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Adjunctive aids for the detection of oral squamous cell carcinoma and oral potentially malignant disorders: A systematic review of systematic reviews

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ABSTRACT

This study presents the results of systematic reviews on adjunctive tools in screening and diagnosis of oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD) and to determine if the current literature supports their use as either an adjunctive tool or replacement of gold standard techniques. Systemic reviews and meta-analysis that evaluated adjunctive tools including chemiluminescence, tissue autofluorescence, tissue fluorescence spectroscopy, vital staining and cytology techniques were systematically examined using AMSTAR II. Twenty-seven systematic reviews were included. Five studies had a low quality of evidence, and nine studies had a critically low quality of evidence. This review found limited evidence to recommend chemiluminescence, tissue autofluorescence tools and vital staining as diagnostic tools, but only serve as clinical adjuncts to conventional oral examination. Cytology techniques and narrow-band imaging may be utilised as a non-invasive diagnostic adjunctive tool for the detection of OSCC and the malignant transformation of OPMD. In conclusion, this paper provides evidence on several types of adjunctive tools and provides recommendations on their use in clinical practice. These tools are considered useful as clinical adjuncts but there is insufficient evidence for their use as a diagnostic tool to replace gold standard conventional oral examination and surgical biopsy.

1. Introduction

Oral squamous cell carcinoma (OSCC) is considered a devastating disease and accounts for up to 90% of malignancies that arise in the oral cavity. It may affect any anatomical sub site within the oral cavity.[1,2] In many populations OSCC is often preceded by oral potentially malignant disorders (OPMDs).[3].

Despite advances in treatment modalities of OSCC, currently, the survival rate for oral cancer remains around 50% after 5 years in most countries.[4–6] The poor prognosis of OSCC can be attributed to the late stage diagnosis of OSCC, whereas the 5-year survival rate improves dramatically when diagnosed at an early stage.[7] The tumour-node-metastasis (TNM) classification system is commonly utilised to stage OSCC. Stage I tumours have a 5-year survival rate of approximately 80%, whereas the survival rate of stage III and stage IV tumours falls below 50%.[8] As a result, early detection and diagnosis of OSCC is considered key to improved patient survival.

OPMDs commonly precede OSCC. As the name suggests, OPMD are oral disorders that have the potential to progress to malignancy.[3] The prevalence of OPMD is reported to be 4.75%.[9] The most common OPMDs are leukoplakia, erythroplakia, proliferative verrucous leukoplakia, actinic cheilitis, submucous fibrosis and oral lichen planus.

Adjunctive tools can be utilised for both screening and diagnostic purposes.[10] Screening is not intended to be diagnostic. Instead, it aims to identify individuals who are seemingly well when they are actually suffering from disease.[11] Several studies have evaluated the effectiveness of the conventional oral examination (COE) as a screening test.[12] To date, only one randomised control study conducted in Kerala, India has demonstrated long term success of repeated screening, leading to improved rates of cancer survival.[13].

Currently the gold standard for diagnosing OSCC and OPMD is a conventional oral examination and histopathological investigation via a surgical biopsy- either an incisional or excisional biopsy. A range of adjunctive tools are reported in the literature for screening or

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diagnosing OSCC and OPMD.[14] Adjunctive tools can be classified as utilised in primary, secondary and tertiary settings.[15] In primary settings adjunctive tools are essentially utilised to scan the oral mucosa, focusing on lesion detection or discrimination. They include chemiluminescence, tissue fluorescence, spectroscopy, and narrow-band imaging. Commercially available models of chemiluminescence include ViziLite Plus and Microlux D/L, while available tissue autofluorescence chair-side tools include VELscope and Bioscreen. In secondary settings, the aim is to assess the lesion, including evaluation of cells specifically from the affected or distant sites. These include cytology techniques such as oral brush biopsy and liquid based cytology, and vital staining such as the application of toluidine blue. In the tertiary settings, they are used as risk assessment tools. Currently available platforms focus on biochemical testing of saliva and serum and include a range of molecular tests, including DNA, RNA and protein from affected sites or body fluids. Other adjunctive tools include imaging techniques such as FDG-PET and optical coherence tomography (OCT).

A systemic review of systemic reviews provides a tertiary level of evidence.[16] This novel type of review provides evidence collected from systemic reviews and meta-analyses with the intention of translating its results to provide evidence for improving clinical practice. In this study, a PICO framework was utilised to aid in formulating a research question and guiding the search strategy. The research question proposed is "to date, what does the current literature describe as effective adjunctive tools in the screening and diagnosis of OSCC and OPMD." In this study, we aim to present the results of systematic reviews and meta-analyses on adjunctive tools in screening and diagnosis of OSCC and OPMD in primary and secondary care and determine if current literature supports their use as either an adjunctive tool or for replacement of gold standard techniques. An evaluation of current studies will also be included.

2. Materials and methods

This systemic review of systematic reviews and meta-analyses was conducted following two different methods. "The Preferred Reporting Items from Systematic Reviews and Meta-Analysis- PRISMA 2020 [17] and the based reporting checklist and the Cochrane collaboration criteria.[18] This systematic review has been registered with PROSPERO, an international prospective register of systematic reviews (Ref: CRD42023447409).

2.1. Search strategy

Searched databases included: Web of Science, Scopus, MEDLINE (via PubMed) and the Cochrane Database of Systematic Reviews. Regarding search dates, no lower date limit was set, and the upper date limit was July 2023. (Supplementary table 1) The search strategy was guided by the Peer Review of Electronic Search Strategies- PRESS.[19] To maximise sensitivity, a combination of related free terms were used as well as a built in combined MeSH terms were utilised. References were managed via Endnote V20.2 and duplicate references were eliminated.

2.2. Eligibility criteria

Studies reporting either systematic reviews or meta-analyses were included in this study. To be included, the systematic review or meta-analysis requires a clearly formulated research question with a clearly defined search methodology with relevant research articles critically appraised.[20] Articles meeting the eligibility criteria must evaluate adjunctive tools in the screening or diagnosing OSCC or OPMD. This systematic review is intended to be for a global population and hence no geographic restrictions were set. Exclusion criteria included articles with a different study design to systematic reviews or meta-analyses, articles considered off topic, and articles that were not written in English. Exclusion criteria also include tertiary examination techniques which include molecular analysis, biochemical analysis of saliva and serum, as well as radiographic imaging techniques. A list of excluded studies is presented in Supplementary Table 2. A second part of this systematic review of systematic review is planned for a separate publication on molecular and biochemical analysis as adjunctive tools for the screening or diagnosis of OSCC and OPMD.

2.3. Study selection and screening

Using the eligibility criteria set out above, two authors (JL and GO) independently conducted a literature search. Duplicate articles were deleted. In the first round of screening, all titles and abstracts were screened by the same two authors to determine if they met the selection criteria. All articles that apparently met the inclusion criteria were then read with their full text before a decision was made to determine if they met the eligibility criteria. Any discrepancies were resolved with discussion with the senior author (OK).

2.4. Data extraction

The data extracted from the included systematic reviews and meta-analysis was recorded in a standardised fashion using Microsoft Excel v. 365. Data gathered included characteristics such as the first authors, journal published and its impact factor, the type of study, its study population, the number of primary studies in included, overall sample size, use of a systematic review reporting guideline, its search strategy, its inclusion and exclusion criteria, risk of bias analysis, adjunctive tools analysed, and reported accuracy of test results.

2.5. Evaluation of quality and risk of bias

Each article that was read in full was critically appraised for its methodology, quality and risk of bias using "A MeaSurement Tool to Assess systematic reviews (AMSTAR2) checklist.[21] In order to assess for risk assessment bias, the AMSTAR2 checklist assesses 16 different domains. (Supplementary table 3) The AMSTAR2 checklist considers 7 of the 16 items as critical domains, namely items: 2, 4, 7, 9, 11 and 15. An overall rating confidence was given based on the scoring from the critical domains. (Supplementary table 4) The overall confidences consist of four levels: critically low (More than one critical flaw with or without non-critical weaknesses), low (one critical flaw with or without non-critical weaknesses), moderate: (more than one non-critical weakness) and high (no or one non-critical weakness). Two authors (JL and GO) undertook the assessment of quality of included studies independently. Any disputes were discussed with the senior author (OK) to reach a consensus.

2.6. Recommendation review

Recommendations were extracted following analysis and data extraction. Levels of evidence and classes of recommendations were reported using "Grading of Recommendations Assessment, Development and Evaluation" (GRADE).[22].

3. Results

3.1. Results of the literature search

An initial search strategy to evaluate systematic reviews using adjunctive tools to diagnose or screen OSCC or OPMD produced 1293 publications. 372 articles were from MEDLINE/PubMed, 299 from Web of Science, 555 from Scopus and 67 from Cochrane Library. After the duplicates were removed, 1076 articles remained. After screening these articles via their titles and abstracts, 51 articles remained for full text evaluation. 24 articles did not meet the selection criteria (Supplementary Table 2), while 27 articles that met the selection criteria are

included in this study. (Fig. 1).

3.2. Study characteristics

The main characteristics of each included systematic review and meta-analysis are summarised in Table 1. Studies were published in a range of journals with Oral Oncology and the Journal of Oral Medicine & Pathology being the most prominent journals (with 3 studies each). 27 of the studies analysed were systematic reviews, while 12 of the studies included were meta-analyses. Regarding database searches MEDLINE/PubMed was used by all studies. Other database searches included Scopus, Web of Science, Embase, Cochrane Central Register of Controlled Trials, ScienceDirect, Livivo database, Medion and Multidisciplinary Digital Publishing Institute. Google Scholar was also included by some systematic reviews as a grey literature search. In the systematic reviews, the studies included ranged from 9 to 63. In the meta-analysis, the studies included ranged from 10 to 48 studies. The total amount of patients or lesions accessed in each review ranged from 536 to 7942. All studies examined either OSCC and/or OPMD. Of the 27 studies, 2 studies solely evaluated OSCC, and 6 studies evaluated only OPMDs and 19 studied evaluated a population of both OSCC and OPMDs as a mixed group. In analysing the risk of bias, 12 studies utilised QUADAS-2, 3 studies used a modified Newcastle-Ottawa Scale, and 7 studies had no risk of bias analysed. (Table 2).

Adjunctive tools evaluated in this analysis included light-based detection (chemiluminescence, autofluorescence, narrow band imaging, spectroscopy), vital staining and oral cytology. Regarding light-based detection techniques, there were 7 studies that evaluated chemiluminescence, 18 studies with autofluorescence, 6 with narrow band imaging and 3 with spectroscopy. There were 10 studies evaluating vital staining and 7 studies evaluating oral cytology. Specific devices and stains utilised included: Vizilite Plus with toluidine blue, ViziLite, MicroluxDL, Orascoptic DK, VELscope, Laser-induced Autofluorescence Spectroscopy, Diffuse Reflectance Spectroscopy, toluidine blue, Narrow Band Imaging, High-Resolution Microendoscopy (HRME), Optical Spectroscopy, oral brush cytology (Baby toothbrush Cytobrush, OralCDx, Orcellex), and Vital staining (toluidine blue, vital stain colorants). (Table 1).

3.3. Qualitative evaluation of systematic reviews and meta-analysis

The quality of each systematic review and meta-analysis was assessed through A Measurement Tool to Assess systemic Reviews (AMSTAR2). Following assessment, an overall confidence rating was given for each systematic review arranging from critical low quality to high quality of evidence depending on if it scored weaknesses in critical domains. 10 studies reached a high-quality overall rating, 3 studies had a moderate quality of evidence, 5 studies had a low quality of evidence and 9 studies had a critically low quality of evidence. (Fig. 2).

Critical items of AMSTAR2 are items 2, 4, 7, 9, 11, 13 and 15. Most studies provided an explicit statement of review methods prior to the conduct of the review in item 2. Item 4 reviews the use of comprehensive literature search strategy, and no studies displayed a high potential for bias. One common finding across most systematic reviews and meta-

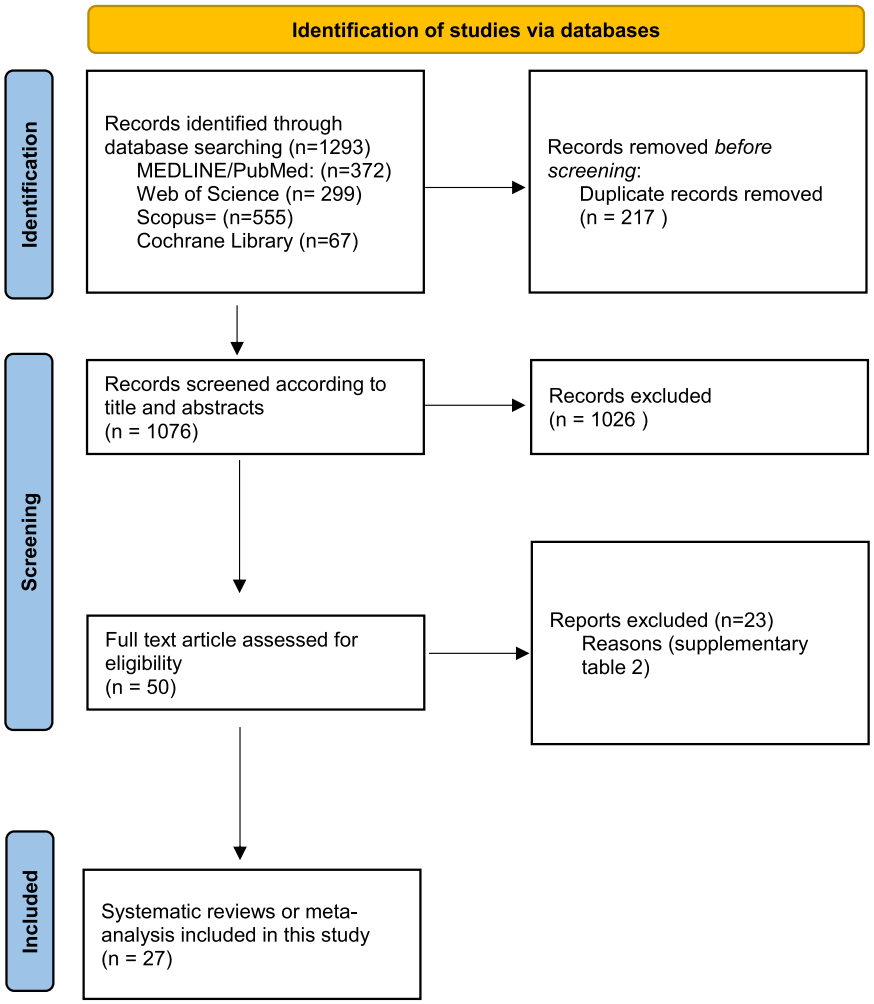

Fig. 1. Flow diagram of the identification and selection of systematic reviews and meta-analysis addressing adjunctive tools in the detection of OSCC and OPMD.

Table 1
Characteristics of the studies included in this systematic review of systemic reviews and meta-analysis.

Author	Journal published and impact factor (2021)	Type of study	Study population	Overall studies included	Reporting guidelines	Search strategy	Inclusion and exclusion criteria	Risk of bias analysis	Condition diagnosed	Adjunctive tools analysed	Statistically significant adjunctive tools or recommendations	Adjunctive tools with insufficient evidence	Funding or conflict of interest
Patton(2003) [23]	Oral Oncology (IF: 5.34)	systematic review	oral cancer	13 studies	none	MEDLINE EBM Reviews—ACP Journal Club Cochrane Controlled Trials Register Cochrane Database of Systematic Reviews	Inclusion criteria: effectiveness of adjunctive techniques	none stated	oral cancer	Oral Cytobrush Toluidine blue	Fair evidence to support use of toluidine blue to aid in the diagnosis of oral cancer	Insufficient evidence of Oral Cytobrush	No
Patton et al. (2008) [24]	The Journal of the American Dental Association (IF: 3.454)	systematic review	OPMD	23 studies	none	PubMed ISI Web of Sceiene Cochrane library (Feb 2008)	English language Studies with confirmed histological confirmation of lesions Data with sensitivity, specificity, positive predictive value, negative predictive value relative histopathology gold standard results	criteria by Hardorn et al.	OPMD	Toluidine blue Vizilite Plus with Toluidine Blue ViziLIte MicroluxDL Orascoptic DK VELscope OralCDx	None	Insufficient evidence to support or refute visually based examination adjuncts	Yes
Fuller et al. (2015) [25]	Journal of the sciences and specialities of the head and neck (IF: 3.82)	systematic review and meta-analysis	OPMD	48 studies (25 studies in quantitative synthesis)	PRISMA	PubMed Cochrane Library search	Inclusion: Oral cancer adjunct tested against gold standard tissue biopsy 10 or more patients studied English language publications only Published in peer-reviewed journal Adult population only Gold standard used for definitive diagnosis in all patients or in all patients within a prospectively-determined subgroup Adjunct attempts to diagnose dysplasia, rather than simply indicating a correlation Quantitative data	not stated	OPMD	Oral cytology Toluidine Blue Staining Laser-induced Autofluorescence Spectroscopy Diffuse Reflectance Spectroscopy	Most specific technique- was cytology (89.8%) Most accurate tests were diffuse reflectance spectroscopy (96.5%) Laser-induced autofluorescence (95.9%)	Least specific technique was toluidine blue (52.8%) Least accurate test was toluidine blue (66.7%)	No

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Table 1 (*continued*)

Author	Journal published and impact factor (2021)	Type of study	Study population	Overall studies included	Reporting guidelines	Search strategy	Inclusion and exclusion criteria	Risk of bias analysis	Condition diagnosed	Adjunctive tools analysed	Statistically significant adjunctive tools or recommendations	Adjunctive tools with insufficient evidence	Funding or conflict of interest
							presented that allows for the abstraction of 2 × 2 contingency table (disease vs. test result) If multiple tests evaluated, clinical characteristics could not be used to determine which adjunct was used Patients have no history of cancer No history or anticancer treatment for the lesion in question English language publications reporting primary studies disease studied: OSCC or OPMD optical device used for screening outcomes- positive/ negative results						
Rashid et al. (2015) [26]	Journal of Oral Pathology & Medicine (IF: 3.54)	systematic review	oral cancer OPMD	25 studies	none	MEDLINE Ovid PubMed		modified Newcastle-Ottawa Scale	OSCC OPMD	ViziLite Plus with toluidine blue ViziLite MicroLux D/L VELscope	Chemiluminescence and autofluorescence is better suited in specialist clinics	Limited evidence for chemiluminescence and autofluorescence in primary care	No
Awan et al. (2016) [27]	Journal of contemporary dental practice (IF: 1.01)	systematic review	oral cancer OPMD	11 studies	none	MEDLINE Ovid	Exclusion: experimental studies review articles letters to the editor unpublished data articles not in English	modified Newcastle-Ottawa Scale	OPMD Oral cancer	VELscope	Visually enhanced lesions showed high sensitivity values in detecting OPMD and malignant lesions	Insufficient evidence to show direct tissue fluorescence visualization has a capability to be used as an oral cancer screening tool	No
Nagi et al. (2016) [28]	Journal of Oral Medicine and Pathology (IF: 3.539)	systematic review	oral cancer OPMD	22 studies	none	PubMed Web Science	Inclusion: OSCC, OPMD Publications in English Exclusion: case reports, reviews	not stated	oral cancer OPMD	Clinical trials utilized ViziLite Microlux TM/DL Visual Enhanced Light scope (VELscope)	Large range of sensitivity with VELscope detecting malignancy Poor sensitivity of Vizilite	Both luminescence and chemiluminescence have limited ability to discriminate the high-risk lesions and have limitations which limit their use	No
Giovannacci et al. (2016) [29]	Journal of Oral Medicine and Pathology (IF: 3.539)	systematic review	oral cancer OPMD	35 studies	Oxford Evidence-based Medicine	MEDLINE Scopus Web of Knowledge	Exclusion: Not in English case reports, case series- less than 10 patients, editorials, conference proceedings studies that analysis COE, invasive	Oxford Evidence-based Medicine	oral cancer OPMD	Autofluorescence Toluidine blue Chemiluminescence associated with toluidine blue	None reported	Great inhomogeneity of the reported values	No

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Table 1 (*continued*)

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							diagnostic tools or minimally invasive diagnostic tools alone studies that analyse salivary biomarkers studies including other head and regions						
Alsarraf et al. (2018) [30]	Journal of Oral Medicine & Pathology (IF: 3.539)	systematic review	oral cancer OPMD	36 studies	PRISMA	MEDLINE EMBASE PubMed SCOPUS Cochrane Library Web of Science	Inclusion criteria: English language brush for oral mucosal cell collection from humans	not stated	oral cancer OPMD	Oral brush cytology: Baby toothbrush Cytobrush OralCDx Orcelle	Oral brush cytology with the use of liquid-based technology offers significant advantages compared to conventional exfoliative cytology	Brush cytology studies have shown poor sensitivity and specificity	No
Lingen et al. (2017) [31]	Journal of the American Dental Association (IF: 3.45)	systematic review	OPMD	37 studies	AMSTAR	MEDLINE Embase Cochrane Central Register of Controlled Trials to identify randomized controlled trials Diagnostic test accuracy patients' values and preferences	Inclusion criteria: cross-sectional, cohort diagnostic test accuracy (DTA) studies and randomized controlled trials (RCTs) Assessing effectiveness or accuracy of adjuncts. Exclusion criteria: case-control studies, case reports, case series, abstracts, uncontrolled reports	QUADAS-2	OPMD	Cytologic testing Autofluorescence Vital staining Salivary adjuncts	Cytologic testing appears to be the most accurate adjunct among those included in this review.	Studies assessing cytologic testing, autofluorescence were generally of low and very low quality	Yes
Bustiuc et al. (2018) [32]	International Journal of Medical Dentistry (IF: 2.44)	systematic review	oral cancer OPMD	15 studies	none	MEDLINE Science direct	Inclusion criteria: English language data on sensitivity and specificity light detection devices compared to gold standard histopathology	not stated	oral cancer	Light detection devices: VELscope ViziLite/Microlux/ DL	Velscope, Microlux/ DL, VIziLite devices can be used as supporting methods.	large range of sensitivity and specificity of VELScope, and chemiluminescent devices	No
Cicciu et al. (2019) [33]	Dentistry Journal (IF:2.77)	systematic review	oral cancer OPMD	25 studies	PRISMA	PUBMED EMBASE SCOPUS MDPI (Multidisciplinary Digital Publishing Institute).	Inclusion criteria: VELscope- assessing clinical efficiency RCT of clinical trials human studies	risk of bias performed where information was adequate	oral cancer OPMD	VELscope	None reported	VELscope does not have the capacity to discern between a benign lesion, a malignant one, or a simple acute inflammation.	No
Chaitanya et al.	South Asian journal of cancer (IF: 0.6)	systematic review and	oral cancer OPMD	12 studies	none	PubMed Cochrane	Exclusion criteria: Reports in languages other than English	not stated	dysplastic changes-OPMD	VELscope	None reported	Autofluorescence using devices may be used as adjunct to	No

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Table 1 (*continued*)

Author	Journal published and impact factor (2021)	Type of study	Study population	Overall studies included	Reporting guidelines	Search strategy	Inclusion and exclusion criteria	Risk of bias analysis	Condition diagnosed	Adjunctive tools analysed	Statistically significant adjunctive tools or recommendations	Adjunctive tools with insufficient evidence	Funding or conflict of interest
(2019) [34]		meta-analysis				EBSCO Google scholar	case reports, cohort studies, articles with only abstract being available and review articles.					determine the location of a biopsy in altered mucosal conditions.	
Tiwari et al. (2020) [35]	Oral Diseases (IF: 4.10)	systematic review	oral cancer OPMD	27 studies	PRISMA	MEDLINE Web of Science Embase Scopus	Inclusion criteria: Randomised, non-randomised control trials, prospective or retrospective cohort and cross-sectional studies in English Adopting autofluorescence tools in a general dental or specialist practitioner setting Investigating and evaluating the efficacy of both COE and Optical fluorescence imaging Studies had to report efficacy values or had enough data reported that these could be calculated.	QUADAS-2	oral cancer OPMD	Optical fluorescence imaging	None reported	Only six of the 27 included studies showed a low risk of bias that have demonstrated promising results for the role of adjunctive optical fluorescence imaging to COE.	Yes
Kim et al. (2020) [36]	Journal of the sciences and specialities of the head and neck (IF: 3.82)	systematic review	oral cancer OPMD	28 studies	SROC analysis - summary receiver operating characteristic	PubMed the Cochrane Central Register of Controlled Trials Embase Web of Science SCOPUS Google Scholar	Inclusion criteria: use of autofluorescence prospective or retrospective study comparison of autofluorescence with toluidine blue staining or clinical examination sensitivity and specificity analyses evaluation of inter-rater agreement.	QUADAS-2	oral cancer OPMD	Autofluorescence toluidine blue staining.	Diagnostic odds ratio for autofluorescence was 8.197	autofluorescence and toluidine blue staining can not reliably be used alone for screening or a diagnostic workup.	Yes
Buenahora et al. (2021) [37]	Clinical Oral Investigations (IF: 3.61)	systematic review and meta-analysis	oral cancer OPMD	40 studies	Protocol registered by PROSPERO	MEDLINE EMBASE	Inclusion criteria: adult patients with OPMD, oral cancer comparison of visual inspection, light based test, biopsy of lesions	QUADAS-2	oral cancer OPMD	Autofluorescence chemiluminescence	autofluorescence (sensitivity: 86%, specificity: 72%)	chemiluminescent (sensitivity: 67%, specificity: 48%)	No
Mazur et al. (2021) [38]	International Journal of Environmental	systematic review and	OPMD	43 studies-qualitative synthesis,	PRISMA	MEDLINE (PubMed) Scopus	Inclusion criteria: studies published in English, French,	Jadad Scale Newcastle-Ottawa scale	OPMD	Imaging-based techniques: Autofluorescence	Promising results of narrow band imaging	No technique can replace biopsy as the gold standard	No

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Table 1 (*continued*)

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	Research and Public Health (IF: 4.61)	meta-analysis		34 papers-meta-analysis		Google Scholar Cochrane Library	German, Spanish, Polish, Albanian, and Romanian. randomized clinical trials (RCTs), clinical trials, cohort studies, cross-sectional studies, case control studies, pilot studies, prospective, observational studies Use of imaging band techniques	Cochrane guidelines		High-Resolution Microendoscopy Optical Spectroscopy Narrow Banding Imaging Vital Stain Colorants			
Moffa et al. (2021) [39]	Oral Oncology (IF: 5.34)	systematic review and Meta-analysis	oral cancer OPMD	26 studies	PRISMA-DTA	SCOPUS PubMed/ MEDLINE Google Scholar	Inclusion criteria: Examination of OMPD or oral cancer with autofluorescence or chemiluminescence retrospective and prospective cohort studies. Exclusion criteria: studies not in English, insufficient data less than 10 sample size	QUADAS-2	oral cancer OPMD	Autofluorescence chemiluminescence	High sensitivity of autofluorescence and chemiluminescence	Poor specificity, and reduction of the false positive rate of both autofluorescence and chemiluminescence compared with COE.	No
Lima et al. (2021) [40]	Photodiagnosis and Photodynamic Therapy (IF: 3.43)	systematic review	oral cancer	45 studies	PRISMA	PubMed Scopus Embase Web of Science	Inclusion criteria: autofluorescence and fluorescent probes diagnosis, treatment of oral cancer in humans	The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Diagnostic Test Accuracy Studies	oral cancer	Autofluorescence-VELscope fluorescent	Autofluorescence and fluorescent probes can provide an accurate diagnosis of oral cancer	None reported	No
Saraniti et al. (2021) [41]	Iranian Journal of Otorhinolaryngology (IF: 0.259)	systematic review	oral cancer OPMD	9 studies	PRISMA	PubMed Scopus Web of Science	Inclusion criteria: use of NBI in patients affected by oral cavity lesions Exclusion criteria: languages other than English	none stated	oral cancer OPMD	Narrow Band Imaging	NBI has a higher specificity, sensitivity, positive and negative predictive values and accuracy compared to white light examination	None reported	No

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Table 1 (*continued*)

Author	Journal published and impact factor (2021)	Type of study	Study population	Overall studies included	Reporting guidelines	Search strategy	Inclusion and exclusion criteria	Risk of bias analysis	Condition diagnosed	Adjunctive tools analysed	Statistically significant adjunctive tools or recommendations	Adjunctive tools with insufficient evidence	Funding or conflict of interest
Kim et al. (2021) [42]	Journal of Clinical Otolaryngology (IF: 2.72)	systematic review and meta-analysis	oral cancer OPMD	10 studies	QUADAS-2	PubMed Scopus Web of Science Embase Google Scholar Cochrane Central Register of Controlled Trials	Inclusion criteria: Use of NBI - prospective or retrospective study comparison of NBI, WLI	QUADAS-2	oral cancer OPMD	Narrow Band Imaging	Narrow-band imaging considered more accurate than white-light imaging when using the class III criteria	None reported	No
Walsh et al. (2021) Updated paper from Macey et al. 2015 [43]	Cochrane Database of Systematic Reviews (IF: 11.87)	systematic review	oral cancer OPMD	63 studies	QUADAS-2	MEDLINE Ovid Cochrane Diagnostic Test Accuracy Studies Register EMBASE MEDION	Inclusion: OPMD, OSCC cross-sectional diagnostic tests randomised studies Exclusion: not specifying reference standard	QUADAS-2	OPMD Oral cancer	Vital staining cytology light-based detection	Adjunctive tests cannot be recommended as replacement of gold standard scalpel biopsy and histological assessment	Overall-poor quality of studies	Yes
Dos Santos et al. (2022) [44]	Photodiagnosis and Photodynamic Therapy (IF: 3.43)	systematic review and meta-analysis	OPMD	25 studies	PRISMA	PubMed Scopus Web of Science LIVIVO databases	Inclusion criteria: Tissue autofluorescence regarding OMPD Exclusion criteria: Languages other than English	Joanna Briggs Institute Critical Appraisal Checklist for Diagnostic Test Accuracy Studies.	OPMD	Tissue autofluorescence	None reported	Promising results regarding auto-fluorescence based methods	Yes
Kim DH et al. (2022) [45]	Brazilian Journal of Otorhinolaryngology (IF: 2.48)	meta-analysis	oral cancer OPMD	22 studies	Preferred Items of Systematic Reviews and Meta-analysis for NMA	MEDLINE SCOPUS The Cochrane Register of Controlled Trials Google scholar	Inclusion criteria: use of non-invasive adjunctive diagnostic tools prospective or retrospective study protocol	QUADAS-2	OPMD Oral cancer	AutofluorescenceC hemiluminescenceC ytology Narrow band imagingT oluidine blue	NBI is useful in detecting OPMD.	Autofluorescence, chemiluminescence, cytology, and toluidine blue have little benefit.	Yes
Shaw et al. (2022) [46]	Journal of Clinical and Diagnostic Research (1.15)	systematic review and meta-analysis	OPMD	24 studies	PRISMA-DTA	PubMed Google Scholar EBSCOhost	Inclusion criteria: Observational studies or Clinical trials comparing the diagnostic accuracy of chemiluminescence. OMPD diagnosis	QUADAS-2	OPMD	Chemiluminescence	Chemiluminescence overall had good sensitivity and specificity values along with good AUC.	None reported	No
Kim DH et al. (2022) [47]	Brazilian Journal of Otorhinolaryngology (IF: 2.48)	systematic review and meta-analysis	oral cancer OPMD	16 studies	None reported	MEDLINE SCOPUS Embase The Cochrane Register of Controlled Trials Google scholar	Inclusion criteria: use of chemiluminescence prospective or retrospective study protocol comparison of chemiluminescence with toluidine blue or clinical examination	QUADAS-2	OPMD Oral cancer	Chemiluminescence	Chemiluminescence overall has good sensitivity.	Chemiluminescence is comparable or worse than toluidine blue and clinical examination	Yes

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Table 1 (*continued*)

Author	Journal published and impact factor (2021)	Type of study	Study population	Overall studies included	Reporting guidelines	Search strategy	Inclusion and exclusion criteria	Risk of bias analysis	Condition diagnosed	Adjunctive tools analysed	Statistically significant adjunctive tools or recommendations	Adjunctive tools with insufficient evidence	Funding or conflict of interest
Mendonca et al. (2022) [48]	Oral Oncology (IF: 5.34)	systematic review and meta-analysis	oral cancer OPMD	44 studies	PRISMA	PubMed Science direct Cochrane Library electronic database	Inclusion criteria: original research histopathology as the gold standard of diagnosis non-invasive imaging is used for screening, as a diagnostic tool	QUADAS-2	OPMD Oral cancer	Autofluorescence (AFI) Chemiluminescence (CHEM) Narrow Band Imaging (NBI) Fluorescence Spectroscopy (FS) Diffuse Reflectance Spectroscopy (DRS) 5aminolevulinic acid induced protoporphyrin IX fluorescence (5ALA)	Analysed non-invasive imaging techniques suggest higher accuracy levels in the diagnosis of OSCC when compared to dysplastic OPMDs	None reported	No
Zhang et al. (2022) [49]	Frontiers in surgery (IF: 2.57)	systematic review and meta-analysis	oral cancer OPMD	11 studies	PRISMA	PubMed Science direct Cochrane Library Embase	Inclusion criteria: OSCC, OPMD detected by narrow band imaging Classification of narrow band imaging based on IPCL grading	QUADAS-2	OPMD Oral cancer	Narrow Band Imaging	Narrow band imaging is a promising adjunctive tool for identifying malignant transformations of OPMDs.	None reported	Yes

Table 2
Summary of findings of included systematic reviews and meta-analysis.

Author	Number of studies	Number of participants or lesions	Adjunctive tools with sufficient evidence	Adjunctive tools with insufficient evidence	Overall sensitivity, specificity, accuracy, positive predictive value or negative predictive value	Overall recommendation and conclusion	Publication bias	Methodological limitations
Patton (2003) [23]	13	Participants 4872	Toluidine blue	Oral Brush cytology-OralCDx	Toluidine blue (sensitivity: 72 - 100%, specificity: 45-93%)	Fair evidence to support use of toluidine blue to aid in the diagnosis of oral cancer	Not reported	No reporting guidelines for systematic reviews (eg PRISMA) English language restriction Titles and abstracts not duplicated by multiple people Publication of bias analysis not specifically evident
Patton et al. (2008)[24]	23	subjects: 3687 lesions: 3323	Toluidine blue	Insufficient evidence to support or refute the use of visually based examination adjuncts. Chemiluminescence: ViziLite	Toluidine blue (median sensitivity: 85%, median specificity: 67%, median PPV: 85%, median NPV: 83%) ViziLite (median sensitivity: 100%, median specificity: 0%, median PPV: 20%, median NPV: 0%)	Toluidine blue is an effect diagnostic adjunct for OPMD	Not reported	No reporting guidelines for systematic reviews (eg PRISMA) English language restriction Titles and abstracts not duplicated by multiple people Publication of bias analysis not specifically evident
Fuller et al. (2015)[25]	48	Subjects: 2184 lesions: 1887	Oral cytology Diffuse reflectance spectroscopy Laser-induced autofluorescence	Toluidine Blue	Cytology (sensitivity: 89.8%, specificity: 89.8%, accuracy: 85.7%) diffuse reflectance spectroscopy (sensitivity: 98.6%, specificity: 83.2%, accuracy: 96.5%) Laser-induced autofluorescence (sensitivity: 97.7%, specificity: 84.4%, accuracy: 95.9%) Toluidine blue (sensitivity: 82.1%, specificity: 52.8%, accuracy: 66.7%)	Significant improvement in diagnostic quality of oral cytology	Not reported	English language restriction Publication of bias analysis not specifically evident
Rashid et al. (2015)[26]	25	subjects: 1133 lesions: 1182	Chemiluminescence and autofluorescence is better suited in specialist clinics	Limited evidence for chemiluminescence and autofluorescence in primary care	VELscope (sensitivity: 30-100%) ViziLite (sensitivity: 77.3-100%) ViziLite with toluidine blue (sensitivity: 0-59%)	Limited evidence for chemiluminescence and autofluorescence in primary care	Modified Newcastle-Ottawa Scale (NOS)	No reporting guidelines for systematic reviews (eg PRISMA) English language restriction
Awan et al. (2016)[27]	11	subjects: 3838	None reported	Autofluorescence: VELscope	VELscope (sensitivity: 30-100%, specificity: 15-92.3%, PPV: 6.4-58.1%, NPV: 57.1-100%)	Insufficient evidence to show direct tissue fluorescence visualization has a capability to be used as an oral cancer screening tool	Not reported	English language restriction No reporting guidelines for systematic reviews (eg PRISMA) Titles and abstracts not duplicated by multiple people

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Table 2 (*continued*)

Author	Number of studies	Number of participants or lesions	Adjunctive tools with sufficient evidence	Adjunctive tools with insufficient evidence	Overall sensitivity, specificity, accuracy, positive predictive value or negative predictive value	Overall recommendation and conclusion	Publication bias	Methodological limitations
Nagi et al. (2016)[28]	22	subjects: 543	None reported	Chemiluminescence: ViziLite Autofluorescence: VELscope	ViziLite (sensitivity: 77.1-100%, specificity: 0-27.8%) VELscope (sensitivity: 22-100%, specificity: 16-100%)	Both chemiluminescence and autofluorescence may aid an experienced clinician. In literature, limited discrimination in high risk lesions.	Not reported	English language restriction No reporting guidelines for systematic reviews (eg PRISMA) Titles and abstracts not duplicated by multiple people
Giovannacci et al. (2016) [29]	35	patients: 3137	None reported	Autofluorescence Chemiluminescence Toluidine blue Chemiluminescence associated with toluidine blue	Autofluorescence: sensitivity (mean: 72.4% range: 20-100%) specificity: (mean: 63.75%, range 15-100%), PPV: mean 55.74%, NPV: mean: 79.76% Chemiluminescence: sensitivity (mean: 86.75% range 69.6-100%). Specificity: (mean: 38.37- range: 14.2%–81.5%) PPV: mean 74.5%, NPV: mean: 63% Toluidine blue: sensitivity (mean: 72.5%, range: 56.1-95%) specificity: mean: 61.4% range: 25-74%)PPV: mean 58.16%, NPV: mean: 95.3% chemiluminescence associated with toluidine blue: sensitivity (mean: 53.93% range 0-81.8%). Specificity: (mean: 66.44- range: 37.5%–97.5%) mean 87.2%, NPV: mean: 76.1%	Great inhomogeneity of the reported values	Not reported	English language restriction No reporting guidelines for systematic reviews (eg PRISMA)
Alsarraf et al. (2018)[30]	36	lesions: 4302	None reported	Brush cytology	Brush cytology (sensitivity: 60-100%, specificity: 32-100%)	Meaningful evidence-based recommendations cannot be given from this study.	Not reported	English language restriction
Lingen et al. (2017)[31]	37	lesions: 5390	Cytology	Autofluorescence vital staining Tissue reflectance Cytologic testing and vital staining together	Cytology (sensitivity: 92%, specificity: 94%) Autofluorescence (sensitivity: 90%, specificity: 72%) vital staining (sensitivity: 87%, specificity: 71%) Tissue reflectance (sensitivity: 75, specificity: 31%) Cytologic testing and vital staining together (sensitivity: 95%, specificity: 68%)	Cytologic testing used in suspicious lesions appears to have the highest accuracy among adjuncts	QUADAS-2	Studies identified only covered secondary and tertiary settings
Bustiuc et al. (2018)[32]	15	Lesions: 2364	None reported	Autofluorescence: VELscope Chemiluminescent devices	Velscope (sensitivity: 22-100%, specificity: 8.4-96.3%) Chemiluminescent devices (sensitivity: 67-100%, specificity: 10-100%)	Velscope, Microlux/DL, VIziLite devices can be used assupporting methods.	Not reported	English language restriction No reporting guidelines for systematic reviews (eg PRISMA) Titles and abstracts not duplicated by multiple people

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Table 2 (*continued*)

Author	Number of studies	Number of participants or lesions	Adjunctive tools with sufficient evidence	Adjunctive tools with insufficient evidence	Overall sensitivity, specificity, accuracy, positive predictive value or negative predictive value	Overall recommendation and conclusion	Publication bias	Methodological limitations
Cicciu et al. (2019)[33]	25	Lesions: 1693	None reported	Autofluorescence: VELscope	VELscope (sensitivity mean: 70.19%, sensitivity range: 8.4-100%, specificity mean: 66.95%, specificity range: 8.4-100%)	VELscope does not have the capacity to discern between a benign lesion, a malignant one, or a simple acute inflammation.	Risk of bias analysis completed	English language restriction
Chaitanya et al. (2019)[34]	12	patients: 1643	None reported	Autofluorescence: VELscope	VELscope (sensitivity: 40%, specificity: 80%)	Autofluorescence using devices may be used as adjunct to find the exact location of the biopsy in altered mucosal conditions.	Not reported	English language restriction No reporting guidelines for systematic reviews (eg PRISMA) Titles and abstracts not duplicated by multiple people
Tiwari et al. (2020)[35]	27	sample size: 6415	None reported	Autofluorescence - varied sensitivity and sensitivity-large range	Autofluorescence (sensitivity: 17-99.2%, specificity: 38-97.9%)	Optical fluorescence should be used as a clinical adjunct rather than a specific diagnostic adjunct	QUADAS-2	English language restriction
Kim et al. (2020) [36]	28	sample size: 1166	None reported	Autofluorescence Toluidine blue	Autofluorescence (sensitivity: 79.1%, specificity: 50.9%, NPV: 59.8%) Toluidine blue (sensitivity: 75.4%, specificity: 60.3%, NPV: 68.5%)	autofluorescence and toluidine blue staining can not reliably be used alone for screening or a diagnostic workup.	QUADAS-2	English language restriction
Buenahora et al. (2021)[37]	40	autofluorescence sample size: 5562 chemiluminescence sample size: 1353	Autofluorescence	Chemiluminescent	autofluorescence (sensitivity: 86%, specificity: 72%) chemiluminescent (sensitivity: 67%, specificity: 48%)	Autofluorescence devices displayed superior accuracy levels in the identification of premalignant lesions and early neoplastic changes	QUADAS-2	Only 2 database searches were used
Mazur et al. (2021)[38]	43 studies-qualitative synthesis, 34 papers-meta-analysis	Vital staining: 536	None reported	Autofluorescence High-Resolution Microendoscopy (HRME) Optical Spectroscopy Narrow Banding Imaging Vital Stain Colorants	Autofluorescence: I^2: 84.7% Q= 71.67 High-Resolution Microendoscopy (HRME): I^2: 77.6% Q= 18.27 Optical Spectroscopy: I^2: 80% Q= 30.18 Narrow Banding Imaging: I^2: 19.7% Q= 1.24 Vital Stain Colorants: I^2: 87.6% Q= 36.63	No technique can replace biopsy as the gold standard	Jadad Scale Newcastle-Ottawa scale Cochrane guidelines	Language restriction to English, French, German, Spanish, Polish, Albanian, and Romanian. No excluded list of studies published
Moffa et al. (2021)[39]	26 studies	2631 oral lesions	None reported	Autofluorescence Chemiluminescence	Autofluorescence (sensitivity: 81.3%, specificity: 52.1%) chemiluminescence (sensitivity: 84.9%, specificity: 51.8%)	Poor specificity, and reduction of the false positive rate of both autofluorescence and chemiluminescence compared with COE.	QUADAS-2	English language restriction Studies with a sample size under 10 patients
Lima et al. (2021)[40]	45 studies		None reported	Autofluorescence: VELscope 5-Aminolevulinic acid	VELscope (sensitivity: 33-100%, specificity: 12-88.6%) 5-Aminolevulinic acid (sensitivity: 90-100%, specificity: 51-96%)	Autofluorescence and fluorescent probes can provide an accurate diagnosis of oral cancer, but can not replace histopathology	The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews Checklist for Diagnostic Test Accuracy Studies	No excluded list of studies published

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Table 2 (*continued*)

Author	Number of studies	Number of participants or lesions	Adjunctive tools with sufficient evidence	Adjunctive tools with insufficient evidence	Overall sensitivity, specificity, accuracy, positive predictive value or negative predictive value	Overall recommendation and conclusion	Publication bias	Methodological limitations
Saraniti et al. (2021)[41]	9 studies	number of lesions: 1507	None reported	Narrow band imaging	Narrow band imaging- large range of sensitivities, specificity, PPV and NPV	NBI has a higher specificity, sensitivity, positive and negative predictive values and accuracy compared to white light examination	not reported	English language restriction Publication of bias analysis not specifically evident
Kim et al. (2021) [42]	10 studies	patients: 1374	Narrow Band Imaging- class III	Narrow Band Imaging - Class I or class II criteria:	Narrow band imaging- class III pooled sensitivity: 88.5%, pooled specificity: 90.1%, pooled NPV: 96.7%) Narrow band Imaging - Class I or class II: sensitivity: 79.1% (class I), 95.6% (class II) specificity: 29.7% (class I), 19.9% (class II)	NBI considered more accurate than white-light imaging when using the class III criteria	QUADAS-2	No reporting guidelines for systematic reviews (eg PRISMA) Selection criteria was not detailed
Walsh et al. (2021) Updated paper from Macey et al. 2015 [43]	63 studies	lesions: 7942	None reported	Vital staining Cytology Light-based detection	vital staining (overall sensitivity: 86%, specificity: 68%) cytology (overall sensitivity: 90%, specificity: 94%) light-based detection (overall sensitivity: 87%, specificity: 50%)	adjunctive tests cannot be recommended as replacement of gold standard scalpel biopsy and histological assessment	QUADAS-2	no excluded list of studies published
Dos Santos et al. (2022)[44]	25 studies	patients: 2249	None reported	Autofluorescence: VELscope	VELscope (sensitivity: 74%, specificity: 57%)	Promising results regarding auto-fluorescence based methods	Joanna Briggs Institute Critical Appraisal Checklist for Diagnostic Test Accuracy Studies.	English language restriction no excluded list of studies published
Kim DH et al. (2022)[45]	24 studies	patients: 1914	Narrow band imaging	Autofluorescence Chemiluminescence Cytology Toluidine blue	Narrow band imaging (sensitivity: 77.9%, specificity: 83.5%, NPV: 83.5%, PPV: 72.5%, accuracy: 90.8%) cytology (sensitivity: 72.1%, specificity: 86.2%, NPV: 84.9%, PPV: 75.1%, accuracy: 81.9%) Autofluorescence (sensitivity: 85.6%, specificity: 48.8%, NPV: 86.6%, PPV: 49.3%, accuracy: 66.4%) chemiluminescence (sensitivity: 87.5%, specificity: 56.8%, NPV: 83.3%, PPV: 66.4%, accuracy: 74.5%) toluidine blue (sensitivity: 71.4%, specificity: 81.1%, NPV: 70.8%, PPV: 81.1%, accuracy: 75.9%)	narrow band imaging showed higher sensitivity, specificity, negative predictive value, positive predictive value	QUADAS-2	no excluded list of studies published
Shaw et al. (2022)[46]	24 studies	patients: 1783	Chemiluminescence of OPMDs including: Leukoplakia Oral lichen planus Oral sub mucous fibrosis	None reported	Chemiluminescence- accuracy of Leukoplakia (sensitivity: 75% specificity: 98%) OLP (sensitivity: 78%, specificity: 60%) Oral sub mucous fibrosis	Chemiluminescence overall had good sensitivity and specificity values for the diagnosis of OPMDs.	QUADAS-2	no excluded list of studies published

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Table 2 (*continued*)

Author	Number of studies	Number of participants or lesions	Adjunctive tools with sufficient evidence	Adjunctive tools with insufficient evidence	Overall sensitivity, specificity, accuracy, positive predictive value or negative predictive value	Overall recommendation and conclusion	Publication bias	Methodological limitations
Kim DH et al. (2022)[47]	16 studies	patients: 998	None reported	Chemiluminescence Toluidine blue	(sensitivity: 89%, specificity: 76%) Chemiluminescence (sensitivity: 83.1%, specificity: 41.5%, NPV: 67.4%) Toluidine blue (sensitivity: 83.2%, specificity: 42.9%, NPV: 74.7%)	chemiluminescence is comparable or worse than toluidine blue and clinical examination	QUADAS-2	Limited information on included studies no excluded list of studies published No reporting guidelines for systematic reviews (eg PRISMA)
Mendonca et al. (2022)[48]	44 studies	lesions: 3317	Detection of dysplastic OPMD: Autofluorescence Chemiluminescence Narrow Band Imaging Fluorescence Spectroscopy Diffuse Reflectance Spectroscopy 5-aminolevulinic acid induced protoporphyrin IX fluorescence	Detection of OSCC: Autofluorescence Narrow Band Imaging Fluorescence Spectroscopy Diffuse Reflectance Spectroscopy	Detection of dysplastic OPMD: Autofluorescence (sensitivity: 75%, specificity: 50%) Chemiluminescence (sensitivity: 74%, specificity: 47%) Narrow Band Imaging (sensitivity: 31%, specificity: 90%) Fluorescence Spectroscopy (sensitivity: 72%, specificity: 96%) Diffuse Reflectance Spectroscopy (sensitivity: 79%, specificity: 86%) 5aminolevulinic acid induced protoporphyrin IX fluorescence (sensitivity: 91%, specificity: 78%) Detection of OSCC: Autofluorescence (sensitivity: 0.96, specificity: 0.58) Narrow Band Imaging (sensitivity: 0.97, specificity: 0.89) Fluorescence Spectroscopy (sensitivity: 0.93, specificity: 0.97) Diffuse Reflectance Spectroscopy (sensitivity: 0.93, specificity: 0.90)	Analysed non-invasive imaging techniques suggest higher accuracy levels in the diagnosis of OSCC when compared to dysplastic OPMDs	QUADAS-2	English language restriction no excluded list of studies published
Zhang et al. (2022)[49]	11 studies	patients: 1179	Narrow band imaging IPCL II lesions		Narrow band imaging – IPCL II lesions: Sensitivity: 87%, specificity: 83%	Narrow band imaging is a promising adjunctive tool for identifying malignant transformations of OPMDs.	QUADAS-2	No excluded list of studies published

Fig. 2. Plot representing the risk of bias, assessed using AMSTAR II.

analyses was that studies did not explicitly provide an excluded list of studies except for 3 studies as noted in item 7. When using a satisfactory technique for assessing the risk of bias in item 9, 4 studies had a high risk of bias with limited to no risk of assessing bias, and 8 studies had a moderate potential for bias. Item 11 addresses the appropriate methods for statistical combination in meta-analysis. All studies with a meta-analysis addressed this item appropriately. When discussing or interpreting results, 1 study had a high potential for bias by not accounting for risk of bias- item 13. In item 15, small study bias and its likely impact, all studies scored either a low or moderate risk of bias.

4. Overview of effectiveness of primary oral examination adjunctive tools

4.1. Light based detection systems

Regarding light-based detection techniques of chemiluminescence and tissue autofluorescence, there is insufficient evidence for their use as adjunctive tools. Several studies noted a large range of sensitivities and specificities (Table 2). Awan et al. noted a range of sensitivity of 22–100%, and specificity of 16–100% in detecting both OSCC and OPMD.[27] Similarly, Cicciu et al. and Bustiuc et al., in their systematic reviews, also noted a large range with sensitivities of 8.4–100% and specificities of range 8.4–100%.[32,33] In a meta-analysis, Walsh *et al.*, in their Cochrane Review, reported the overall sensitivity of light based detection techniques as 87% with a specificity of 50% in detecting OPMDs and OSCC.[43] Bustiuc et al. specifically assessed its use for oral cancer screening, and concluded that both chemiluminescence and tissue autofluorescence could only be considered as supporting methods.[32] Kim et al. reported that autofluorescence and chemiluminescence had a lower specificity than visual examination.[45].

4.2. Narrow band imaging

There were 6 systematic reviews and/or meta-analysis that discussed the effectiveness of narrow band imaging as an adjunctive tool for diagnosing OSCC or OPMD. Zhang et al. in a meta-analysis reported it to have relatively high overall diagnostic accuracy for the malignant transformation of OPMD for intraepithelial papillary capillary loop (IPCL) grade II lesions, with a sensitivity of 87% and a specificity of 83% across 11 studies among a total of 1179 analysed patients.[49] In another study, Mendonca et al. noted a significant difference in the accuracy of NBI between the detection of dysplastic OPMD and OSCC. In detecting dysplastic OPMD, the reported sensitivity was 31% and specificity was 90%, and for detection of OSCC, a sensitivity of 97% and specificity of 89% were reported.[48] In another systematic review and

meta-analysis study by Kim et al., there was a clear difference in sensitivity and specificity between IPCL grading of grade III compared with either grade 1 or 2. A pooled sensitivity of 88.5% and a pooled specificity of 90.1% was found for IPCL grade III. In comparison, IPCL grade 1 had a pooled sensitivity of 79.1% and specificity of 29.7%; and grade II had a sensitivity of 95.6% and specificity of 19.9%.[42].

5. Overview of effectiveness of secondary oral adjunctive tools

5.1. Vital staining

In the systematic reviews analysed, toluidine blue was the most assessed vital staining technique. There was a total of 8 reviews that analysed the effectiveness of toluidine blue as an adjunctive tool. The results were variable. Patton reported a sensitivity of between 72–100% and a specificity of 45–93% when assessing its use in detecting OSCC.[23] In a meta-analysis and systematic review assessing OPMDs, Fuller reported toluidine blue as the least accurate and the least specific technique of all the adjunctive tools tested at 66.7% and 52.8% respectively.[25] Adding to the variable results, Walsh *et al.* reported an overall sensitivity of 86% and a specificity of 50% regarding vital staining in detecting OPMDs and OSCC.[43] Similarly, Lingen *et al.* reported an overall sensitivity of suspicious lesions of 87% and a specificity of 71%.[31].

5.2. Cytology techniques

Six of the study's systematic reviews analysed reviewed cytology, particularly oral brush biopsy. Overall the accuracy of cytology is reasonable, although authors have variable conclusions about its clinical viability. In a systematic review of 37 papers and a total of 5390 lesions, Lingen *et al.* reported an overall sensitivity of 92% and specificity of 94% in diagnosing OPMDs.[31] The study reported it appeared to have the highest accuracy among adjuncts tested, including autofluorescence, vital staining and tissue reflectance. In a Cochrane review by Walsh et al., the authors summarised estimates obtained from their meta-analysis for oral cytology with a sensitivity of 90% (95% confidence interval of 82 to 94%) and a sensitivity of specificity of 94% (95% confidence interval of 88 to 97%) in detecting OPMDs and OSCC. This was across 20 studies with a moderate level of certainty of evidence.[43] In contrast, Alsarraf et al., in a systematic review, concluded that brush cytology studies have shown poor sensitivity and specificity and that no evidence-based recommendations could be drawn from the study.[30].

6. Discussion

6.1. Mechanisms of Adjunctive Tools

6.1.1. Light based detection systems

Light based detection systems utilise the principles of tissue reflectance, refraction and tissue autofluorescence. When mucosal tissue undergoes changes, such as dysplasia, it may undergo abnormal metabolic or structural changes. When the tissue is exposed to specific wavelengths of light, a different absorbance or reflectance profile may result. Generally, they can be subdivided into several categories including tissue fluorescence imaging, chemiluminescence and tissue fluorescence spectroscopy.

6.1.2. Tissue fluorescence imaging:

Tissue fluorescence imaging utilises a monochromatic light and facilitates the visualisation of fluorescence of the oral cavity of the oral cavity. Tissue fluorescence includes many commercial products including VELscope, Identafi 3000, Bioscreen, Oral ID, etc. When a specific wavelength of light, i.e. between 400 nm and 460 nm for VELscope, is emitted into the oral cavity, endogenous fluorophores become excited. Examples of fluorophores oxidized flavin adenine dinucleotide (FAD), nicotine adenine dinucleotide (NADH), collagen, elastin and keratin.[50] Overall, the principles of tissue fluorescence are due to scattering, absorption and reflection of light from the surface. Where there is cellular atypia or alterations, a concentration of fluorophores can be observed, resulting in a different profile of scattering and absorption of light. In the event of dysplastic tissue, a loss of fluorescence can be visualised.

6.1.3. Tissue fluorescence spectroscopy

Tissue fluorescence spectroscopy includes narrow band imaging (NBI). NBI utilises blue and green light with retrospective wavelengths of 415 and 540 nm. These specific wavelengths of light are able to penetrate the mucosal surface are subsequently absorbed by superficial blood vessels. Comparing white light to NBI, the contrast of blood vessels in NBI is significantly increased providing images of distinct capillaries.[49].

Currently, the classification of NBI is based on vascularity morphology, especially the intraepithelial papillary capillary loop (IPCL) approach. IPCL-I and IPCL-II indicate normal and inflammatory mucosa. IPCL-1 contains normal mucosa and brown spots. IPCL-II features dilation and crossing of blood vessels. IPCL-III and part of IPCL-IV can be categorised as borderline between benign and malignant lesions. IPCL-III has features of elongation and winding of vessels, and IPCL- IV shows destruction of structure and winding vessels. IPCL-V1 indicates carcinoma in situ, with features of dilatation, calibre change, meandering and non-uniformity of IPCL.[51].

6.1.4. Chemiluminescence

Chemiluminescence is a tissue based reflectance device that can be utilised to detect abnormal tissues. Some common commercial brands include ViziLite Plus and Microlux D/L. Regarding its mechanism of action, the mouth is initially rinsed with acetic acid. Surface coagulation of cellular proteins and cell dehydration ensues. There is also a reduction in cellular transparency. Malignant or dysplastic tissue has an increased nucleus to cytoplasmic ratio, which will lead to an increased light reflectance.[52] As a result, normal cells typically appear blue under chemiluminescence, while abnormal cells may appear white.

6.1.5. Vital staining

The most commonly used vital stain in adjunctive tools for diagnosing OSCC or OPMD is toluidine blue. Other forms of vital staining include 5% acetic acid, methylene blue, Lugol's iodine, Rose Bengal and iodine staining. Toluidine blue is also known as tolonium chloride and is a basic thiazine metachromatic dye.

Toluidine blue was the only vital staining technique used as an adjunctive tool included in systematic reviews that fit our diagnostic criteria. Toluidine blue can be used both *in vivo* and *in vitro*. As a metachromatic dye, it selectively binds to free anionic groups including phosphate, sulphate and carboxylate radicals of large molecules. Its clinical application stems from the fact that it can bind to phosphate groups of nucleic acids, which are noted in intercellular space of epithelial dysplasia.[53] Where there is a loss of heterozygosity, malignant or tissue with dysplasia may retain toluidine blue.[54] The benefits of toluidine blue are that it is practical, rapid and inexpensive.

6.1.6. Cytology techniques

Cytopathology is considered a secondary examination technique. It is the microscopic study of cell samples. It may be collected from mucosal surfaces or internal sites via techniques such as fine needle aspiration.[50] Adjunctive techniques typically utilised for OSCC or OPMD include oral brush cytology and liquid based cytology. Liquid based samples are where the tissue sample is immediately fixed in a liquid medium after being obtained.

6.1.7. Oral brush cytology

Oral brush cytology is considered a minimally invasive technique,

safe and generally painless.[55,56] Epithelial cells are collected from the area of interest. Superficial cells can be scraped, and a cytology brush can remove cells from deeper layers of epithelium. The collected samples are fixed, stained and analysed via a microscopic by a cytopathologist. In some cases, computer assisted brush cytology (OralCDx) can be utilised ~~which~~ to detect precancerous and cancerous cells. The computer technology can assess for abnormal cellular morphology, staining characteristics and keratinisation.[57].

6.1.8. Current standard

A question remains: What sensitivity or specificity can be considered to replace the gold standard: conventional oral examination and a biopsy with histopathology? A systematic review of 18 studies noted that COE has a pooled sensitivity of 71% and a specificity of 85% for diagnosing dysplastic or malignant lesions.[58] A Cochrane systematic review found these COE generally has a variable sensitivity (50–99%), but a high specificity of over 80%.[12] There are no current criteria for the definition of "gold standard". A gold standard refers to a benchmark under reasonable conditions. It is not defined as perfect sensitivity or specificity, but as the best and most accurate standard.[59] It is reasonable to consider that to replace the current gold standard diagnosis, adjunctive tools will require at least a 90–95% sensitivity and specificity.

By the same token, no current standard of sensitivity or specificity exists for adjunctive tools in the diagnosis of OSCC or OPMD to be considered statistically significant. This study has recommended a threshold of 80% specificity and sensitivity to be considered statistically significant.

Recommendations: The quality of evidence and strength of recommendations are according to GRADE guidelines.[22,60] (Supplementary Table 5).

Recommendation 1: Our study does not recommend chemiluminescence, tissue autofluorescence tools or vital staining as diagnostic tools to replace a COE or biopsy. They may be utilised only as clinical adjuncts.

(Conditional recommendation, moderate quality of evidence).

Recommendation 2: Our study recommends that narrow band imaging can be utilised as a non-invasive diagnostic adjunctive tool for detecting OSCC or the malignant transformation of OPMD. The results of NBI should be taken as a guide for the next steps in diagnosis, including the gold standard tissue biopsy.

(Conditional recommendation, moderate quality of evidence).

Recommendation 3: Our study recommends that the use of oral cytology techniques can be utilised as a minimally invasive diagnostic adjunctive tool for the detection of OSCC or the malignant transformation of OPMD. When a biopsy cannot be performed, oral cytology offers a way of assessing tissue with reasonable accuracy. While it has a high specificity and sensitivity in detecting OSCC and OPMD, it cannot replace a tissue biopsy as the main diagnostic method.

(Conditional recommendation, moderate quality of evidence).

Recommendation 4: Our study recommends that future studies present sensitivities and specificities of adjunctive tool separately for OSCC and OPMDs, rather than pooling the data. (Conditional recommendation, moderate quality of evidence).

6.2. Effectiveness of adjunctive tools for individual OPMDs

While most systematic reviews and meta-analyses grouped OPMDs into one category, the meta-analysis by Shaw et al. had sufficient data to examine the sensitivity and specificity of chemiluminescence for specific OPMD conditions, including leukoplakia, oral lichen planus and oral submucous fibrosis. Leukoplakia had a respective specificity and sensitivity of 75% and 98%, oral lichen planus was 78% and 60% and oral submucous fibrosis was 89% and 76%.[46].

Only three other studies had solely studied the detection of OPMDs using adjunctive tools. Lingen reported a high sensitivity of 92% and a specificity of 94% with cytology testing. Other adjunctive tools including, autofluorescence, vital staining and tissue reflectance had poor specificity.[31] In an earlier study, Patton et al. also reports similar findings when examining the evidence of toluidine blue as a diagnostic adjunct for OPMD and concludes it is an effective adjunct tool for diagnosing OPMDs. However, the study reports a low specificity of 67%.[24] Given the low specificity, this may lead to consistent false positive diagnosis, increased clinical time and increased stress and anxiety for patients. Mazur et al. also reported inconsistent findings and concluded that no technique can replace biopsy as the gold standard.[38].

6.3. Is there a significant difference between the detection of OPMD and OSCC using adjunctive tools?

Only a few studies separately reported on the use of adjunctive tools on OSCC and OPMDs. Mendonca et al. directly compared the detection of dysplastic OPMDs to the detection of OSCC.[48] Generally the sensitivity and specificity of adjunctive tools in detecting OSCC is significantly greater than dysplastic OPMD. Autofluorescence, narrow band imaging and diffuse reflectance spectroscopy have respective sensitivity of 96%, 97%, 93% and 93% in the detection of OSCC. In comparison, the sensitivity of OPMDs was 75% for autofluorescence, 31% for narrow band imaging, 72% for fluorescence spectroscopy and 79% for diffuse reflectance spectroscopy. In addition, narrow band imaging is also considered a promising adjunctive tool for identifying malignant transformations of OPMDs. In the systematic review and meta-analysis by Zhang et al., IPCL II lesions had an overall diagnostic accuracy for the malignant transformation of OPMDs with a sensitivity of 87%, and a specificity of 83%.[49].

6.4. Screening

Overall, there is a lack of evidence for the use of adjunctive tools for the purposes of screening for oral cancer or OPMDs. Generally, a specialist in oral diseases and properly tested adjunctive tools is necessary to administer adjunctive tools effectively. There is limited evidence for the use of light based adjunctive tools and toluidine blue in the detection of OPMD and OSCC in screening and in primary care.[26,36] A screening study conducted in Taiwan reported a 5% increased detection of OPMD using toluidine blue compared with a control group. However, the authors did not report whether toluidine blue improved the sensitivity or specificity in screening.[61] To date, no adjunctive tools can be utilised to replace a conventional oral examination for screening for OSCC.[12].

The limitations of our review are restricted to the studies included in this systematic review of systematic review and meta-analysis. Of the 27 studies included, 14 studies had low or critically low-quality evidence, according to AMSTAR II. Despite no geographic limitations set, our study had an exclusion criterion of systematic reviews and meta-analyses that were not written in English. Given this, our data may not be considered a true representation of the global population. Furthermore, tertiary oral examination techniques, including biochemical analysis of saliva and serum and molecular analysis were not included in this study. The potential for these assessment forms should be critically analysed as a systemic review of systemic reviews and is planned as a future study.

In conclusion, none of the adjunctive tools tested so far that were evaluated in this systematic review of systematic reviews and meta-analysis can replace the current gold standard - a clinical visual examination and surgical biopsy with histological analysis in diagnosing OPMD and OSCC. NBI and cytology techniques generally show high levels of specificity and sensitivity and show that they can be utilised strictly as clinical adjuncts. Furthermore, adjunctive tools such as chemiluminescence, tissue autofluorescence tools and vital staining demonstrate varied sensitivity and specificity in the literature and subsequently cannot be recommended as diagnostic tools. When utilised by

a trained specialist such as an Oral Medicine specialist, Maxillo-facial surgeon or Ear Nose Throat Doctor, using such tools as a clinical adjunct may have some merit. To aid early detection of OSCC, future robust studies of adjunctive tools should be carried out to separately assess their utility on OPMD and OSCC and also assess the risk for malignant transformation of OPMDs.

Ethical approval

No ethical approval was required for this project.

Funding

No funding was obtained for this review.

Conflict of interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jdsr.2023.12.004.

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