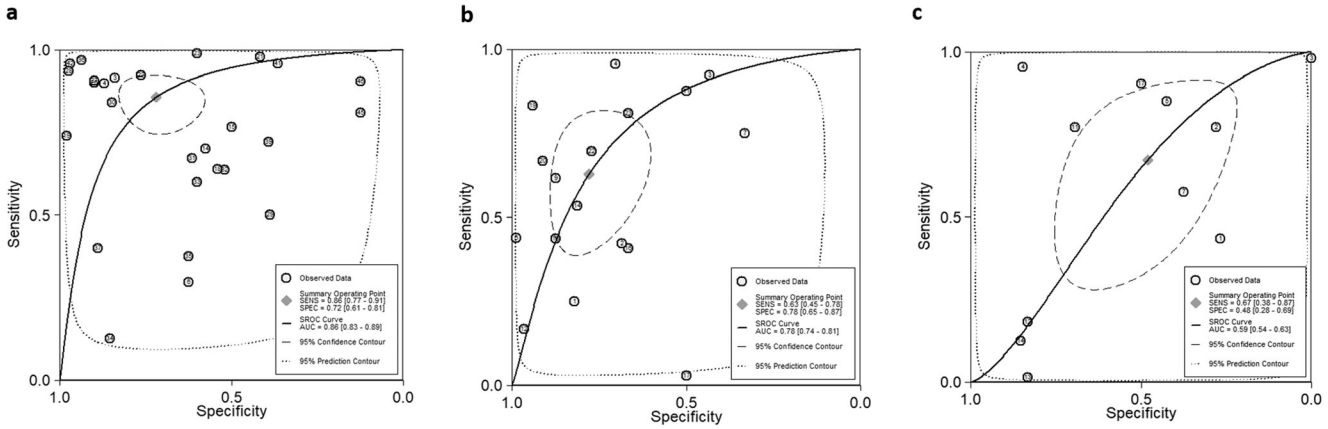

Fig. 6 Bivariate approach: SROC with the confidence and prediction regions around the mean sensitivity and the point of specificity for (a) fluorescence test, (b) clinical examination, (c) chemiluminescence test

Limitations of the review process

In this SR, some limitation to the review process should be discussed. First, it has been found that most of the studies that evaluated autofluorescence did so using the instruments of a single commercial house thus limiting the variability that could exist with other devices in the market. Second, none of the studies included in this review evaluated autofluorescence, chemiluminescence, and clinical examination within the same publication. Fourth, despite all the efforts to retrieve data not available in the original papers, very few non-published information could be retrieved following communication with the authors of some studies (i.e., it was not possible to confirm most of the data of unclear or inconsistent patients). In addition, most studies do not report all performance evaluation measures of diagnostic test evaluation, making the extraction of data difficult as well as its subsequent analysis.

Conclusions

Autofluorescence devices displayed superior accuracy levels in the identification of premalignant lesions and early neoplastic changes compared to clinical examination and chemiluminescence. Autofluorescence devices attached to the visual clinical examination could help the clinician more accurately identify premalignant lesions and early neoplastic changes, but previous training is required. However, the biopsy remains the gold standard for the definitive diagnosis of oral and oropharyngeal premalignant and malignant lesions.

Implications for clinical management

The phases for detection and diagnosis of OPMD, OC, and OPC are the following: (1) clinical history; (2) clinical examination, given the estimates of this SR and the good capacity of the EC for the identification

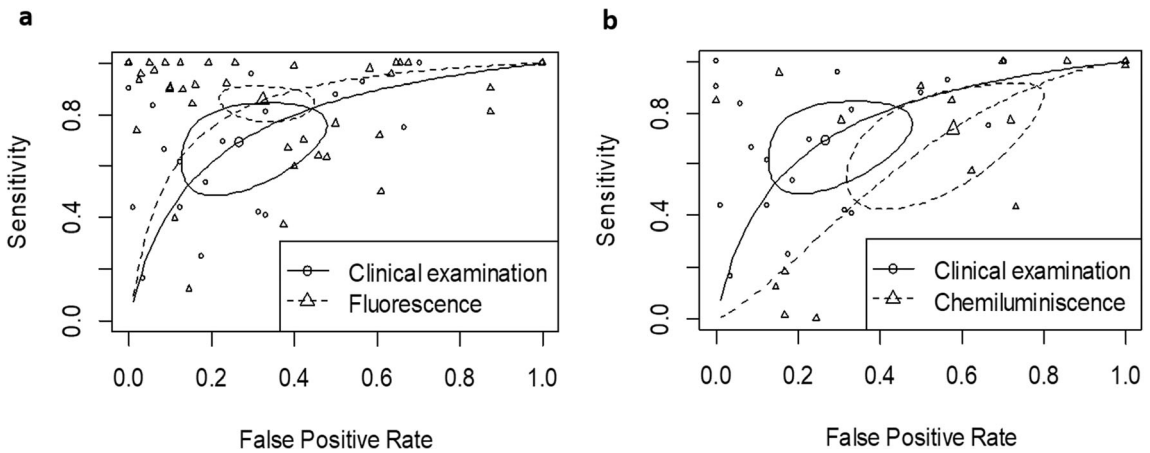

Fig. 7 Summary graph of the comparison of the ROC curves with the confidence regions for (a) clinical examination compared with fluorescence test, (b) clinical examination compared with chemiluminescence test

with enough precision in lesions that do not show dysplastic changes; (3) complementary tests, including light-based tests, which favor better decision-making when there is an injury that must be analyzed in greater depth; and, given the simplicity of use of the test in the patient and during the consultation; these tests should be performed bearing in mind that, given the speed of technological advances in the use of devices, their use must always be accompanied by adequate training and constant updating; and (4) Biopsy for diagnostic confirmation.

Implications for future research

Future studies should consider the following: (a) the simultaneous evaluation of autofluorescence, chemiluminescence, and clinical examination; (b) the use of chemiluminescence performance in order to improve performance evaluation; (c) studies should strive to clarify the demographic variables of the patients included and differentiate this information in relation to the samples evaluated, especially to articles that evaluate more than one sample by patient (d) regarding the tests and the evaluation times between them, we recommend an increase in studies where the evaluation of the different tests is carried out by at least two trained professionals in order to increase precision and accuracy; and (e) if possible, it is suggested that the studies report all the results that are of interest: sensitivity, specificity, prevalence, PPV, NPV, LR+ and LR.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-020-03746-y.

Funding This research received no specific grant from funding agencies in the public, commercial, or non-profit sectors. The work was supported by the dental school and the research vice-rectory of the El Bosque University.

Compliance with ethical standards

Conflict of interest María Rosa Buenahora declares that she has no conflict of interest. Alberto Peraza L declares that he has no conflict of interest. David Díaz-Báez declares that he has no conflict of interest. Jairo Bustillo declares that he has no conflict of interest. Iván Santacruz declares that he has no conflict of interest. Tamy Goretty Trujillo declares that she has no conflict of interest. Gloria Inés Lafaurie declares that she has no conflict of interest. ,Leandro Chambrone declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

References

1. Hussein AA, Helder MN, de Visscher JG, Leemans CR, Braakhuis BJ, de Vet HCW, Forouzanfar T (2017) Global incidence of oral and oropharynx cancer in patients younger than 45 years versus older patients: a systematic review. Eur J Cancer 82:115–127. https://doi.org/10.1016/j.ejca.2017.05.026
2. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, Rosenberg PS, Bray F, Gillison ML (2013) Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol 31:4550–4559. https://doi.org/10.1200/JCO.2013.50.3870
3. Awadallah M, Idle M, Patel K, Kademani D (2018) Management update of potentially premalignant oral epithelial lesions. Oral Surg Oral Med Oral Pathol Oral Radiol 125:628–636. https://doi.org/10.1016/j.oooo.2018.03.010
4. Warnakulasuriya S, Johnson NW, van der Waal I (2007) Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med 36:575–580. https://doi.org/10.1111/j.1600-0714.2007.00582.x
5. Hwang JTK, Gu YR, Shen M, Ralhan R, Walfish PG, Pritzker KPH, Mock D (2017) Individualized five-year risk assessment for oral premalignant lesion progression to cancer. Oral Surg Oral Med Oral Pathol Oral Radiol 123(3):374–381. https://doi.org/10.1016/j.oooo.2016.11.004
6. Awan KH, Morgan PR, Warnakulasuriya S (2015) Assessing the accuracy of autofluorescence, chemiluminescence and toluidine blue as diagnostic tools for oral potentially malignant disorders–a clinicopathological evaluation. Clin Oral Investig 19:2267–2272. https://doi.org/10.1007/s00784-015-1457-9
7. Nair DR, Pruthy R, Pawar U, Chaturvedi P (2012) Oral cancer: premalignant conditions and screening–an update. J Cancer Res Ther 8(Suppl 1):S57–S66. https://doi.org/10.4103/0973-1482.92217
8. Diamanti N, Duxbury AJ, Ariyaratnam S, Macfarlane TV (2002) Attitudes to biopsy procedures in general dental practice. Br Dent J 192:588–592. https://doi.org/10.1038/sj.bdj.4801434
9. Tyagi KK, Khangura RK, Grewal DS, Salgotra V (2017) Knowledge, attitude and practices of general dental practitioners towards oral biopsy in Ghaziabad, Uttar Pradesh. International Journal of Contemporary Medicine Surgery and Radiology. Int J Contemp Med Surg Radiol 1:5–9
10. Carreras-Torras C, Gay-Escoda C (2015) Techniques for early diagnosis of oral squamous cell carcinoma: systematic review. Med Oral Patol Oral Cir Bucal 20(3):e305–e315. https://doi.org/10.4317/medoral.20347
11. Mota-Ramírez A, Silvestre FJ, Simó JM (2007) Oral biopsy in dental practice. Med Oral Patol Oral Cir Bucal 12(7):E504–E510
12. Croce AC, Bottiroli G (2014) Autofluorescence spectroscopy and imaging: a tool for biomedical research and diagnosis. Eur J Histochem 58(4):2461. https://doi.org/10.4081/ejh.2014.2461
13. Giovannacci I, Magnoni C, Vescovi P, Painelli A, Tarentini E, Meleti M (2019) Which are the main fluorophores in skin and oral mucosa? A review with emphasis on clinical applications of tissue autofluorescence. Arch Oral Biol 105:89–98. https://doi.org/10.1016/j.archoralbio.2019.07.001
14. Shashidara R, Sreeshyla HS, Sudheendra US (2014) Chemiluminescence: a diagnostic adjunct in oral precancer and cancer: a review. J Cancer Res Ther 10:487–491. https://doi.org/10.4103/0973-1482.138215
15. Mercadante V, Paderni C, Campisi G (2012) Novel non-invasive adjunctive techniques for early oral cancer diagnosis and oral lesions examination. Curr Pharm Des 18(34):5442–5451. https://doi.org/10.2174/138161212803307626

16. Altman DG, Bland JM (1994) Diagnostic tests 2: predictive values. BMJ 309(6947):102. https://doi.org/10.1136/bmj.309.6947.102
17. Kim KW, Lee J, Choi SH, Huh J, Park SH (2015) Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers–part I. general guidance and tips. Korean J Radiol 16(6):1175–1187. https://doi.org/10.3348/kjr.2015.16.6.1175
18. Lee J, Kim KW, Choi SH, Huh J, Park SH (2015) Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers–part II. Statistical methods of meta-analysis. Korean J Radiol 16(6):1188–1196. https://doi.org/10.3348/kjr.2015.16.6.1188
19. Cicciù M, Cervino G, Fiorillo L, D'Amico C, Oteri G, Troiano G, Zhurakivska K, Lo Muzio L, Herford AS, Crimi S, Bianchi A, di Stasio D, Rullo R, Laino G, Laino L (2019) Early diagnosis on oral and potentially oral malignant lesions: a systematic review on the Velscope® fluorescence method. Dent J 7(3):93. https://doi.org/10.3390/dj7030093
20. Awan KH, Patil S (2015) Efficacy of autofluorescence imaging as an adjunctive technique for examination and detection of oral potentially malignant disorders: a Systematic Review. J Contemp Dent Pract 16(9):744–749. https://doi.org/10.5005/jp-journals-10024-1751
21. Nagi R, Reddy-Kantharaj YB, Rakesh N, Janardhan-Reddy S, Sahu S (2016) Efficacy of light based detection systems for early detection of oral cancer and oral potentially malignant disorders: systematic review. Med Oral Patol Oral Cir Bucal 21(4):e447–e455. https://doi.org/10.4317/medoral.21104
22. Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JL, Lingen MW, Ogden GR, Warnakulasuriya S, Scully C (2015) Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. Cochrane Database Syst Rev 5:CD010276. https://doi.org/10.1002/14651858.CD010276.pub2
23. Whiting PF, Rutjes AWS, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM (2011) Quadas-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155(8):529–536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009
24. Chainani-Wu N, Madden E, Cox D, Sroussi H, Epstein J, Silverman S (2015) Toluidine blue aids in detection of dysplasia and carcinoma in suspicious oral lesions. Oral Dis 21(7):879–885. https://doi.org/10.1111/odi.12358
25. Mojsa I, Kaczmarzyk T, Zaleska M, Stypulkowska J, Zapala-Pospiech A, Sadecki D (2012) Value of the ViziLite Plus System as a diagnostic aid in the early detection of oral cancer/premalignant epithelial lesions. J Craniofac Surg 23:e162–e164. https://doi.org/10.1097/SCS.0b013e31824cdbea
26. Kaur J, Jacobs R (2015) Combination of autofluorescence imaging and salivary protoporphyrin in oral precancerous and cancerous lesions: Non-invasive tools. J Clin Exp Dent 7(2):e187–e191. https://doi.org/10.4317/jced.52100
27. Lalla Y, Matias MAT, Farah CS (2016) Assessment of oral mucosal lesions with autofluorescence imaging and reflectance spectroscopy. J Am Dent Assoc 147(8):650–660. https://doi.org/10.1016/j.adaj.2016.03.013
28. Moro A, De Waure C, Di Nardo F et al (2015) The GOCCLES® medical device is effective in detecting oral cancer and dysplasia in dental clinical setting. Results from a multicentre clinical trial. Acta Otorhinolaryngol Ital 35(6):449–454. https://doi.org/10.14639/0392-100X-922
29. Scheer M, Fuss J, Derman MA, Kreppel M, Neugebauer J, Rothamel D, Drebber U, Zoeller JE (2016) Autofluorescence imaging in recurrent oral squamous cell carcinoma. Oral Maxillofac Surg 20(1):27–33. https://doi.org/10.1007/s10006-015-0520-7
30. Simonato L, Tomo S, Miyahara GI, Navarro R, Villaverde A (2017) Fluorescence visualization efficacy for detecting oral lesions more prone to be dysplastic and potentially malignant disorders: a pilot study. Photodiagn Photodyn Ther 17:1–4. https://doi.org/10.1016/j.pdpdt.2016.10.010
31. Awan KH, Morgan PR, Warnakulasuriya S (2011) Evaluation of an autofluorescence based imaging system (VELscopeTM) in the detection of oral potentially malignant disorders and benign keratoses. Oral Oncol 47(4):274–277. https://doi.org/10.1016/j.oraloncology.2011.02.001
32. Farah CS, McIntosh L, Georgiou A, McCullough MJ (2012) Efficacy of tissue autofluorescence imaging (velscope) in the visualization of oral mucosal lesions. Head Neck 34(6):856–862. https://doi.org/10.1002/hed.21834
33. Güneri P, Epstein JB, Kaya A, Veral A, Kazandi A, Boyacioglu H (2011) The utility of toluidine blue staining and brush cytology as adjuncts in clinical examination of suspicious oral mucosal lesions. Int J Oral Maxillofac Surg 40(2):155–161. https://doi.org/10.1016/j.ijom.2010.10.022
34. Jayanthi JL, Subhash N, Stephen M, Philip EK, Beena VT (2011) Comparative evaluation of the diagnostic performance of autofluorescence and diffuse reflectance in oral cancer detection: a clinical study. J Biophotonics 4(10):696–706. https://doi.org/10.1002/jbio.201100037
35. Mashberg A (1980) Reevaluation of toluidine blue application as a diagnostic adjunct in the detection of asymptomatic oral squamous carcinoma: a continuing prospective study of oral cancer III. Cancer 46(4):758–763. https://doi.org/10.1002/1097-0142(19800815)46:4<758::AID-CNCR2820460420>3.0.CO;2-8
36. Moro A, Di Nardo F, Boniello R, Marianetti TM, Cervelli D, Gasparini G, Pelo S (2010) Autofluorescence and early detection of mucosal lesions in patients at risk for oral cancer. J Craniofac Surg 1(6):1899–1903. https://doi.org/10.1097/SCS.0b013e3181f4afb4
37. Rahman MS, Ingole N, Roblyer D, Stepanek V, Richards-Kortum R, Gillenwater A, Shastri S, Chaturvedi P (2010) Evaluation of a low-cost, portable imaging system for early detection of oral cancer. Head Neck Oncol 2:10. https://doi.org/10.1186/1758-3284-2-10
38. Scheer M, Neugebauer J, Derman A, Fuss J, Drebber U, Zoeller JE (2011) Autofluorescence imaging of potentially malignant mucosa lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2:10–577. https://doi.org/10.1016/j.tripleo.2010.12.010
39. Bhatia N, Matias MAT, Farah CS (2014) Assessment of a decision making protocol to improve the efficacy of VELscopeTM in general dental practice: a prospective evaluation. Oral Oncol 50(10):1012–1019. https://doi.org/10.1016/j.oraloncology.2014.07.002
40. Chaudhry A, Manjunath M, Ashwatappa D, Krishna S, Krishna AG (2016) Comparison of chemiluminescence and toluidine blue in the diagnosis of dysplasia in leukoplakia: a cross-sectional study. J Investig Clin Dent 7(2):132–140. https://doi.org/10.1111/jicd.12141
41. Hanken H, Kraatz J, Smeets R, Heiland M, Blessmann M, Eichhorn W, Clauditz TS, Gröbe A, Kolk A, Rana M (2013) The detection of oral pre- malignant lesions with an autofluorescence based imaging system (VELscopeTM) - a single blinded clinical evaluation. Head Face Med 9:23. https://doi.org/10.1186/1746-160X-9-23
42. Kämmerer PW, Rahimi-Nedjat RK, Ziebart T, Bemsch A, Walter C, Al-Nawas B, Koch FP (2015) A chemiluminescent light system in combination with toluidine blue to assess suspicious oral lesions—clinical evaluation and review of the literature. Clin Oral Investig 19(2):459–466. https://doi.org/10.1007/s00784-014-1252-z
43. Marzouki HZ, Vu TTV, Ywakim R, Chauvin P, Hanley J, Kost KM (2012) Use of fluorescent light in detecting malignant and premalignant lesions in the oral cavity: a prospective, single-blind study. J Otolaryngol Head Neck Surg 41(3):164–168. https://doi.org/10.2310/7070.2012.00022
44. Petruzzi M, Lucchese A, Nardi GM, Lauritano D, Favia G, Serpico R, Grassi FR (2014) Evaluation of autofluorescence and toluidine

blue in the differentiation of oral dysplastic and neoplastic lesions from non dysplastic and neoplastic lesions: a cross-sectional study. J Biomed Opt 19(7):76003. https://doi.org/10.1117/1.jbo.19.7.076003
45. Ibrahim SS, Al-Attas SA, Darwish ZE, Amer HA, Hassan MH (2014) Effectiveness of the Microlux/DLTM chemiluminescence device in screening of potentially malignant and malignant oral lesions. Asian Pac J Cancer Prev 15:6081–6086. https://doi.org/10.7314/apjcp.2014.15.15.6081
46. Ujaoney S, Motwani M, Degwekar S, Wadhwan V, Zade P, Chaudhary M, Hazarey V, Thakre T, Mamtani M (2012) Evaluation of chemiluminescence, toluidine blue and histopathology for detection of high risk oral precancerous lesions: a cross-sectional study. BMC Clin Pathol 12:6. https://doi.org/10.1186/1472-6890-12-6
47. Vashisht N, Ravikiran A, Samatha Y, Chandra Rao P, Naik R, Vashisht D (2014) Chemiluminescence and toluidine blue as diagnostic tools for detecting early stages of oral cancer: an invivo study. J Clin Diagn Res 8(4):ZC35–ZC38. https://doi.org/10.7860/JCDR/2014/7746.4259
48. Rana M, Zapf A, Kuehle M, Gellrich NC, Eckardt AM (2012) Clinical evaluation of an autofluorescence diagnostic device for oral cancer detection: a prospective randomized diagnostic study. Eur J Cancer Prev 21(5):460–466. https://doi.org/10.1097/CEJ.0b013e32834fdb6d
49. Epstein JB, Silverman S, Epstein JD, Lonky SA, Bride MA (2008) Analysis of oral lesion biopsies identified and evaluated by visual examination, chemiluminescence and toluidine blue. Oral Oncol 44(6):538–544. https://doi.org/10.1016/j.oraloncology.2007.08.011
50. Ram S, Siar CH (2005) Chemiluminescence as a diagnostic aid in the detection of oral cancer and potentially malignant epithelial lesions. Int J Oral Maxillofac Surg 34(5):521–527. https://doi.org/10.1016/j.ijom.2004.10.008
51. Zheng W, Soo KC, Sivanandan R, Olivo M (2002) Detection of squamous cell carcinomas and pre-cancerous lesions in the oral cavity by quantification of 5-aminolevulinic acid induced fluorescence endoscopic images. Lasers Surg Med 31(3):151–157. https://doi.org/10.1002/lsm.10105
52. Leunig A, Betz CS, Mehlmann M, Stepp H, Arbogast S, Grevers G, Baumgartner R (2000) Detection of squamous cell carcinoma of the oral cavity by imaging 5- aminolevulinic acid-induced protoporphyrin IX fluorescence. Laryngoscope 172(6):674–677. https://doi.org/10.1097/00005537-200001000-00015
53. Kulapaditharom B, Boonkitticharoen V (1998) Laser-induced fluorescence imaging in localization of head and neck cancers. Ann Otol Rhinol Laryngol 110(1):45–52. https://doi.org/10.1177/000348949810700310
54. Allegra E, Lombardo N, Puzzo L, Garozzo A (2009) The usefulness of toluidine staining as a diagnostic tool for precancerous and cancerous oropharyngeal and oral cavity lesions. Acta Otorhinolaryngol Ital 29(4):187–190. https://doi.org/10.1177/000348940111000109
55. Mehrotra R, Singh M, Thomas S, Nair P, Pandya S, Nigam NS, Shukla P (2010) A cross-sectional study evaluating chemiluminescence and autofluorescence in the detection of clinically innocuous precancerous and cancerous oral lesions. J Am Dent Assoc 141(2):151–156. https://doi.org/10.14219/jada.archive.2010.0132
56. Awan KH, Morgan PR, Warnakulasuriya S (2011) Utility of chemiluminescence (ViziLiteTM) in the detection of oral potentially malignant disorders and benign keratoses. J Oral Pathol Med 40(7):541–544. https://doi.org/10.1111/j.1600-0714.2011.01048.x
57. Amirchaghmaghi M, Mohtasham N, Delavarian Z, Shakeri MT, Hatami M, Mosannen Mozafari P (2018) The diagnostic value of the native fluorescence visualization device for early detection of premalignant/malignant lesions of the oral cavity. Photodiagn Photodyn Ther 21:19–27. https://doi.org/10.1016/j.pdpdt.2017.10.019
58. Shi L, Li C, Shen X, Zhou Z, Liu W, Tang G (2019) Potential role of autofluorescence imaging in determining biopsy of oral potentially malignant disorders: a large prospective diagnostic study. Oral Oncol 98:176–179. https://doi.org/10.1016/j.oraloncology.2019.08.006
59. Simonato LE, Tomo S, Scarparo Navarro R, Balbin Villaverde AGJ (2019) Fluorescence visualization improves the detection of oral, potentially malignant, disorders in population screening. Photodiagn Photodyn Ther 27:74–78. https://doi.org/10.1016/j.pdpdt.2019.05.017
60. Farah CS, McCullough MJ (2007) A pilot case control study on the efficacy of acetic acid wash and chemiluminescent illumination (ViziLite) in the visualisation of oral mucosal white lesions. Oral Oncol 43(8):820–824. https://doi.org/10.1016/j.oraloncology.2006.10.005
61. Shukla A, Singh NN, Adsul S, Kumar S, Shukla D, Sood A (2018) Comparative efficacy of chemiluminescence and toluidine blue in the detection of potentially malignant and malignant disorders of the oral cavity. J Oral Maxillofac Pathol 22(3):442. https://doi.org/10.4103/jomfp.JOMFP_261_17
62. Rajmohan M, Rao UK, Joshua E, Rajasekaran ST, Kannan R (2012) Assessment of oral mucosa in normal, precancer and cancer using chemiluminescent illumination, toluidine blue supravital staining and oral exfoliative cytology. J Oral Maxillofac Pathol 16(3):325–329. https://doi.org/10.4103/0973-029X.102476
63. Rashid A, Warnakulasuriya S (2015) The use of light-based (optical) detection systems as adjuncts in the detection of oral cancer and oral potentially malignant disorders: a systematic review. J Oral Pathol Med 21(4):e447–e455. https://doi.org/10.1111/jop.12218
64. Fuller C, Camilon R, Nguyen S, Jennings J, Day T, Gillespie MB (2015) Adjunctive diagnostic techniques for oral lesions of unknown malignant potential: systematic review with meta-analysis. Head Neck 37(5):755–762. https://doi.org/10.1002/hed.23667
65. Walsh T, Liu JLY, Brocklehurst P, Glenny AM, Lingen M, Kerr AR, Ogden G, Warnakulasuriya S, Scully C (2013) Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. Cochrane Database Syst Rev 11:CD010173. https://doi.org/10.1002/14651858.CD010173.pub2
66. Lingen MW, Tampi MP, Urquhart O et al (2017) Adjuncts for the evaluation of potentially malignant disorders in the oral cavity: diagnostic test accuracy systematic review and meta-analysis—a report of the American Dental Association. J Am Dent Assoc 148(11):797–813.e52. https://doi.org/10.1016/j.adaj.2017.08.045
67. Kim DH, Song EA, Kim SW, Hwang SH (2020) Efficacy of toluidine blue in the diagnosis and screening of oral cancer and precancer: A systematic review and meta-analysis. Clin Otolaryngol (Aug 1). https://doi.org/10.1111/coa.13613