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REVIEW ARTICLE

WILEY ORAL DISEASES

Optical fluorescence imaging in oral cancer and potentially malignant disorders: A systematic review

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Abstract

Objectives: This study aimed to systematically review the efficacy of direct optical fluorescence imaging as an adjunct to comprehensive oral examination in the clinical evaluation, risk assessment and surgical management of oral cancer and potentially malignant disorders.

Methods: Studies adopting autofluorescence devices, evaluating the efficacy of comprehensive oral examination and optical fluorescence imaging in detection, visualisation or management of oral squamous cell carcinoma or oral potentially malignant disorders, as well as discriminating oral epithelial dysplasia from other mucosal lesions, were included in the literature search across bibliographic databases until October 2018.

Results: Twenty-seven studies were found to be eligible for inclusion in qualitative analysis. Of these, only six studies demonstrated a low risk of bias across all domains of the methodological assessment tool (QUADAS-2). Optical fluorescence imaging demonstrated positive results, with higher sensitivity scores, increased lesion detection and visualisation than comprehensive oral examination alone in the clinical evaluation of oral squamous cell carcinoma and oral potentially malignant disorders.

Conclusions: This review provides promising evidence for the utilisation of optical fluorescence imaging as an adjunct to comprehensive oral examination in varying clinical settings. It is important that devices utilising optical fluorescence imaging are viewed strictly as clinical adjuncts and not specifically as diagnostic devices.

KEYWORDS

autofluorescence, optical fluorescence imaging, oral cancer, oral potentially malignant disorders, systematic review

1 | BACKGROUND

Oral squamous cell carcinoma (OSCC) is a major health burden responsible for a significant proportion of morbidity and mortality worldwide (Shield et al., 2017). The overall 5-year survival rate is around 50% but it can reach as low as 15% depending on the stage of diagnosis (Farah et al., 2014; McCullough, Prasad, & Farah, 2010). Early-stage OSCC and oral epithelial dysplasia (OED) often manifest as subtle mucosal changes classified as oral potentially malignant disorders (OPMD) (Epstein, Güneri, Boyacioglu, & Abt, 2012; Speight, Khurram, & Kujan, 2018). Early detection and effective management of these lesions are crucial for improving survival rates and preventing oral cancer progression (Epstein et al., 2012).

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Current practice for detection of OPMD involves a conventional oral examination (COE) with visual and tactile examination under white light (Epstein et al., 2012; Lingen, Kalmar, Karrison, & Speight, 2008). To confirm clinical findings, patients are usually referred to a specialist centre for surgical biopsy of suspicious lesions for definitive diagnosis and management (Epstein et al., 2012; Lingen et al., 2008). The decision to biopsy is currently based on the clinical judgement of the practitioner, which is significantly influenced by the findings from COE. Unfortunately, COE has been shown to be a poor predictor of OSCC and OED, with a sensitivity and specificity of 93% and 31%, respectively, consequently introducing limitations to the diagnostic process (Epstein et al., 2012; Lingen et al., 2008; Macey et al., 2015).

As a result, many diagnostic adjuncts have been developed; however, these have been utilised and assessed in a manner to replace, rather than complement, COE (Bhatia, Lalla, Vu, & Farah, 2013). Optical fluorescence imaging (OFI) has been extensively scrutinised as a diagnostic adjunct, with many studies outlining poor diagnostic yield for OSCC and OED, or demonstrating inconclusive results due to poor study design and heterogeneity (Lingen, Tampi et al., 2017; Luo et al., 2016; Macey et al., 2015). Furthermore, there has been much debate with regard to how OFI is utilised in clinical settings. Based on previous systematic reviews, the American Dental Association have recently recommended against the use of autofluorescence imaging for the assessment of clinically evident lesions (Lingen, Abt et al., 2017). While this comment may hold true if based purely on diagnostic capability of the device, adjunctive OFI has demonstrated use in other aspects of clinical practice providing the practitioner more clinical information, in the form of lesion detection, lesion assessment and lesion management, than information gathered by COE alone (Bhatia et al., 2013). At present, there is no published systematic review assessing OFI in this capacity. This review therefore aimed to provide contemporary evidence on the efficacy of direct OFI as an adjunctive tool to COE in the clinical evaluation, risk assessment and management of OPMD and OSCC.

2 | METHODS

2.1 | Data sources and search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Liberati et al., 2009). Electronic databases Medline, Web of Science, Embase and Scopus were searched until October 2018 using a combination of "MESH terms" outlined in Supporting Information Table S1. In addition, references were hand-checked from bibliographies in relevant articles and included in this review.

2.2 | Selection process based on PICO model

The inclusion criteria used in the selection of literature for this review were as follows:

- 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 OFI in
  - detection of OPMD and/or OSCC
  - visualisation of OPMD and/or OSCC
  - discrimination of benign oral lesions from OPMD and/or OSCC
  - detection of OED in OPMDs
  - surgical management of OPMD and/or OSCC
  - long-term surveillance of OPMDs
- Studies had to report efficacy values or had enough data reported that these could be calculated.

Exclusion criteria:

Studies utilising indirect autofluorescence examinations or algorithms as diagnostic tools were excluded as this form of examination did not meet our objective.

2.3 | Types of participants

Participants who underwent examination with both conventional oral examination and optical autofluorescence imaging either in a general dental practitioner setting or in a specialist centre setting.

2.4 | Types of interventions and comparator

Studies for inclusion had to have a COE comparison to tissue autofluorescence. Studies discriminating benign oral lesions from OPMD and/or OSCC, detecting OED and OSCC, or discussing surgical management of OPMD and/or OSCC with the aid of OFI had to have histopathological confirmation. Studies evaluating autofluorescence imaging in a general dental setting or for long-term surveillance of lesions did not require histopathological confirmation as the oral medicine specialist was considered the gold standard in these scenarios.

2.5 | Types of outcome measures

2.5.1 | Primary outcomes

Primary outcome measures for this review focused on evaluating the efficacy of OFI in clinical evaluation, risk assessment or management of OPMD and/or OSCC. These categories were further divided into specific outcome measures (Supporting Information Table S2).

2.5.2 | Secondary outcomes

Secondary outcomes with regard to the efficacy of OFI as an adjunct to COE in general dental practice and its value in long-term surveillance of OPMDs were also assessed.

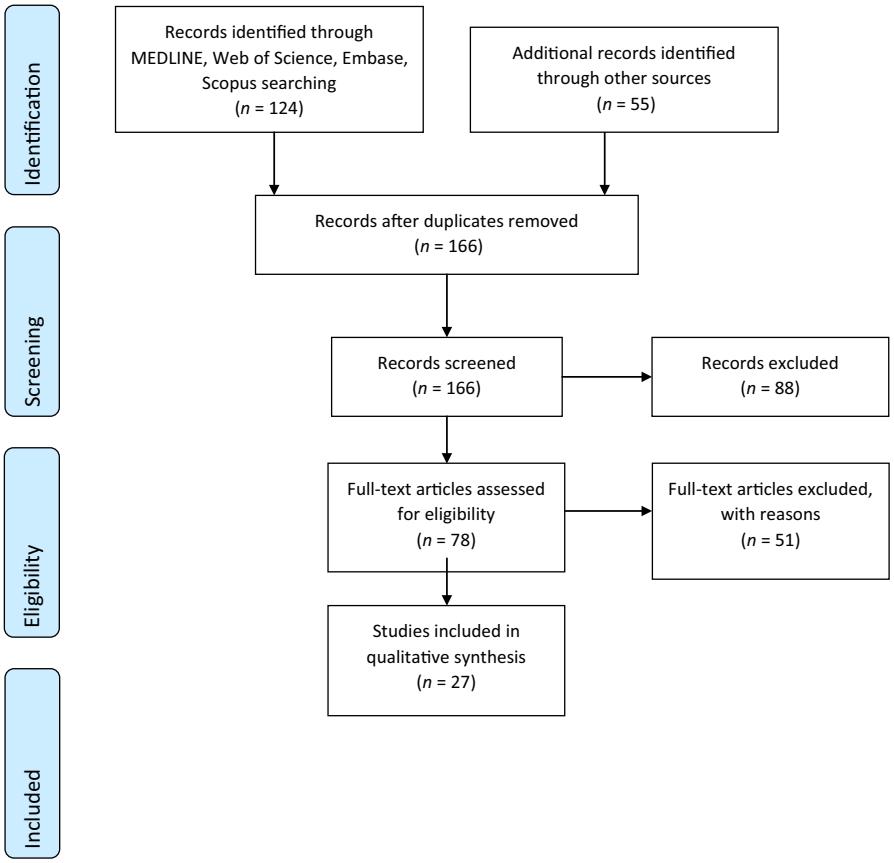

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of screened studies

3 | RESULTS

3.1 | Study selection

A total of 166 studies were screened by title and abstract, with 78 full-text articles assessed for eligibility and only 27 studies meeting the inclusion criteria (Figure 1). For each study, data were extracted using a standardised data collection form and studies were qualitatively assessed using the QUADAS-2 tool (Supporting Information Table S3). Two reviewers (LT and OK) independently evaluated the articles included in the study. Data were extracted and summarised in Tables 1 and 2 based on primary and secondary outcome measures, respectively. Of the 27 included studies, six demonstrated a low risk of bias across all QUADAS-2 domains (Bhatia, Matias, & Farah, 2014; Farah, McIntosh, Georgiou, & McCullough, 2012; Lalla, Matias, & Farah, 2015,2016; Paderni et al., 2011; Rana, Zapf, Kuehle, Gellrich, & Eckardt, 2012).

3.2 | Efficacy of autofluorescence in clinical evaluation of OPMD and OSCC

Fifteen studies reported efficacy on detection of OPMD and/or OSCC, with significant heterogeneity and risk of bias noted across the methodologies used (Awan, Morgan, & Warnakulasuriya, 2011; Betz et al., 2002; Bhatia et al., 2014; Cânjău, Todea, Sinescu, Pricop, & Duma, 2018; Chiang et al., 2018; Farah et al., 2012; Koch, Kaemmerer, Biesterfeld, Kunkel, & Wagner, 2011; Lalla, Matias, & Farah, 2016; Marzouki et al., 2012; Moro et al., 2010; Onizawa, Saginoya, Furuya, & Yoshida, 1996; Petruzzi et al., 2014; Sawan & Mashlah, 2015; Scheer et al., 2016; Sweeny et al., 2011). Only three of 15 studies demonstrated low risk of bias across all QUADAS-2 domains (Bhatia et al., 2014; Farah et al., 2012; Lalla et al., 2016). Two studies assessed the efficacy of VELscope as an adjunct to COE (Bhatia et al., 2014; Farah et al., 2012). Farah et al. (2012) utilised VELscope in the specialist dental setting, evaluating red and white lesions, using histopathology as a gold standard, while Bhatia et al. (2014) utilised VELscope in a general dental clinic with a referral to an oral medicine specialist as the gold standard. Both studies demonstrated higher sensitivity values (Bhatia et al., 2014; Farah et al., 2012). Farah et al. reported a combined sensitivity score of 46% compared to 25% with COE alone (Farah et al., 2012), while Bhatia et al. (2014) reported a combined sensitivity score of 73.9% compared to 44% with COE alone in the detection of OPMD and/or OSCC. A reduction in specificity values was noted in both studies when VELscope was utilised as an adjunct to COE compared to the use of COE alone, with Farah et al. (2012) reporting a combined specificity of 68% compared to 82% and Bhatia et al. (2014) reporting a combined specificity of 97.1% compared to

TABLE 1 Efficacy of autofluorescence imaging in detection of OPMD and/or OSCC, as an adjunctive tool to COE and discriminating the presence of dysplasia or neoplasia from other mucosal lesions

No	Author, publication year	General or specialist setting	Sample size	Population type assessed	Was COE done prior to AF?	Was WL used
OFI in detection of OPMD and/or OSCC						
1	Scheer et al. (2016)	Specialist oral surgery	41	Post-treatment OC patients with undiagnosed mucosal lesions	Yes	Not specified
2	Bhatia et al. (2014)	General dental practice	222	Patients presenting to a general dental clinic for general check-up	Yes	No. Incandescent operatory light
3	Betz et al. (2002)	Specialist otolaryngology	214	Patients with proven malignancy or clinically suspicious lesions of the oral cavity or oropharynx	Yes	Yes
4	Koch et al. (2011)	Specialist oral surgery	78	Patients with clinically diagnosed SCC or suspicious mucosal lesions	Yes	Yes. Diagnosis based on photographs
5	Farah et al. (2012)	Specialist oral medicine	118	Patients with an oral mucosal lesion (white, mixed white-red)	Yes	No. Incandescent operatory light
6	Sawan and Mashlah (2015)	Specialist centre	71	No inclusion or exclusion criteria	Unclear	Unclear
7	Petruzzi et al. (2014)	Specialist oral medicine	56	Patients presenting with oral lesions suspicious for SCC, with history of oral lesions or at high risk for an oral lesion	Yes	No. Incandescent operatory light
8	Onizawa et al. (1996)	Specialist oral surgery	32	Patients with oral mucosal lesions	Yes	Unclear
9	Marzouki et al. (2012)	Specialist head and neck oncology	33	Patients with smoking and alcohol history, suspicious lesions, or history of treated oral cancer	Yes	Unclear
10	Moro et al. (2010)	Specialist oral medicine	32	Patients with a history of oral cancer, presence of OPMD or suspicious lesion	Yes	Unclear
11	Sweeny et al. (2011)	Specialist oral medicine	17	Patients with history of treated head and neck cancer	Yes	Yes

AF device and technique	Use of diascopy	Was there histopathological confirmation of dysplasia or carcinoma	Positive outcome measure	Sensitivity (%)	Specificity (%)
VELscope. Fluorescence characteristics based on photographs. LAF indicates dysplasia or carcinoma	No	Yes	Histopathological confirmation of carcinoma	AF alone: 33.3	AF alone: 88.6
VELscope. LAF or negative diascopy considered positive for dysplasia/SCC. 2 week review protocol used for positive diascopy	Yes	Yes	1. A referral decision to oral medicine specialist 2. Histopathological diagnosis of biopsied lesions	COE alone: 44 AF alone: 64 Combined: 73.9	COE alone: 99 AF alone: 54.3 Combined: 97.9
Modified short xenon lamp for in vivo tissue excitation. Subjective darker shade of green was considered positive for malignancy	Unclear	Yes	Histopathological confirmation of carcinoma only	COE: 99.2 AF alone: 87.8 Combined: 100	COE: 42.9 AF alone: 56.4 Combined:51.3
VELscope. AF determined from photographs. Low, absent or red AF signal considered positive for dysplasia/SCC	Unclear	Yes	Histopathological confirmation of carcinoma only	COE: 96.6 AF alone: LAF parameter only: 93 Red AF only: 20	COE: 95.8 AF alone: LAF parameter only: 15 Red AF only: 98
VELscope. LAF and negative diascopy was considered indicative for dysplasia/SCC	Yes	Yes	Histopathological diagnosis for dysplasia on histopathology	COE: 25 AF alone: 30 Combined: 46	COE: 82 AF alone: 63 Combined: 68
VELscope. AF parameters not defined	No	Yes	Histopathological diagnosis of carcinoma only	AF alone: 100	AF alone: 74.14
VELscope. LAF was considered positive for dysplasia or malignancy	No	Yes	Histopathological diagnosis of dysplasia or carcinoma.	AF alone: detection of dysplasia + malignancy: 70 AF alone: detection of moderate/severe OED/SCC (mild dysplasia considered negative): 76.47	AF alone: detection of dysplasia + malignancy: 57.69 AF alone: detection of moderate/severe OED/SCC (mild dysplasia considered negative): 51.28
Autofluorescence photography. Orange fluorescence was considered positive for malignancy	No	Yes	Histopathological confirmation of carcinoma only	AF alone: 88	AF alone: 94
VELscope. LAF was deemed positive for dysplasia or carcinoma	No	Yes	Histopathological confirmation of dysplasia or carcinoma	COE: 61.5 AF alone: 92	COE: 87.5 AF alone: 77
Prototype. LED lamp emitting 450 nm. No defined parameters	No	Yes	Histopathological confirmation of dysplasia or carcinoma	AF alone: 100	AF alone: 93
Identafi 3,000 ultra. AF parameters not defined	No	Yes	Histopathological confirmation of dysplasia or carcinoma	WL: 50 AF: 50 Tissue reflectance: 0	WL: 98 AF: 81 tissue reflectance: 86

(Continues)

TABLE 1 (Continued)

No	Author, publication year	General or specialist setting	Sample size	Population type assessed	Was COE done prior to AF?	Was WL used
12	Lalla et al. (2016)	Specialist oral medicine	233	Patients presenting with white, red, mixed red-white lesions	Yes	Yes
13	Awan et al. (2011)	Specialist oral medicine	126	Patients presenting with white, red and mixed white/red patches	Yes	No, incandescent operatory light
14	Cânjău et al. (2018)	Specialist oral surgery	18	No inclusion or exclusion criteria	Yes	Unclear, overhead light used
15	Chiang et al. (2018)	Specialist oral surgery	126	Patients with mucosal disorders and history of alcohol, tobacco and betel quid	Yes	Unclear
OFI as adjunctive tool to COE						
1	Bhatia et al. (2014)	General dental practice	222	Patients presenting to a general dental clinic for general check-up	Yes	No. Incandescent operatory light
2	Jayaprakash et al. (2009)	Specialist oral medicine	249	(a) clinically suspicious oral lesions (b) a history of treated OSCC (c) recently diagnosed untreated OPMD or OSCCs	Yes	Yes
3	Betz et al. (2002)	Specialist otolaryngology	214	Patients with proven malignancy or clinically suspicious lesions of the oral cavity or oropharynx	Yes	Yes
4	Rana et al. (2012)	Specialist oral surgery	COE group: *N* = 166 COE + AF group: *N* = 123	Patients with oral premalignant lesions randomly allocated into two groups	Yes	No. Overhead incandescent light
5	Hanken et al. (2013)	Specialist oral medicine	120	Patients with suspicious oral premalignant lesions	Yes	Yes
6	Farah et al. (2012)	Specialist oral medicine	118	Patients with an oral mucosal lesion (white, mixed white-red)	Yes	No. Incandescent operatory light

AF device and technique	Use of diascopy	Was there histopathological confirmation of dysplasia or carcinoma	Positive outcome measure	Sensitivity (%)	Specificity (%)
Identafi. LAF & negative diascopy positive for dysplasia or SCC	Yes	Yes	1. COE for confirmation of presence of OPMD 2.Histopathological confirmation of dysplasia	Clinical: WL: 100 Violet light: 27.5 Green-Amber light: 40 Histopathology: WL: 47.35 Violet light: 12.5 Green-Amber light: 37.3	Clinical: WL: 100% Violet light: 27.5% Green-Amber light: 40 Histopathology: WL: 87.5 Violet light: 85.4 Green-Amber light: 62.5
Velscope. LAF considered positive for diseased tissue	No	Yes	COE used as gold standard to diagnose OPMD	AF alone: 87.1	AF alone: 21.4
VELscope. LAF considered positive for malignancy	Unclear	Yes	Histopathological confirmation of carcinoma only	AF alone: 94.44	AF alone: 100
Autofluorescence digital photography. Unclear parameters	No	Yes	Histopathological confirmation of dysplasia or malignancy	AF alone: 77.94	AF alone: 35.42
VELscope. LAF or negative diascopy considered positive for dysplasia/SCC. 2 week review protocol used for positive diascopy	Yes	Yes	1. A referral decision to oral medicine specialist 2. Histopathological diagnosis of biopsied lesions	COE alone: 44 AF alone: 64 Combined: 73.9	COE alone: 99 AF alone: 54.3 Combined: 97.9
Fluorescence imaging and point spectroscopy. LAF considered positive for dysplasia or carcinoma	Unclear	Yes	Histopathological confirmation of dysplasia or carcinoma	All grades of OPMD and OSCC: WLE:52 AF alone:72 Combined:83	All grades of OPMD and OSCC: WLE:70 AF alone:50 Combined: 38
Modified short xenon lamp for in vivo tissue excitation. Subjective darker shade of green considered positive for malignancy	Unclear	Yes	Histopathological confirmation of carcinoma only	COE: 99.2 AF alone: 87.8 Combined: 100	COE: 42.9 AF alone: 56.4 Combined:51.3
VELscope. LAF indicated dysplasia/malignancy. Negative diascopy also considered positive for dysplasia/malignancy	Yes	Yes	Histopathological confirmation of dysplasia or carcinoma	COE: 17 Combined: 100	COE: 97 Combined:74
VELscope LAF indicates underlying dysplasia/malignancy	Unclear	Yes	Histopathological confirmation of dysplasia or malignancy	COE: 5.9 Combined: 97.9	COE: 33.3 Combined: 41.7
VELscope. LAF and negative diascopy was considered indicative for dysplasia/malignancy	Yes	Yes	Histopathological diagnosis for dysplasia on histopathology	COE: 25 AF alone: 30 Combined: 46	COE: 82 AF alone: 63 Combined: 68

(Continues)

TABLE 1 (Continued)

No	Author, publication year	General or specialist setting	Sample size	Population type assessed	Was COE done prior to AF?	Was WL used
7	Amirchaghmaghi et al. (2018)	Specialist oral medicine	54	Patients presenting with soft tissue lesions needing incisional or excisional biopsies	Yes	No, Incandescent operatory light
Discriminating the presence of dysplasia or neoplasia from other mucosal lesions						
1	Mehrotra et al. (2010)	Specialist oral medicine	100	Patients with the presence of clinically innocuous lesions	Yes	No. Overhead dental light
2	Awan et al. (2015)	Specialist oral medicine	116	Consecutive sample of patients with white, red and mixed white and red patches	Yes	Unclear
3	Jayaprakash et al. (2009)	Specialist oral medicine	249	(a) clinically suspicious oral lesions (b) a history of treated OSCC (c) recently diagnosed untreated OPMD or OSCCs	Yes	Yes
4	Scheer et al., 2011)	Specialist oral and maxillofacial surgery	64	Patients referred to rule out invasive SCC	Yes	Not specified. Possible use of photos for diagnosis
5	Betz et al. (2002)	Specialist otolaryngology	214	Proven malignancy or clinically suspicious lesions of the oral cavity or oropharynx	Yes	Yes
6	Rana et al. (2012)	Specialist oral surgery	COE group: *N* = 166 COE + AF group: *N* = 123	Only patients with oral premalignant lesions randomly allocated into two groups	Yes	No. Overhead incandescent light
7	Hanken et al. (2013)	Specialist oral medicine	120	Patients with suspicious oral premalignant lesions	Yes	Yes
8	Koch et al. (2011)	Specialist oral surgery	78	Patients with clinically diagnosed SCC or suspicious mucosal lesions	Yes	Yes. Diagnosis based on photographs

AF device and technique	Use of diascopy	Was there histopathological confirmation of dysplasia or carcinoma	Positive outcome measure	Sensitivity (%)	Specificity (%)
VELscope. Regions with LAF or that seen as red/orange were considered suspicious	No	Yes	Histopathological confirmation of dysplasia or carcinoma	Dysplastic lesions only: COE: 75 AF alone: 83 Combined: 100 Dysplasia + SCC: COE: 81 AF alone: 90 Combined: 100 Oral Mucosal Lesions: COE: 86 AF alone: 90 Combined: 100	Dysplastic lesions only: COE: 71 AF alone: 12 Combined: 11 Dysplasia + SCC: COE: 67 AF alone: 12 Combined: 6 Oral Mucosal Lesions: COE: 85 AF alone: 15 Combined: 12
VELscope. LAF indicates dysplasia or carcinoma	No	Yes	Histopathological confirmation of dysplasia or carcinoma	AF alone: 50	AF alone: 38.9
VELscope. LAF indicates dysplasia	No	Yes	Histopathological confirmation of dysplasia	AF alone: 84.1	AF alone: 15.3
Fluorescence imaging and point spectroscopy. LAF considered positive for dysplasia or carcinoma	Unclear	Yes	Histopathological confirmation of dysplasia or carcinoma	All grades of OPMD + OSCC: COE:52 AF alone:72, Combined:83	All grades of OPMD + OSCC: COE:70 AF alone:50 Combined: 38
VELscope. AF judgement based on photos. LAF considered positive for dysplasia/malignancy	Unclear	Yes	Histopathological confirmation of dysplasia or carcinoma	AF alone: 100	AF alone: 80.8
Modified short xenon lamp for in vivo tissue excitation Subjective darker shade of green considered positive for malignancy	Unclear	Yes	Histopathological confirmation of carcinoma only	COE: 99.2 AF alone: 87.8 Combined: 100	COE: 42.9, AF alone: 56.4 Combined:51.3
VELscope. LAF indicated dysplasia/malignancy. Negative diascopy also considered positive for dysplasia/malignancy	Yes	Yes	Histopathological confirmation of dysplasia or carcinoma	COE: 17 Combined: 100	COE: 97 Combined:74
VELscope. LAF indicates underlying dysplasia/malignancy	Unclear	Yes	Histopathological confirmation of dysplasia or malignancy	COE: 5.9 Combined: 97.9	COE: 33.3 Combined: 41.7
VELscope. Characteristics of AF determined from photographs. A low or absent AF signal, as well as red AF signal was considered positive for dysplasia or SCC.	Unclear	Yes	Histopathological confirmation of carcinoma only	COE: 96.6 AF alone: LAF parameter only: 93 Red AF only: 20	COE: 95.8 AF alone: LAF parameter only: 15 Red AF only: 98

(Continues)

TABLE 1 (Continued)

No	Author, publication year	General or specialist setting	Sample size	Population type assessed	Was COE done prior to AF?	Was WL used
9	Paderni et al. (2011)	Specialist oral medicine	175	Patients with at least one oral mucosal lesion with clinical suspicion of OPMD or OSCC	Yes	Yes
10	Farah et al. (2012)	Specialist oral medicine	118	Patients with an oral mucosal lesion (white, mixed white-red)	Yes	No. Incandescent operatory light
11	Petruzzi et al. (2014)	Specialist oral medicine	56	Patients with oral lesions suspicious for malignancy and who had a history of oral lesions or were at high risk for an oral lesion	Yes	No. Incandescent operatory light
12	Marzouki et al. (2012)	Specialist head and neck oncology	33	Patients with high smoking and alcohol history, with suspicious lesion, or patients with history of treated oral cancer on review for recurrence or second primary	Yes	Unclear
13	Lalla et al. (2016)	Specialist oral medicine	233	Patients presenting with white, red, mixed red-white lesions	Yes	Yes
14	Moro et al. (2010)	Specialist oral medicine	32	Patients with a history of oral cancer, presence of OPMD or suspicious lesion	Yes	Unclear
15	Amirchaghmaghi et al. (2018)	Specialist oral medicine	54	Patients presenting with soft tissue lesions needing incisional or excisional biopsies	Yes	No, Incandescent operatory light

AF device and technique	Use of diascopy	Was there histopathological confirmation of dysplasia or carcinoma	Positive outcome measure	Sensitivity (%)	Specificity (%)
VELscope. Abnormally dark on fluorescence in the body or boundary of lesion was considered positive for dysplasia or malignancy.	Yes	Yes	Histopathological confirmation of dysplasia or carcinoma	AF alone: Lesions with dysplasia versus lesions w/o dysplasia: 65.5 (sig) Lesions with mild dysplasia versus lesions w/o dysplasia: 60 (sig) Lesions with moderate/severe dysplasia versus lesions without dysplasia: 71.4 (sig) High risk lesions versus low risk lesions: 75 (sig)	AF alone: Lesions with dysplasia versus lesions w/o dysplasia: 97.4 (sig) Lesions with mild dysplasia versus lesions w/o dysplasia: 97.4 (sig) Lesions with moderate/severe dysplasia versus lesions without dysplasia: 97.4 (sig) high risk lesions versus low risk lesions: 92.3 (sig)
VELscope. LAF and negative diascopy was considered indicative for dysplasia/malignancy	Yes	Yes	Histopathological diagnosis of dysplasia on histopathology	COE: 25 AF alone: 30 Combined: 46	COE: 82 AF alone: 63 Combined: 68
VELscope. LAF was considered positive for dysplasia or malignancy	No	Yes	Histopathological diagnosis of dysplasia or carcinoma	AF alone: detection of dysplasia + malignancy: 70 AF alone: detection of moderate/severe OED/SCC (mild dysplasia considered negative): 76.47	AF alone: detection of dysplasia + malignancy: 57.69 AF alone: detection of moderate/severe OED/SCC (mild dysplasia considered negative): 51.28
VELscope. LAF was deemed positive for dysplasia or carcinoma	No	Yes	Histopathological confirmation of dysplasia or carcinoma	COE: 61.5 AF alone: 92	COE: 87.5 AF alone: 77
Identafi. LAF & partial blanching positive for dysplasia or malignancy	Yes	Yes	1. COE for confirmation of presence of OPMD 2. Histopathological confirmation of dysplasia	Clinical: WL: 100 Violet light: 27.5 Green-Amber light: 40 Histopathology: WL: 47.35 Violet light: 12.5 Green-Amber light: 37.3	Clinical: WL: 100 Violet light: 27.5 Green-Amber light: 40 Histopathology: WL: 87.5 Violet light: 85.4 Green-Amber light: 62.5
Prototype. LED lamp emitting 450 nm. No defined parameters	No	Yes	Histopathological confirmation of dysplasia or carcinoma	AF alone: 100	AF alone: 93
VELscope. Regions with LAF or that seen as red/orange were considered suspicious	No	Yes	Histopathological confirmation of dysplasia or carcinoma	Dysplastic lesions only: COE: 75 AF alone: 83 Combined: 100 Dysplasia + SCC: COE: 81 AF alone: 90 Combined: 100 Oral Mucosal Lesions: COE: 86 AF alone: 90 Combined: 100	Dysplastic lesions only: COE: 71 AF alone: 12 Combined: 11 Dysplasia + SCC: COE: 67 AF alone: 12 Combined: 6 Oral Mucosal Lesions: COE: 85 AF alone: 15 Combined: 12

(Continues)

TABLE 1 (Continued)

No	Author, publication year	General or specialist setting	Sample size	Population type assessed	Was COE done prior to AF?	Was WL used
16	Awan et al. (2011)	Specialist oral medicine	126	Patients presenting with white, red and mixed white/red patches	Yes	No. Incandescent operatory light
17	Simonato et al. (2017)	Screening clinic, OFI device used by dental student and specialist in oral medicine	5	Prospective, random selection from patients in screening clinic	Yes	Yes
18	Babiuch et al. (2012)	Specialist oral surgery	18	Patients with history of lip and oral cavity cancer enrolled	Yes	No. Incandescent operatory light
19	Chiang et al. (2018)	Specialist oral surgery	126	Patients with mucosal disorders and history of alcohol, tobacco and betel quid	Yes	Unclear
20	Sawan and Mashlah (2015)	Specialist centre	71	No inclusion or exclusion criteria.	Unclear	Unclear
21	Lane et al. (2006)	Specialist oral medicine	50	Patients with history of biopsy confirmed oral dysplasia or SCC	Yes	Yes

COE: conventional oral examination; OPMD: oral potentially malignant disorders; OSCC: Oral squamous cell carcinoma.

99%. The third, prospective cross-sectional study deemed to have low risk of bias assessed the efficacy of Identafi's multispectral light (Lalla et al., 2016). Identafi's white light demonstrated equivalent accuracy to COE conducted under extra-oral LED white light, while the violet (autofluorescence) light alone demonstrated low sensitivity and specificity values for the detection of OPMD and/or OSCC based on both clinical outcomes (27.5%, 27.5%) and histopathology (12.5%, 85.4%; Lalla et al., 2016). The authors, however, did not report efficacy values for Identafi as an adjunctive tool (Lalla et al., 2016).

3.2.1 | Autofluorescence in visualisation of an oral mucosal lesion

Eight studies reported data on visualisation of oral mucosal lesions (Betz et al., 2002; Bhatia et al., 2014; Farah et al., 2012; Jayaprakash et al., 2009; Lalla, Matias, & Farah, 2015; Lalla et al., 2016; Marzouki et al., 2012; Paderni et al., 2011), with three of eight studies having a low risk of bias across all QUADAS-2 domains (Bhatia et al., 2014; Farah et al., 2012; Lalla et al., 2016). Six of eight studies reported additional lesion detection with AF compared to COE alone (Betz et al., 2002; Bhatia et al., 2014; Farah et al., 2012; Jayaprakash et al., 2009; Lalla et al., 2016; Marzouki et al., 2012). Three of five studies reporting border distinctness noted subjectively, greater improvements in border distinctness with AF compared to COE alone (Betz et al., 2002; Bhatia et al., 2014; Lalla et al., 2016). Two of five studies noted improved visibility (Bhatia et al., 2014; Paderni et al., 2011), while the other three did not note any significant difference when compared with LED WL and magnification loupes (Farah et al., 2012; Lalla et al., 2015, 2016).

3.2.2 | Autofluorescence as an adjunctive tool to COE

A large range in efficacy values on adjunctive OFI in detecting OPMD/OSCC was noted across seven studies (sensitivity: COE alone vs. AF as adjunct: 17%–99.2% vs. 73.9%–100%, specificity: COE alone vs. AF as adjunct: 33.3%–99% vs. 38%–97.9%;

AF device and technique	Use of diascopy	Was there histopathological confirmation of dysplasia or carcinoma	Positive outcome measure	Sensitivity (%)	Specificity (%)
VELscope. LAF considered positive for diseased tissue, no mention if it indicates dysplasia or malignancy	No	Yes	COE used as gold standard to diagnose OPMD	AF alone: 87.1	AF alone: 21.4
Evince. LAF considered positive for malignancy or dysplasia	Unclear	Yes	COE used as gold standard to diagnose OPMD Histopathological confirmation of dysplasia or carcinoma	Unskilled in detection of OED: COE: 50 AF alone: 100 Skilled clinician in detection of OED COE: 100 AF alone: 100	Unskilled in detection OED: COE: 46.15 AF alone: 46.15 Skilled clinician in detection of OED: COE: 38 AF alone: 46
VELscope. LAF considered positive for malignancy	Unclear	Yes	Histopathological confirmation of dysplasia or malignancy	AF alone: 100	AF alone: 12.5
Autofluorescence digital photography. Unclear parameters	No	Yes	Histopathological confirmation of dysplasia or malignancy	AF alone: 88.89	AF alone: 43.86
VELscope. Positive measures not defined.	No	Yes	Histopathological diagnosis of carcinoma only	AF alone: 100	AF alone: 74.14
Cone of blue excitation light emitted from handheld unit prototype LAF positive for abnormality	No	Yes	Histopathological diagnosis of dysplasia or carcinoma	AF alone: 98	AF alone: 100

Supporting Information Table S1; Amirchaghmaghi et al., 2018; Betz et al., 2002; Bhatia et al., 2014; Farah et al., 2012; Hanken et al., 2013; Jayaprakash et al., 2009; Rana et al., 2012). Three of seven studies were deemed to have a low risk of bias across all QUADAS-2 domains (Bhatia et al., 2014; Farah et al., 2012; Rana et al., 2012). Bhatia et al. (2014), Farah et al. (2012) and Rana et al. (2012) all reported higher sensitivity values when using AF as an adjunctive tool (73.9%, 46% and 100%, respectively) compared to COE alone (44%, 25% and 17%, respectively) and however decreased specificity when compared to COE alone (97.1%, 68% and 74%, respectively, vs. 99%, 82% and 97%, respectively).

3.3 | Efficacy of autofluorescence in the risk assessment of oral mucosal lesion

3.3.1 | Aiding in the decision to biopsy

No included studies reported data on this parameter.

3.3.2 | Discrimination of benign oral lesions from dysplastic or cancerous lesions

Twenty-one studies reported efficacy on optical autofluorescence in discriminating between benign, dysplastic and neoplastic oral lesions (Amirchaghmaghi et al., 2018; Awan et al., 2011; Awan, Morgan, & Warnakulasuriya, 2015; Babiuch, Chomyszyn-Gajewska, & Wyszyńska-Pawelec, 2012; Betz et al., 2002; Chiang et al., 2018; Farah et al., 2012; Hanken et al., 2013; Jayaprakash et al., 2009; Koch et al., 2011; Lalla et al., 2016; Lane et al., 2006; Marzouki et al., 2012; Mehrotra et al., 2010; Moro et al., 2010; Paderni et al., 2011; Petruzzi et al., 2014; Rana et al., 2012; Sawan & Mashlah., 2015; Scheer et al., 2011; Simonato, Tomo, Miyahara, Navarro, & Villaverde, 2017 2017). Significant heterogeneity and variation in reported efficacy (COE alone: sensitivity: 5.9%–96.6%; specificity: 42.9%–97.8%, OFI alone: sensitivity: 30%–100%; specificity: 12.5%–93%, combined examination: sensitivity: 46%–100%; specificity: 6%–74%) were noted. An overall reduction in specificity was noted when OFI was utilised (alone or as an adjunct) compared to COE.

TABLE 2 Autofluorescence imaging in visualisation of oral mucosal lesions

No	Author, publication year	General or specialist setting	Sample size	Population type assessed	COE done prior to AF?	Was WL used	AF device and technique
Autofluorescence in visualisation of oral mucosal lesions							
1	Bhatia et al. (2014)	General dental practice	222	Patients presenting to a general dental clinic for general check-up	Yes	No. Incandescent operatory light	VELscope. LAF or negative diascopy considered positive for dysplasia/SCC. 2 week review protocol used for positive diascopy
2	Jayaprakash et al. (2009)	Specialist oral medicine	249	(a) Clinically suspicious oral lesions (b) A history of treated OSCC (c) Recently diagnosed untreated OPMD or OSCCs	Yes	Yes	Fluorescence imaging and point spectroscopy. LAF considered positive for dysplasia or carcinoma
3	Betz et al. (2002)	Specialist otolaryngology	214	Patients with proven malignancy or clinically suspicious lesions of the oral cavity or oropharynx	Yes	Yes	Modified short xenon lamp for in vivo tissue excitation. Subjective darker shade of green considered positive for malignancy
4	Paderni et al. (2011)	Specialist oral medicine	175	Patients with at least one oral mucosal lesion with clinical suspicion of OPMD or OSCC	Yes	Yes	VELscope. Abnormally dark on fluorescence in the body or boundary of lesion was considered positive for dysplasia or malignancy
5	Farah et al. (2012)	Specialist oral medicine	118	Patients with an oral mucosal lesion (white, mixed white-red)	Yes	No. Incandescent operatory light	VELscope. LAF and negative diascopy was considered indicative for dysplasia/malignancy
6	Marzouki et al. (2012)	Specialist head and neck oncology	33	Patients with high smoking and alcohol history, with suspicious lesion, history of treated oral cancer	Yes	Unclear	VELscope. LAF was deemed positive for dysplasia or carcinoma
7	Lalla et al. (2016)	Specialist oral medicine	233	Patients presenting with white, red, mixed red-white lesions	Yes	Yes	Identafi. LAF & partial blanching positive for dysplasia or malignancy
8	Lalla et al. (2015)	General dental practice	161	Patients presenting for general dental check	Yes	No. Incandescent operatory light	Identafi. LAF & partial blanching positive for dysplasia or malignancy

3.4 | Efficacy of autofluorescence in the management of OPMD and/or OSCC

3.4.1 | Efficacy of AF determining surgical margins in excisions of OPMD and/or OSCC

No studies met the inclusion criteria for management of surgical excision margins.

3.5 | Secondary outcomes

One study assessed autofluorescence examination as an adjunctive tool to COE in general dental practice (Bhatia et al., 2014). This study was deemed to have a low risk of bias and demonstrated higher sensitivity values with a slight reduction in specificity compared to COE alone in the detection of oral mucosal lesions (73.9%, 97.1% vs. 44%, 99%; Bhatia et al., 2014). No studies reported

Was diascopy used	Clinical lesions detected	Lesions detected by AF device	Border distinctness	Lesion visibility
Yes	161	222 Additional 61 lesions were discovered using VELscope. 58 of which displayed LAF. Lesion detection enhanced by 20%	Border distinctness increased in 21 lesions with VELscope (13%), while COE provided greater border distinctness in 7 (4.3%)	VELscope increased visibility of 16 (9.9%) of lesions detected with COE while 7 (4.3%) were more visible under COE
Unclear	249	325 Additional 76 suspicious lesions identified after WLE with AF and underwent biopsy	Not recorded	Not recorded
Unclear	214	AF alone: 137 Combined: 199	Subjective Border demarcation of SCC cases: COE: Poor: 8.9%, Sufficient: 54.7% Good: 36.7% AF alone: Poor: 37.5% Sufficient: 30.4% Good: 32.1% Combined: Poor: 10.3% Sufficient: 26.5% Good: 63.2%	Not recorded
Yes	175	175	18.4% of lesions noted slight improvement while 66% noted marked improvement, 32.7% decreased distinction with VELscope	49% slight improvement, 28.6% decreased improvement in lesion visibility with VELscope
Yes	113	118 Additional 5 lesions detected with VELscope	No significant difference between border distinctness	No significant difference between visibility
No	17	33 16 additional suspicious lesions were detected with VELscope. Lesion detection enhanced by 31%	Not recorded	Not recorded
Yes	231	233 Additional 2 lesions detected by Identafi	Not recorded	Identafi's WL was equivalent to WL used with use of overhead LED & magnification
Yes	161	161	COE = 30.1% WL = 42.6% Violet light = 55.9% Green-amber = N/A	COE = 75% WL = 84.5% Violet = 77.9% Green-amber = N/A

efficacy of autofluorescence in the long-term surveillance of OPMDs.

4 | DISCUSSION

Of the 27 included studies, six demonstrated a low risk of bias across all QUADAS-2 domains (Supporting Information Table S2; Bhatia et al., 2014; Farah et al., 2012; Lalla et al., 2015; Lalla et al., 2016; Paderni et al., 2011; Rana et al., 2012). Out of these six studies, only three studies utilised OFI as an adjunctive tool, demonstrating promising evidence that detection of OPMD and OSCC can be improved in clinical practice with the use of adjunctive OFI (Bhatia et al., 2014; Farah et al., 2012; Rana et al., 2012). Rana et al. (2012) was the only study identified to use a randomised control study protocol. The results from this study reported a 100% sensitivity when OFI was used

as an adjunct compared to 17% with COE alone. A similar result was seen by both Farah et al. (2012) and Bhatia et al. (2014) who reported higher sensitivity scores with adjunctive OFI than COE alone in a specialist and general dental setting, respectively, using a prospective cross-sectional study design. All three studies assessed the efficacy of VELscope®, with appropriate autofluorescence examination techniques as per manufacturer's instructions, defining a positive autofluorescence parameter as loss of fluorescence and negative diascopy (no blanching) as indicative for dysplasia or malignancy (Bhatia et al., 2014; Farah et al., 2012; Rana et al., 2012). Furthermore, Rana et al. (2012) and Bhatia et al. (2014) also employed a 2-week review protocol for lesions that were suspicious of acute inflammatory origin or where loss of autofluorescence (LAF) could not be clinically accounted for, in an attempt to reduce the rate of false-positive results, further contributing to their high sensitivity scores.

Lesion visualisation and clinical appearance are vital to COE for appropriate diagnosis of OPMD and OSCC (Epstein et al., 2012). It has been shown that visualisation of oral mucosal lesions is greatly influenced by the type of light source used to conduct the examination (McIntosh, McCullough, & Farah, 2009). A study by McIntosh et al. noted better visualisation of lesions using white light emitted from a LED headlight compared to standard dental incandescent yellow light during COE (McIntosh et al., 2009). It is interesting to note that in the current review, only 9 of 27 studies utilised white light to conduct COE (Betz et al., 2002; Cânjău et al., 2018; Hanken et al., 2013; Jayaprakash et al., 2009; Lalla et al., 2016; Lane et al., 2006; Paderni et al., 2011; Simonato et al., 2017; Sweeny et al., 2011). Given the pre-existing subjectivity of COE, optimisation of COE through the standardised use of white LED light to conduct COE may enhance visualisation of oral mucosal lesions in COE alone, and in turn aid in improving accuracy of diagnosis of oral mucosal lesions. Furthermore, the results from this review demonstrate the potential added benefit of the use of adjunctive OFI in improving visualisation of oral mucosal lesions. An overall increase in the number of lesions detected were noted with OFI compared to COE alone (Betz et al., 2002; Bhatia et al., 2014; Farah et al., 2012; Jayaprakash et al., 2009; Lalla et al., 2016; Marzouki et al., 2012), in addition to reported subjective improvement in border distinctness (Betz et al., 2002; Bhatia et al., 2014; Lalla et al., 2016). Of these studies, Bhatia et al. (2014), Farah et al. (2012) and Lalla et al. (2016) were deemed to have a low risk of bias. All three studies reported additional lesion detection under OFI, with Bhatia et al. reporting the highest number of additional lesions detected in 61 patients, enhancing lesion detection by 20% and changing the provisional diagnosis in 12.8% of patients. Given these preliminary findings, optimisation of COE with the use of white LED light, in addition to OFI, may improve the current diagnostic process by providing the clinician with enhanced lesion information and consequently contributing to a more accurate diagnosis of OPMD or OSCC.

The detection of OED or discrimination between benign, dysplastic or malignant oral mucosal lesions has been extensively researched, with literature reporting overall poorer specificity along with significant heterogeneity in published studies (Awan & Patil, 2015; Lingen, Tampi et al., 2017; Luo et al., 2016). The results from this review are in keeping with previous studies assessing discrimination between oral mucosal lesions, demonstrating significant heterogeneity and variation in reported efficacy (COE alone: sensitivity: 5.9%–96.6%; specificity: 42.9%–97.8%, OFI alone: sensitivity: 30%–100%; specificity: 12.5%–93%, combined examination: sensitivity: 46%–100%; specificity: 6%–74%; Amirchaghmaghi et al., 2018; Awan et al., 2011; Awan et al., 2015; Babiuch et al., 2012; Betz et al., 2002; Chiang et al., 2018; Farah et al., 2012; Hanken et al., 2013; Jayaprakash et al., 2009; Koch et al., 2011; Lalla et al., 2016; Lane et al., 2006; Marzouki et al., 2012; Mehrotra et al., 2010; Moro et al., 2010; Paderni et al., 2011; Petruzzi et al., 2014; Rana et al., 2012; Sawan & Mashlah, 2015; Scheer et al., 2011; Simonato et al., 2017). It is also interesting to note that all studies with a low risk of bias except Paderni et al. reported an overall reduction in specificity using OFI compared to COE alone and at present OFI cannot replace histopathological assessment of a tissue biopsy as the gold standard for the diagnosis of OED or OSCC (Bhatia et al., 2014; Farah et al., 2012; Lalla et al., 2016; Paderni et al., 2011; Rana et al., 2012). Based on the results of this review though, a significant component of the heterogeneity can be attributed to the inconsistent implementation of autofluorescence examination. Many studies have reported that autofluorescence examination is subjective, requires initial training to gain confidence in its interpretation and is often considered a limitation of the device (Bhatia et al., 2013; Farah et al., 2012; Lingen, Tampi et al., 2017; Petruzzi et al., 2014). It is noteworthy, however, that none of the included studies assessed subjectivity of the device via an interobserver agreement method of assessment, making it difficult to reliably comment on the subjectiveness of the examination. Furthermore, inconsistent use of positive autofluorescence parameters was noted throughout the included studies, further adding to the lack of standardised technique and interpretation of autofluorescence findings. Only six of the included 27 studies utilised diascopic fluorescence and included a negative diascopy reading coupled with LAF as a positive finding for dysplasia or malignancy (Bhatia et al., 2014; Farah et al., 2012; Lalla et al., 2015, 2016; Paderni et al., 2011; Rana et al., 2012). Diascopy is a technique advised by the manufacturers of these devices to help delineate underlying vascular or inflammatory lesions and hence differentiate between benign and potentially malignant lesions. Some studies have not supported the use of diascopy due to the perceived lack of evidence available to substantiate its use (Awan et al., 2011, 2015; Mehrotra et al., 2010). A recent study by Kordbacheh, Bhatia, and Farah (2016), however, aimed to elucidate the underlying molecular pathways associated with fluorescence properties found diascopic fluorescence to be strongly associated with inflammatory reactions in oral epithelial hyperplasia and dysplasia, and is a common finding in lesions such as oral lichen planus. Further knowledge of underlying fluorescence properties may provide an avenue for standardisation of the use of these devices and in turn aid in improving overall specificity and utility of OFI.

Currently, there is no clear evidence of effective treatment of OPMD, although some data suggest a role for surgical management of OED in reducing risk of malignant transformation (Lodi et al., 2016; Mehanna, Rattay, Smith, & McConkey, 2009; Speight et al., 2018). Given that molecular abnormalities or even cellular changes

consistent with dysplasia can be present in clinically normal tissue, the current method of excision with a margin of macroscopically normal tissue is not precise and is likely to result in subtle mucosal abnormalities being missed with resultant recurrences or malignant transformation (Farah, Kordbacheh, John, Bennett, & Fox, 2018; Poh et al., 2006). The role of OFI in surgical management of OPMD and OSCC has in fact been reported in the literature; however, these studies failed to meet the inclusion criteria of this review (Farah et al., 2018; Poh et al., 2006). This is an inherent limitation of this review, as the inclusion criteria were limited to those studies reporting efficacy of OFI only. There are two studies providing molecular evidence to support the use of OFI in the surgical excision of OPMD and OSCC (Farah et al., 2018; Poh et al., 2006). Poh et al. (2006) delineated field changes in autofluorescence around OSCC and compared the histopathologic and molecular changes of margin biopsies that retained normal autofluorescence with those margins that showed LAF. Results from that study strongly indicated that LAF within or beyond the clinically apparent tumour area was associated with morphologic high-grade and molecularly high-risk tissue change (Poh et al., 2006). The findings further showed that direct OFI can identify subclinical high-risk fields with cancerous and precancerous changes in the operating room setting and demonstrate a potential for their use in mapping excision margins (Poh et al., 2006). These results were further substantiated by a recent study by Farah et al. (2018) that found distinct molecular differences between excision margins of OPMDs determined by white light compared to autofluorescence; in that OFI-determined margins harboured less molecular abnormalities than margins determined by white light, providing strong evidence for the use of OFI in the surgical management of OPMD.

Finally, the use of OFI in a general dental setting has not been encouraged (Lingen, Tampi et al., 2017); however, a study conducted by Bhatia et al. with a low risk of bias reported the usefulness of OFI as an adjunctive tool to COE in general dental practice with sensitivity and specificity scores of 73.9% and 97.9% compared to 44.0% and 99.0% with COE alone utilising a decision-making protocol and a 2-week reassessment of lesions demonstrating LAF (Bhatia et al., 2014). This finding is in keeping with a study published by Laronde et al. that noted a 2.7-fold increased risk of intermediate and high-risk lesions demonstrating persistent LAF at the review appointment compared to retained fluorescence (Laronde et al., 2014). This latter study was not eligible for inclusion in the systematic review due to a lack of reported efficacy values. Both studies, however, demonstrate the promise for adjunctive OFI examination in the general dental setting, by utilising a decision-making protocol for lesion risk assessment (Bhatia et al., 2014; Laronde et al., 2014).

4.1 | Future direction and minimizing risk of bias

Only six of the 27 included studies showed a low risk of bias that have demonstrated promising results for the role of adjunctive OFI to COE in varying aspects of clinical practice. By enhancing the level of clinical information attained through lesion detection or visualisation, and achieving clearer surgical margins of OPMD and OSCC, OFI can play an important role in improving overall patient management. Despite this, many published studies are of poor quality and therefore future prospective, controlled studies are still required in these areas of clinical practice to build on current evidence supporting the use of these devices. Future studies should avoid the major methodological errors that have been noted in many of the included studies in this review. These include unsatisfactory discussion of patient inclusion and exclusion criteria (Cânjău et al., 2018; Marzouki et al., 2012; Petruzzi et al., 2014; Sawan & Mashlah, 2015; Sweeny et al., 2011), small sample size (Babiuch et al., 2012; Cânjău et al., 2018; Marzouki et al., 2012; Moro et al., 2010; Onizawa et al., 1996; Scheer et al., 2016; Simonato et al., 2017; Sweeny et al., 2011) and insufficient reporting of patient characteristics (Babiuch et al., 2012; Jayaprakash et al., 2009; Marzouki et al., 2012; Moro et al., 2010; Petruzzi et al., 2014). Studies including patients with a history of treated oral cancer should provide clear details of their treatment history, as it has been shown that evaluation of oral soft tissues is challenging with OFI in patients who have undergone oral cancer treatment, especially radiotherapy (Hancock, Epstein, & Sadler, 2003). Studies failing to do this contribute to an unclear or high risk of bias in interpretation of autofluorescence results (Babiuch et al., 2012; Jayaprakash et al., 2009; Marzouki et al., 2012; Moro et al., 2010). Furthermore, future studies should include assessment of subjectivity of autofluorescence examination via an interobserver agreement assessment. This review also noted that many studies assessed the role of OFI devices as a stand-alone diagnostic tool, rather than a true adjunctive device (Awan et al., 2011, 2015; Babiuch et al., 2012; Cânjău et al., 2018; Chiang et al., 2018; Mehrotra et al., 2010; Moro et al., 2010; Onizawa et al., 1996; Paderni et al., 2011; Petruzzi et al., 2014; Sawan & Mashlah, 2015; Scheer et al., 2016,2011). Given the potential promising role of OFI in various clinical settings, it is recommended that this technology be considered as a "clinical" adjunct instead of a "diagnostic" adjunct. Perhaps changing our perspective on the use of these devices may encourage users to redirect their studies from investigating its ability to replace COE, to using it in practice as a complementary tool to COE, as it is intended.

Finally, the importance of standardising the use of OFI cannot be emphasized enough to minimise the risk of bias in future studies and improve accuracy scores of these devices. Based on current evidence with minimal bias, we advise that future studies undertake standardised use of white LED light to conduct COE, utilise diascopy as a standard part of the autofluorescence examination, standardise the autofluorescence parameters to include LAF with negative diascopy as indicative for dysplasia or malignancy, indicate partial versus complete diascopy, incorporate a 2-week review protocol and report efficacy data for COE alone, OFI alone and as a combined examination to provide reliable results and contribute towards meaningful meta-analyses in future.

5 | CONCLUSIONS

The results of this review demonstrate promising evidence for the use adjunctive OFI to COE in varying aspects of clinical practice,

contributing to the overall improvement in patient management. We suggest a change in perspective concerning this tool that it be regarded as a clinical adjunct rather than specifically a diagnostic adjunct. This review has highlighted the significant lack of standardisation of the use of OFI devices with regard to technique and interpretation of findings. As a means to improve overall accuracy of these devices, as well as to provide future meaningful data for meta-analyses, standardisation of the use of these devices is of great importance.

CONFLICT OF INTEREST

Author CSF is senior or lead author on several papers highlighted in this systematic review. He has undertaken multiple laboratory and clinical research projects on optical fluorescence imaging but declares no conflict of interest in relation to any of the devices named in this review or affiliation with their respective manufacturer.

AUTHOR CONTRIBUTIONS

Dr Lalima Tiwari designed the study, analysed the data and drafted the manuscript. Dr Omar Kujan designed the study, analysed the data and refined the manuscript. Professor Camile S. Farah designed the study and refined the data analysis and manuscript production.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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