Universidad Europea

GRADUATION PROJECT

Degree in Dentistry

UPDATE ON DIAGNOSTIC TECHNIQUES IN ORAL SQUAMOUS CELL CARCINOMA.

A SYSTEMATISED REVIEW

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1. ABSTRACT

Oral squamous cell carcinoma (OSCC) remains one of the most widespread and dangerous cancers of the head and neck, partly because it is often diagnosed too late. While traditional diagnostic methods are effective, they tend to be invasive, time-consuming, and impractical for frequent screening. Fortunately, recent advances have introduced a range of less invasive tools that aim to detect OSCC earlier and improve outcomes for patients. This review explores several emerging diagnostic techniques, including advanced imaging technologies like OCT, RCM, NBI, and FV, as well as breath analysis and biomarker testing using saliva, serum, and oral swabs. Special focus is given to promising new approaches such as DNA methylation markers, circulating microRNAs, and artificial intelligence-enhanced systems. A total of 22 studies were included in the results of this review. Although many of these methods show great potential, more standardized protocols and large-scale validation are needed before they can become part of routine clinical practice. Looking ahead, combining these innovations into personalized, tech-driven diagnostic strategies could lead to earlier, more accurate, and less invasive OSCC detection

Keywords: Dentistry, Oral squamous cell carcinoma, Oral cancer, OSCC, diagnostic tools, biomarkers, non-invasive imaging, artificial intelligence, dentistry, early detection.

Resumen

El carcinoma oral de células escamosas (OSCC) sigue siendo uno de los cánceres más frecuentes y letales en la región de cabeza y cuello, en gran parte debido a que suele detectarse en etapas avanzadas. Aunque los métodos diagnósticos tradicionales son efectivos, suelen ser invasivos, consumir mucho tiempo y no son ideales para controles frecuentes. En los últimos años, se han desarrollado herramientas diagnósticas menos invasivas que buscan mejorar la detección temprana y los resultados en los pacientes. Esta revisión examina diversas técnicas emergentes como la imagenología avanzada (OCT, RCM, NBI y FV), el análisis del aliento y el uso de biomarcadores en saliva, suero y muestras orales. Se destaca especialmente el papel de los marcadores epigenéticos, como la metilación del ADN y los microARN circulantes, junto con la incorporación de sistemas diagnósticos basados en inteligencia artificial. A pesar de sus resultados prometedores, aún se requiere una validación más amplia y una estandarización adecuada para su uso clínico rutinario. El futuro del diagnóstico del OSCC probablemente se apoyará en la combinación de métodos tecnológicos, personalizados y no invasivos para lograr una detección más temprana, precisa y accesible.

Palabrasclave: Odontología, Carcinoma oral de células escamosas, cáncer oral, OSCC, herramientas diagnósticas, biomarcadores, imagenología no invasiva, inteligencia artificial, detección temprana.

2. INTRODUCTION:

2.1 Cancer: a major global health concern worldwide

Cancer is recognized as one of the leading global health issues, posing a significant barrier to improving overall life expectancy. (1). In 2019, the World Health Organization (WHO) estimated in 112 out of 183 nations that cancer ranks as the first or second cause of mortality before the age of 70, and third or fourth in an additional 23 countries (2). Furthermore, in 2020 there were 19.3 million new cancer cases and 10 million deaths from cancer worldwide. This is equivalent to a cancer diagnosis every 2 seconds and a cancer death every 3 seconds. By 2040, these estimates are projected to rise by 60%, reaching an expected 30.2 million new cancer cases and 16.3 million deaths annually. (3)

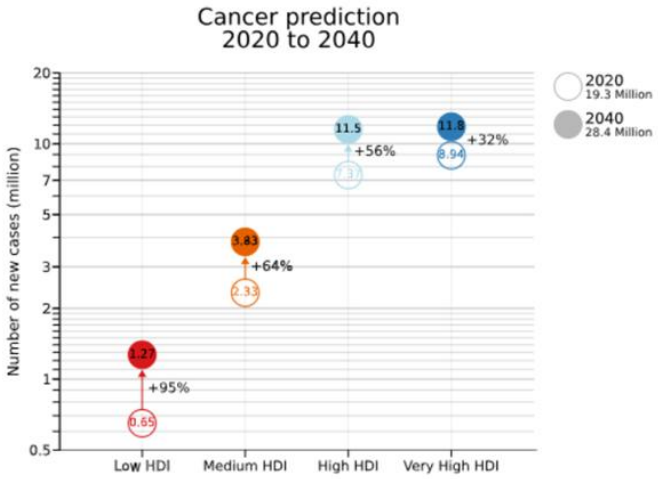


FIGURE 24. Projected Number of New Cases for All Cancers Combined (Both Sexes Combined) in 2040 According to the 4-Tier Human Development Index (HDI). Source: GLOBOCAN 2020.

(3)

Figure 1: Predicted Number of new cases for all Cancers from 2020 to 2040

This burden is attributed to population growth aging and to an increased exposure to risk factors in daily life such as: unhealthy diet, stress, smoking, physical inactivity and environmental carcinogens. (1)

2.2 Overview of oral squamous cell carcinoma (OSCC)

Oral cancers are malignant growths that develop within the oral cavity affecting different parts like the gums, tongue, inside of the cheeks, lips, the floor of the mouth, and the roof of the mouth (palate). (4)

Oral squamous cell carcinoma (OSCC) arises from epithelial tissue within the oral cavity, and its progression can disrupt essential functions such as speech, swallowing, and taste perception (5). Oral squamous cell carcinoma (OSCC) remains a crucial global health concern, with around 390,000 people affected each year worldwide (6). Although the mouth is easy to examine, OSCC is often diagnosed late. As a result, rates of cases and deaths remain high and have shown no progress over the years (5).

Oral squamous cell carcinoma (OSCC) stands as the most prevalent form of head and neck malignancy, comprising over 90% of oral cancer diagnoses and representing a significant burden on global health. It ranks as the 16th most frequently occurring cancer worldwide. Recent global cancer databases indicated that nearly 378,000 individuals were diagnosed with OSCC in 2020, with mortality approaching 178,000. (7)

This highlights the importance of developing comprehensive cancer control strategies, including prevention, prompt diagnosis, and effective treatment. (8)

Currently, men's incidence rates are on average twice is approximately twice that of women. Several reasons, including men's higher use of alcohol and tobacco, which are known risk factors for diseases like oral squamous cell carcinoma (OSCC), could be responsible for this disparity. The observed gender gap may also be influenced by hormonal changes, immunological response variations, and occupational exposure to carcinogens. (9).

Even though the gender gap has closed in some areas because of changing lifestyle choices, men are still much more likely to get various types of cancer and dental conditions. Reducing the overall burden of disease requires addressing these inequities through focused preventative interventions, early detection techniques, and awareness efforts. (1)

2.3 Regional variations and global incidence of oral squamous cell carcinoma (OSCC)

Oral cancer is particularly higher in developing regions of Central and Southeast Asia such as India, Pakistan, Bangladesh, Sri Lanka, Indonesia, and Thailand compared to more industrialized nations. In India specifically, it ranks as the leading cancer among men, comprising 16.1% of all diagnosed cases, and stands as the second most prevalent cancer among women, representing 10.4% of total cases. (9). Elevated incidence is linked to important cultural factors, such as the widespread use of betel quid and tobacco, leading to elevated numbers of cases in those regions (10).

2.4 Oral squamous cell carcinoma (OSCC) premalignant stage and clinical manifestation

Clinically, OSCC is characterized by the appearance of red or white patches with clearly defined edges in the oral cavity. Early stages of the disease tend to be asymptomatic (11). However, as the lesion progresses, it may lead to more pronounced symptoms such as ulceration, nodularity, and a firmer attachment to the underlying tissue. This is the reason why progression is typically indicative of disease evolution and underscores the importance of early detection, as lesions may appear painless at first but can become significantly invasive and symptomatic over time. (12)

OSCC is a disease that develops through multiple stages and undergoes precancerous alterations Oral potentially malignant disorders (OPMDs) represent key precancerous changes that can facilitate the early detection of OSCC and significantly enhance diagnostic precision (13). Among oral potentially malignant disorders (OPMDs), leukoplakia is the most prevalent and is commonly associated with tobacco use. OPMD is usually linked with smoking risk factors (9). Proliferative Verrucous Leukoplakia (PVL) possesses a high likelihood of progression toward malignancy leading to an important need of biopsies to diagnose it (14). Oral lichen planus characterized by submucosal fibrosis and its erosive and atrophic forms also require prompt intervention. (15)

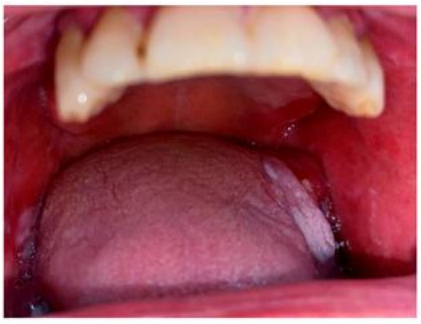


Figure 1. Oral Leukoplakia involving the tongue.

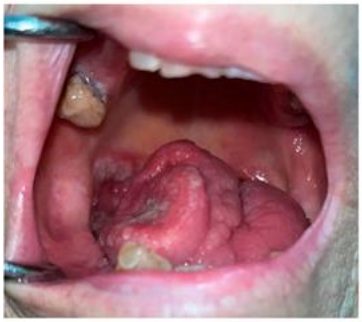


Figure 2. Oral Squamous Cell Carcinoma involving the tongue.

(16)

Figure 2: Oral leukoplakia located on the tongue

Figure 3: Oral Squamous Cell Carcinoma located on the tongue

2.5 Current challenges in Oral squamous cell carcinoma (OSCC) diagnosis

OSCC represents the most aggressive type of oral cancer and is often linked to a poor prognosis, making early detection and treatment especially important (17). Unfortunately, due to the tendency of OSCC of being diagnosed at late stages, the 5 years survival of affected patients remains present over affected populations (18). The WHO reports that nearly 45% of individuals diagnosed with oral cancer do not survive beyond five years. However, when OSCC is identified in its early stages, survival rates dramatically improve, often exceeding 80–90% (17). This underscores the crucial importance of prompt and early-stage diagnosis to improve patient outcomes and survival rates (19)

OPMDs and OSCC diagnosis conventionally relies on a mix of visual inspection and histological investigation through biopsy (20). Although some lesions are frequently visually assessed by clinicians, premalignant alterations or early-stage OSCC lesions can appear normally to the eye and may go unnoticed) (21). Moreover, biopsies offer extensive and deeper cellular and tissular studies but tend to be invasive, time-consuming, and could potentially delay the diagnosis when repeated sampling is required. Furthermore, the reliance on visual inspection for initial screening limits the effectiveness of early intervention and causes delays in diagnosis (22)

2.6 Emerging diagnosis techniques of Oral squamous cell carcinoma (OSCC)

In recent years, progress has been made in addressing the limitations of traditional diagnostic and treatment methods for Oral Squamous Cell Carcinoma (OSCC) through the development of more advanced diagnostic techniques (2). These innovative approaches aim to enhance both the speed and precision of diagnosis, potentially leading to better clinical outcomes (23).

Innovations now span several fields, including molecular biology, cytology, and imaging technologies (24). Each of those has its own strengths which, while OSCC detection and diagnosis processes may be performed across multiple stages, aid to improve the specificity, integrity and efficiency of those processes. Therefore, along with the expansion of the diagnostic methods, there is a continuing development in the degree of complexity of the individualization of the therapy approaches used for the treatment of OSCC and this is a drift forward in the treatment of OSCC (4).

3. OBJECTIVES

Primary objectives:

- To review recent technological advancements used in the diagnosis of Oral Squamous Cell Carcinoma (OSCC).
- To evaluate how these innovations impact the accuracy and speed of diagnosis.
- To assess the potential clinical benefits of these advancements, offer for improving patient outcomes in oncology.
- To explore how emerging diagnostic tools may contribute to earlier detection, less invasive screening, and more efficient treatment planning.

Secondary objective:

- To identify limitations of traditional diagnostic methods and compare them with the innovative ones.

PICO: When compared to traditional approaches like histopathology and biopsy, do innovative diagnostic methods improve accuracy in patients suspected of having Oral Squamous Cell Carcinoma?

4. MATERIAL AND METHODS

A comprehensive literature review was conducted using PubMed as the primary database to identify recent advancements in diagnostic tools and techniques for oral squamous cell carcinoma (OSCC). The following search terms were used, formatted according to standard PubMed syntax: (("Diagnosis technique"[Title]) OR ("Diagnosis tools"[Title]) OR ("Diagnosis update"[Title])) AND (("Oral squamous cell carcinoma"[Title]) OR ("OSCC"[Title]) OR ("Oral cancer"[Title])). The initial search returned 9,154 results. To improve the relevance and quality of the findings, several filters were applied: first, a publication date filter limited results to articles published within the last five years, narrowing the pool to 3,039 articles. Then, a full-text availability filter was applied, further reducing the count to 2,978. To focus on the most rigorous and informative studies, case-control articles were excluded, and only meta-analyses, reviews, systematic reviews, and controlled clinical trials were considered, resulting in 507 articles. A two-step screening process followed. The first step involved a title review to identify studies directly related to diagnostic methods for OSCC, bringing the total down to 205. In the second step, abstracts were reviewed in detail to assess each article's relevance and quality in line with the research objectives. This process ultimately led to the selection of 86 high-quality and relevant articles. These sources were then carefully analyzed and organized to provide insight into diagnostic accuracy, clinical applicability, and emerging innovations in OSCC diagnosis, result in in a thorough and well-supported review.

5. PRISMA DIAGRAM:

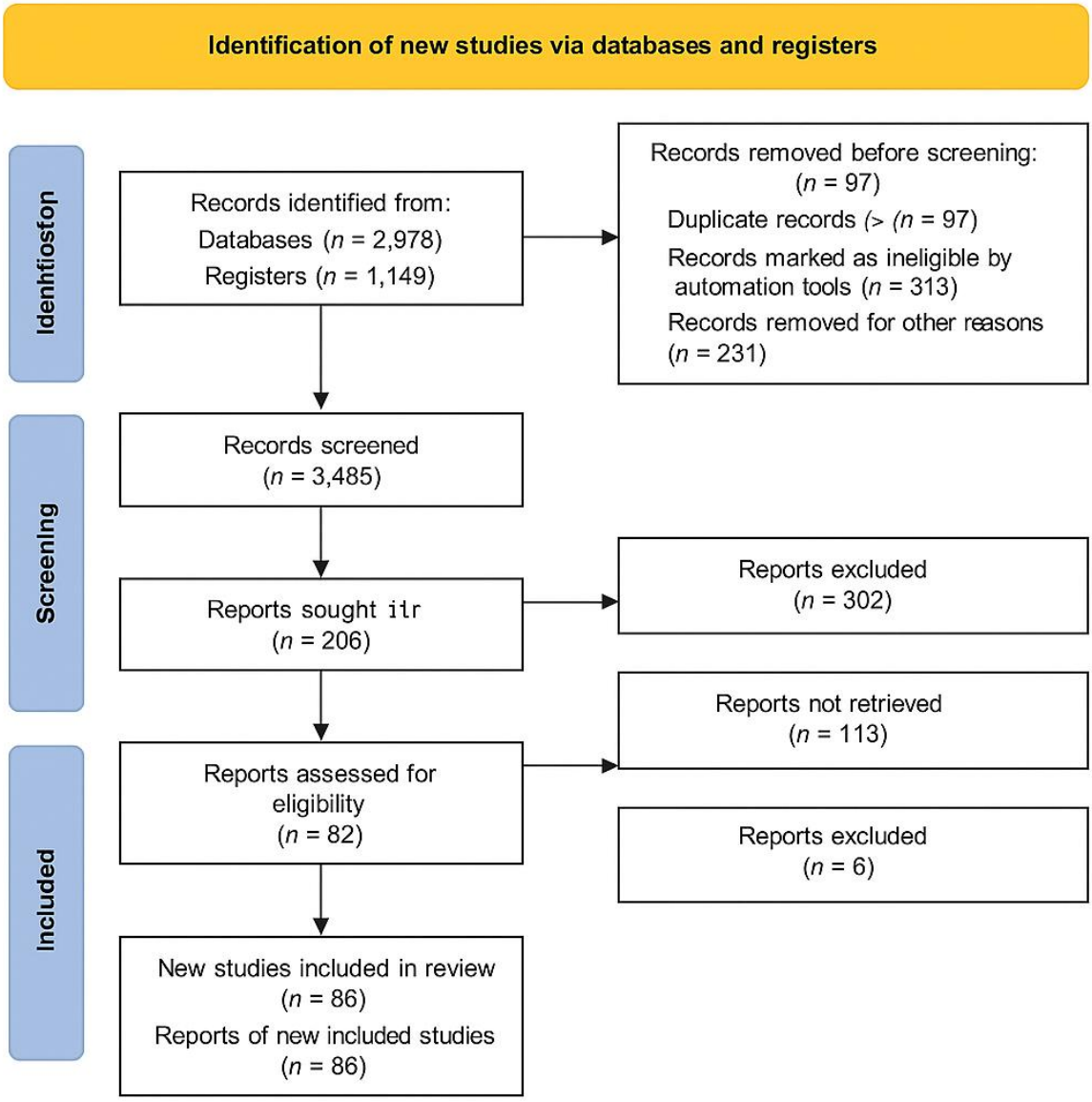


Figure 4: PRISMA Diagram

6.RESULTS

Traditional diagnostic methods such as visual and histological examination remain the gold standard diagnosis for OSCC detection. (1) This requires well trained practitioner and tends to be invasive, hurtful and time consuming for patients. (22)

However, they are often invasive, time-consuming, and not always feasible for repeated assessments. The need for non-invasive, highly sensitive, and specific diagnostic tools has driven the exploration of novel biomarkers and advanced imaging techniques (9)

Reflectance Confocal Microscopy (RCM)

Year Autor	Country	Study Type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
2019 (25) **Peterson et al.**	USA	Pilot study	4 healthy volunteers (imaging normal oral mucosa), 20 patients with oral squamous cell carcinoma (OSCC)	Non invasive imaging, reflectance confocal microscopy (RCM)	OSCC patients, the adjacent normal mucosa (margin) was used as a paired control	Hand-held RCM probe	The video mosaicking technique showed better overview of the lesion including edges, offering a wider perspective compared to Traditional single frames. Sensitivity, 1.000 Specificity, 0.933 PPV, 0.909 NPV 1.00
2020 (26) **Contaldo et al.**	Italy	Prospective case–control study	30 oral sites from 21 patients (including lesions such as [leukoplakia/traumatism], erosive-ulcerative lesions, verrucous lesions, and 2 sites of clinically healthy mucosa as controls).	Reflectance confocal microscoy (RCM)	Histopathological examination via biopsy served as the reference (gold standard) for most lesions. Additionally, the imaging of clinically healthy mucosa provided a baseline control for RCM features.	The VivaScope 3000 confocal laser scanning microscope for acquiring RCM images, and Conventional histopathological analysis of biopsy samples to validate the RCM findings.	RCM detected key signs of OSCC, such as keratin pearls, irregular cell shapes, and disorganized tissue structure. When verrucous lesions were excluded since they were harder to analyzed with RCM the test reached perfect sensitivity and very high overall diagnostic accuracy. Sensitivity: 1.000 Specificity: 0.933 PPV: 0.909 NPV: 1.000

Narrow Band Imaging (NBI)

Year author	Country	Study Type	Sample size	Diagnosis method	Control	Measuring instrument	Outcome
2021 **Nair et al.** (27)	India	Prospective Observational Study	50 patients	Narrow-Band Imaging (NBI) VS White Light (WL)	50 patients (51 lesions)	EVIS EXERA III Xenon Light Source CLV-190	NBI higher sensitivity (92.67%) and specificity (90.16%) vs . WL (74.07% and 79.17%). Overall accuracy: NBI (92.16%) vs. WL (76.47%). Strong interobserver agreement (κ = 0.881). NBI is a Superior Diagnostic tool OSCC detection
2022 **Ota *et al.*** (28)	Japan	Cross-sectional (clinicopathological imaging) study	60 patients with suspected OPMDs or OSCC	Conventional visual inspection (CVI) and white-light endoscopy (WLI) were performed, followed by narrow-band imaging (NBI) to assess intraepithelial papillary capillary loop (IPCL) patterns . IPCL patterns were classified into five types (0–IV) based on established criteria (Type III–IV considered "high-grade")	10 healthy volunteers with normal oral mucosa (no lesions) served as controls (underwent WLI & NBI imaging; no biopsy)	Olympus Evis Lucera Spectrum video endoscopy system (CV-190 processor & CLV-190 light source; Olympus Medical, Tokyo) with standard and NBI optical filters	NBI larger lesion than WLI for OLP and leukoplakia Appeared more extensive under NBI) All confirmed OSCC cases showed high-grade (Type III–IV) IPCL Patterns on NBI

2013 **Yang et al,** (29)	Taiwan	Retrospective Cohort Study	80 OSCC patients	Narrow Band Imaging (NBI)	Not specified	NBI Endoscope (Olympus Medical Systems)	Three intraepithelial patterns identified using NBI with correlation with OSCC sever tumor infiltration depth ($p < 0.0001$), TNM stage, lymph vascular invasion, and perineural

Fluorescence Visualization (FV)

Year author	Country	Study Type	Sample size	Diagnosis method	Control	Measuring instrument	Outcome
2020 **Morikawa et al.** (30)	Japan	Observa-tional (Clinical Study)	502	Histopathol-ogical examination (biopsy); fluo-rescence visualiza-tion (FV)	Normal mucosa from the same sub-site (within patients	Fluorescence visualization devices (ORALOOK® and IllumiScan®)	FV subjective evaluation: high sensitivity (96.8%), low specificity (48.4%). Objective evaluation (Image analysis): high sensitivity (up to 85.1%) and specificity (up to 84.6%).

Autofluorescence Imaging (AFI)

Year Author	Country	Study type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
2017 **Quang et al.** (31)	USA	Prospective observational study	100 patients	Multimodal Optical Imaging (AFI + HRME + AI-based analysis)	Standard histopathology (biopsy)	AFI (Wide-field Autofluorescence Imaging), HRME (High-Resolution Microendoscopy) Automated Image Analysis Algorithm	Improved early detection and diagnostic accuracy. Automated analysis classified 98% of non-neoplastic sites and 95% of neoplastic sites correctly. From 35.42% to 72.73% Accuracy improved to 85.07%.
2019 **Chiang et al** (32).	Taiwan	Comparative observational study	126 patients	Autofluorescence Imaging (AFI) with COE	Standard histopathology (biopsy)	Horus UOC 100 TM Digital auto-Fluorescente Camera	Sensitivity for detecting dysplasia increased From 77.94% to 87.50%, and specifically improved

Optical Coherence Tomography (OCT)

Year Author	Country	Study type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
2022 **Panzarella et al.** (33)	Italy	Pilot Study	30 with OSCC	Optical Coherence Tomography (OCT**)**	Site-matched healthy mucosa OCT scans from volunteers (not specified; at least one per anatomical site)	VivoSight® SS-OCT (Swept-source Fourier-Domain OCT)	Provides high-resolution structural imaging with strong histology correlation and real-time scanning capability.

Breath Analysis

Year Author	Country	Study type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
2021 **Mentel et al.** (34)	Germany	Prospective controlled study	35 OSCC patients	GC–IMS breath analysis + Machine Learning	50 controls	GC–IMS (BreathSpec®); ML algorithms (LR, KNN, RF, etc.)	VOC signatures differenti OSCC from controls with up to 90% accuracy. Promising non-invasive method for early detection.

Artificial Intelligence / Machine Learning Models

Year Aut	Country	Study Type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
2022 **Alanazi et al.** (35)	Saudi Arabia	Experimental Study AI-Based Diagnostic Accuracy Study	Biomedical imaging dataset from Kaggle (exact number of images not specified)	AI-Based Imaging (Deep Learning Model for OSCC Detection)	(non-cancerous images)	DL-OSCDC Model (NasNet + Deep Belief Network)	Accuracy: 95% Sensitivity 94% High-performance AI-based OSCC detection tool
2020 **Qiuyun Fu et al.** (36)	China	Retrospective diagnostic study	Development dataset: 5,775 images Internal validation dataset: 401 images Clinical validation dataset: 666 images External validation dataset: 402 images	Deep learning-based CNN (AI-based imaging)	Normal oral mucosa images and non-OCSCC images (benign lesions).	CNN algorithm	internal validation: Sensitivity: 95%, Specificity: 89% External validation: Sensitivity: 90%, Specificity: 81% Clinical validation: Sensitivity: 91.0%, Specificity: 93.5% Early-stage OSCC detection: Sensitivity: 97%, Specificity: 93% Deep learning model for OSCC screening With high accuracy

Salivary / Serum Biomarkers

Year Aut	Country	Study Type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
2021 **Puneea et al.** (37)	India	Prospective case–control study	50 OSCC cases,	Targeted proteomics (PRM) of salivary proteins	49 Controls	LC–MS/MS with PRM; ELISA for validation	Identification of a biomarker panel (AHSG, KRT6C, AZGP1, KLK1, BPIFB2) with high diagnostic accuracy (e.g., AUC up to 88 % for late-stage OSCC)
2021 **Romani C** (38)	Italy	Case-Control Study	89 OSCC Patients	Salivary miRNA-based biomarker detection for OSCC	58 Controls	RT-qPCR	3-miRNA panel (miR-106b-5p, miR-423-5p, miR-193b-3p) AUC = 0.98, Sensitivity = 97%, Specificity = 94% Highly accurate non-invasive diagnostic biomarker for OSCC. AUC = 0.98, Sensitivity = 97.4%, Specificity = 94.2% for the combined 3-miRNA panel.

Year Author	Country	Study Type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
2019 **Inukai et al.** (39)	South Korea	Primary study (Clinical study	62 OSCC patients	Serum biomarkers (ELISA for IL-6, P. gingivalis IgG, and F. nucleatum IgG)	46 healthy controls	ELISA (enzyme-linked immunosorbent assay)	Sensitivity : P.gingivalis IgG (53%), IL-6 ´ (60%); Specificity: P. gingivalis IgG (84%), IL-6 (71%). Higher IL-6 and P. gingivalis IgG levels in OSCC patients. IL-6 correlated with worse prognosis.
2023 **Rebaudi et al** (40)	Italy	Clinical study	15 OSCC patients	Non-invasive cytobrush biopsy with ELISA for biomarkers (EGFR, Ki67, p53, PD-L1, HLA-E, B7-H6)	Healthy tissue from the same patients	Femtohunter ®ELISA system	Cytobrush-ELISA successfully differentiated OSCC lesions from healthy tissue. Sensitivity & Specificity values were not explicitly reported, but all 6 biomarkers were significantly overexpressed in OSCC tissue ($p < 0.001$). Promising potential for non-invasive OSCC screening.
2024 **Zheng et al.** (41)	China	Case- Control study	OSCC patients: 76 OPMD patients: 30	Salivary and serum biomarker detection using Cellular Prion Protein (PrPC**)**.	78 Healthy controls	ELISA (for PrPC quantification in saliva and serum). Statistical Analysis: Receiver Operating Characteristic (ROC) curves	Salivary PrPC: AUC = 0.807 Sensitivity = 91% Specificity = 63% Serum PrPC: AUC = 0.671 Sensitivity = 56.5% Specificity = 80% Potential salivary biomarker for OSCC detection

						AUC (Area Under Curve) for diagnostic	

Year Author	Country	Study Type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
Muy-Teck Teh et al., 2022 (42)	UK, China, India	Retro--spective Cohort Study (for 5-year OPMD transformation analysis in India)	535 total samples (UK: 282, China: 35, India: 218)	Quantitative Multigene RT-qPCR test (qMIDS V2)	Normal oral mucosa, oral leukoplakia, oral submucous fibrosis, OSCC patients	qPCR system measuring 16-gene expression	UK Cohort (n = 282): Sensitivity: 88% Specificity: 96% Accuracy: 92% China Cohort (n = 35): Sensitivity: 88% Specificity: 91% Accuracy: 89% India Cohort (n = 218): Sensitivity: 97% Specificity: 86% Accuracy: 93%
2016 **Yamada H, et al.** (43)	Not specified	Case-control study	31 patients with oral cancer	Quantitative analysis of circulating microRNAs	31 healthy controls	Microarray analysis and validation tests for miR-223 expression levels	Suggest That Circulating miR-223 could serve as a potential non-invasive biomarker for OSCC diagnosis and may have thera peutic implications in oral cancer mana gement. Sensitivity of 67.7%, and a specificity of 61.3%.
2019 **He L, et al.** (44)	China	Case-control study	49 OSCC patients, 14 healthy controls	Salivary exosomal miRNA analysis	14 healthy individuals	qRT-PCR miRNA microarray, ROC analysis	miR-24-3p was significantly overexpressed in OSCC patients' salivary exosomes. AUC = 0.738, Sensitivity = 64.4%, Specificity = 80%.

							miR-24-3p promotes OSCC prolifera by targeting PER1.
Year Author	Country	Study Type	Sample size	Diagnostic method	Control	Measuring instrument	Outcome (Marginal fit)
2021 **Nakamura K, et al.** (45)	Japan	Case-control study	40 OSCC patients,	Circulating serum microRNA analysis	40 healthy controls	Microarray, qRT-PCR, ROC analysis	A 6-miRNA panel (miR-24, miR-20a, miR-122, miR-150, miR-4419a, miR-5100) achieved high diagnostic accuracy (AUC = 0.844, Sensitivity = 55%, Specificity = 92.5%). Panel outperformed serum SCC-Ag in detecting OSCC.
2022 **Bigagli E, et al.** (46)	Italy	Case-control study	30 OSCC patients, 14 healthy controls	Circulating extracellular vesicle (EV) miR-210 analysis	14 healthy individuals	qRT-PCR, ROC analysis, Kaplan-Meier survival	EV-miR-210 was significantly upregulated in OSCC patients ($p<0.0001$). ROC

7. DISCUSSION

Management of oral squamous cell carcinoma (OSCC) continues to be a public health issue owing to high morbidity and mortality. (19). Early diagnosis is urgent as this is essential for a better survival outcome (7). Although the classic diagnostic methods, such as histopathology and conventional imaging (MRI, CT, and PET scans), provide a reliable approach, they also have weaknesses in specificity, sensitivity, and the ability to detect diseases in the early stage. (47)

They are also invasive and risk missing early-stage malignancies. However, fortunately, improvements in technology are developing non-invasive and minimally invasive techniques which gives a hope for early-stage detection and treatment. (48)

In this discussion, we'll explore new emerging diagnosis approaches, examining their potential benefits as well as the challenges that still need to be addressed.

7.1 Reflectance Confocal Microscopy (RCM)

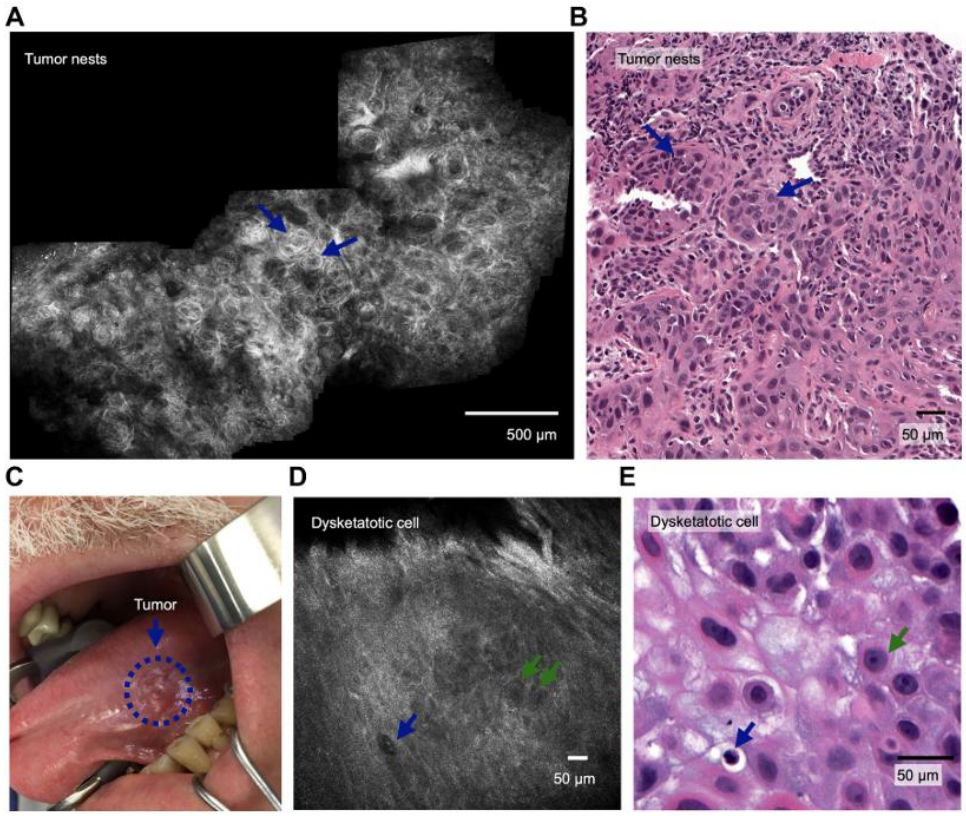
Reflectance Confocal Microscopy (RCM) is an advanced, non-surgical imager that facilitates the direct visualization of tissue structures at the cellular level, providing similar levels of detail to conventional histopathology. In more than three decades, RCM has been an established feature of dermatology, commonly used to diagnose skin cancers, pigmented lesions, and other inflammatory dermal disorders (49).

In recent times, it has begun to gain traction within the specialties of dentistry and oral pathology to enable clinicians to assess both soft and hard oral tissues with greater accuracy (50).

(51)

<u>Figure 5:</u> Design of the reflectance confocal microscopy study. This illustration shows the procedural steps followed in the operating room.

RCM is especially inviting for the way it can detect how various cell constituents refract light to produce detailed images like live histology. In OSCC, it can favorably accentuate structural and cytological variations between malignant and benign tissue. (26).



(51)

Figure 6: RCM imaging of a 68-year-old male, with an 8-year history of tobacco exposure, harboring a 1 cm OSCC of the ventral tongue.

Reflectance Confocal Microscopy (RCM) provides near-histological resolution and is especially useful for assessing epithelial structures without biopsy. This strong correlation suggests RCM could reduce the need for multiple biopsies, particularly when monitoring lesion progression over time (37).

In a study by Peterson et al. (2019) demonstrated excellent diagnostic accuracy using a hand-held RCM probe, reporting sensitivity of 100% and a specificity of 93,3 % when distinguishing OSCC from adjacent normal mucosa. They also used a video mosaicking technique that gave a wider view of the lesion, helping them see the edges more clearly. RCM gives a detailed look at both the lesion and surrounding tissue, which can be helpful during treatment (25).

Another study by Contaldo et al. (2020) looked at different types of oral lesions, not just cancer, and still found that RCM matched well with biopsy results. Even though they focused more on non-cancerous issues like leukoplakia or trauma, their work supports the idea that RCM is a strong tool for telling the difference between normal and abnormal tissue. Like in our study, they

showed that RCM could be a helpful, noninvasive way to check what's really going on in the mouth and possibly even reduce the need for repeated biopsies (26).

In comparison to conventional methods, RCM increases visualization of vascular and cellular structures. In non-keratinized tissues, it can access submucosal layers, providing greater depth below the surface (51).

Still, RCM isn't without its flaws. Originally designed for skin, it doesn't always work well with the complex and varied structure of the oral cavity especially in harder-to-reach areas (50). The system also lacks motorized lens adjustment, so the clinician must manually apply and position it during use. This can cause movement and makes the process even more dependent on the operator's skill (50).

RCM can only reach 200–300 micrometers deep, which isn't enough for assessing deeper lesions. It also lacks motorized lens control, high costs, and has a small imaging field. (52).

Reading the images can also depend on the clinician's experience, bringing some subjectivity into the diagnosis. Benign conditions like leukoplakia or lichen planus can look like early OSCC, so a biopsy is still needed in those cases. (25).

RCM has a promising future, but a few key challenges need to be addressed first. For one, we need probes designed specifically for the unique shapes of the mouth. (26). Adding AI could really help by making it easier to spot signs of cancer and making results more consistent (53). And to really prove its value, we need long-term studies to see how well RCM can track risky changes and help predict which conditions might turn into cancer (54).

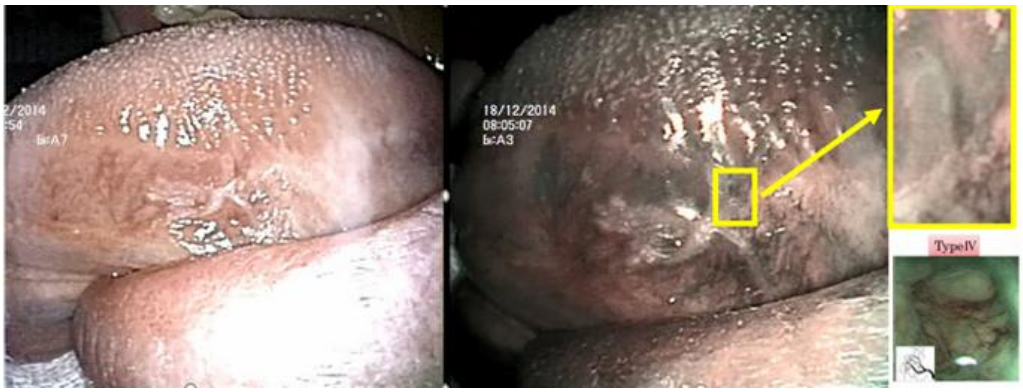
7.2 Narrow Band Imaging system (NBI)

Narrow-band imaging (NBI), also referred to as virtual chromoendoscopy with magnification (VCM), is extensively applied in the diagnosis and monitoring of pharyngeal and esophageal malignancies. This technique allows differentiation of neoplastic vascular patterns from those associated with benign conditions. (55).

NBI combines standard endoscopes with magnification and a traditional white-light source enhanced by narrow-bandwidth filters that can sequentially emit green-blue light, altering the spectral properties of the incoming light (56).

Hemoglobin has a strong absorption of green and blue light; shorter wavelengths penetrate tissues causing good contrast for the mucosal microvasculature highlighting the more superficial

vessels found in the submucosa. The green light, with a wavelength of 540 nm, penetrates deeper into the tissues, showing deeper vessels beyond the mucosa (57).



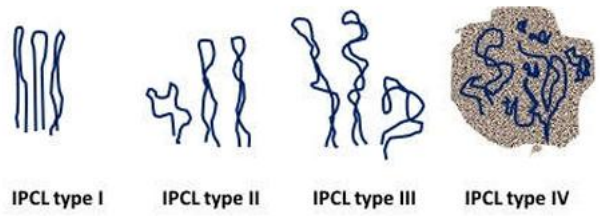
(58)

Figure 7: Example of detection of OSCC through NBI

The blood vessels analyzed, termed intraepithelial papillary capillary loops (IPCLs), are situated close to the connective tissue papillae within the oral mucosa. Their structural characteristics provide insight into changes occurring in the epithelial layer above, often reflecting pathological alterations (59).

In 2010, Takano et al proposed a classification system for intraepithelial papillary capillary loop (IPCL) patterns in the oral mucosa, dividing them into four distinct types that correlate with progressive cancer- related changes.

- Type I, regular loops;
- Type II, dilatated and crossing loops;
- Type III, elongated and meandering loops;
- Type IV, disrupted loops and neoangiogenesis.



(60)

Figure 8: Takano et al classification

- Type I represents regular loops; - Type II dilated and crossing loops; - Type III includes elongated and meandering loops; - Type IV features disrupted loops and neo angiogenesis.

NBI is a helpful tool in oral pathology because it shows blood vessel patterns under the surface of a lesion. IPCL pattern IV is often seen in serious cases like oral cancer and high-grade dysplasia and is usually linked to more advanced disease. In contrast, patterns I and II are mostly found in harmless or non-cancerous conditions like mild leukoplakia or non-inflamed lesions. (61)

IPCL type III appears in both malignant and benign conditions like OSCC, leukoplakia, and inflammation, making diagnosis harder. NBI is less effective in thick keratinized lesions or when bleeding blocks the view of blood vessels. (60)

In such instances, NBI should be conducted at the edges of the lesions, but this approach may underestimate their malignancy (62).

A study validated Takano's IPCL classification by showing that all OSCC cases were linked to type III and IV patterns. High-grade IPCLs were strongly associated with malignancy, with the study reporting 100% sensitivity, 80.9% specificity, and 85.0% accuracy. These findings highlight NBI's potential to improve early OSCC detection by spotting high-risk lesions that white-light imaging might miss. (28). Three defined microvascular patterns have been well identified using NBI which strongly correlated with OSCC severity and tumor infiltration. ($p<0,0001$). (62)

The most crucial finding was that IPCL destruction was potentially associated with advanced stages of diseases, proposing that NBI can serve as a valuable tool for real- time assessment of OSCC severity. (63)

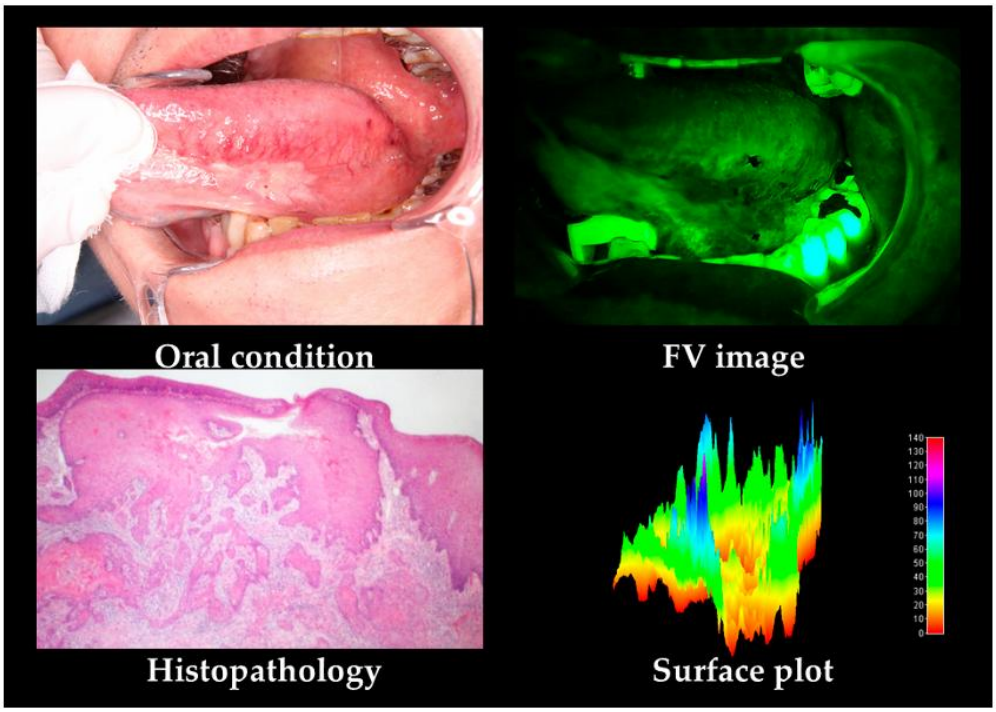
This matches Takano et al.'s IPCL classification, where Type IV is linked to OSCC and higher grades of dysplasia. Seeing this pattern shows that NBI can help tell the difference between cancerous and non-cancerous lesions by looking at their blood vessel patterns (64).

7.3 Fluorescence Vizualization (FV)

Fluorescence visualization (FV) has emerged as a tool in the early detection and management of oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMDs).

By enabling real-time assessment of tissue autofluorescence, FV aids clinicians in identifying lesions that may not be apparent under conventional white light examination. (65)

A study in Japan evaluated the efficacy of FV using devices like ORALOOK® and IllumiScan® in volunteered patients. They demonstrated a high sensitivity of 96.8% but a low specificity of 48.4% (30).



(30) **Figure 9: Early-stage oral squamous cell carcinomas (OSCC) case**

In a Brazilian population screening study, it has been showed that incorporating FV into routine examinations increased the detection rate of OPMDs. The sensitivity and specificity for detecting epithelial dysplasia were reported at 100% and 92.4%, respectively. (66)

In a study assessing the diagnostic value of the VELscope device, the objective FV method demonstrated a sensitivity of 65.4% and a specificity of 82.1% in distinguishing high-risk lesions from low-risk ones. Notably, the sensitivity for detecting oral cancer in the lining mucosa was higher (81.0%) compared to the masticatory mucosa, suggesting that FV may be more effective in certain oral regions (67)

Another investigation evaluated a simple handheld FV device in 175 patients and found a high sensitivity of around 97% for detecting OSCC. However, the device showed lower sensitivity in differentiating between mild and moderate/severe dysplasia, indicating limitations in its ability to stratify lesion severity. (68)

These findings underscore the potential of FV as a non-invasive, real-time diagnostic aid in oral oncology. While FV devices like VELscope can enhance lesion detection, their varying sensitivity and specificity across different oral sites and lesion severities highlight the need for complementary diagnostic approaches. Integrating FV with conventional examination methods and histopathological analysis may improve diagnostic accuracy and patient outcomes. (65)

Fluorescence visualization (FV) studies also showed low specificity, as benign conditions like inflammation or oral lichen planus can also cause fluorescence loss, leading to false positives (66,67). Additionally, results can vary based on the clinician's experience and interpretation, which limits consistency and reliability (68). Another drawback is its limited depth of detection, assessing superficial epithelial layers and may miss deeper or early-stage invasive lesions (65). Finally, FV cannot reliably distinguish between dysplastic, malignant, and benign lesions on its own, (68) making it better suited as an adjunct to clinical examination and biopsy rather than a standalone tool (65).

7.4 Autofluorescence Imaging (AFI/OFI)

Autofluorescence Imaging (AFI), also referred to as Optical Fluorescence Imaging (OFI), has been extensively studied as a supportive tool for the early detection of oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMDs).

One study found that combining Autofluorescence Imaging (AFI) with a standard clinical oral examination (COE) helped sensitivity notable improvement, increasing by approximately 11%. (32). Another study showed reaching near-complete detection (100%) when image interpretation was based on the examiner's judgment (30). However, the improved detection came with a drop in specificity to around 50%, supporting there were more false positives. But when more objective tools were used to analyze the images, specificity importantly increased while sensitivity remained consistently high. (30).

These findings align with broad results from a systematic review of 27 studies on AFI in OSCC and OPMDs (46). That review confirmed that AFI used as an adjunct to COE offers a clear advantage in terms of sensitivity, which ranged between 50% and 100% across the studies. In contrast, COE alone demonstrated a wider and more variable sensitivity range, varying broadly across cases. However, the studies included in this project, AFI's accuracy tended to be very low, in some cases when used as the only diagnostic method (67). While AFI can help spot more lesions, it also risks identifying a higher number of benign or inflammatory lesions as suspicious leading to more false positives (67).

Another review emphasized that AFI performs significantly better when integrated into a structured diagnostic protocol. For example, checking for inflammation with diascopy and then looking at the lesion again after two weeks made the results more accurate. In these cases, the test still caught all true positives (reaching close to 100% sensitivity) while significantly reducing false positives, with specificity rising to about 98%. This approach helps ensure that any observed

fluorescence loss is more likely linked to a real cancer risk rather than temporary inflammation. (68).

AFI also enhances lesion detection by clearly defining lesion margins and revealing subclinical changes not visible under white light. In one low-bias study, AFI helped identify 61 new lesions, boosting detection rates by 20% and leading to a change in diagnosis in nearly 13% of cases (46). Despite these benefits, many of the devices rely heavily on visual interpretation of fluorescence loss, which can vary significantly between clinicians, especially those with less experience. In fact, the review noted that few studies assessed interobserver variability, making it difficult to fully evaluate how consistent AFI results are across different practitioners (68). Additionally, many devices on the market do not come with integrated diagnostic algorithms, leaving interpretation entirely to the clinician's judgment. While some more recent studies have started to incorporate software-assisted analysis to improve objectivity, this remains an area that requires further development and research (68).

Another issue is that studies use different devices, like VELscope® and Identafi®, which can affect results. These tools come with recommended steps like using diascopy, but not all studies followed them. For example, two studies in this review (22,30) didn't mention diascopy or short-term follow-up, which might explain their lower specificity. This lack of consistency makes it hard to compare results and shows why standardized protocols are needed (22, 30).

In conclusion, AFI is a useful adjunct tool for diagnosing OSCC, but its accuracy largely depends on how it is applied. When used within a structured clinical process that includes COE, diascopy, follow-up, and possibly automated image analysis, AFI can improve lesion detection while minimizing false positives. However, using AFI as a standalone method may lead to overdiagnosis and unnecessary biopsies. The findings of this project are consistent with the broader literature, reinforcing that AFI is most effective when carefully integrated into a well-defined and planned diagnostic strategy (68).

7.5 Optical Coherence Tomography (OCT)

The potential of Optical Coherence Tomography (OCT) for diagnosing oral squamous cell carcinoma (OSCC) has been explored in both clinical settings and reviews. In the pilot study included in this project (33), OCT was used in real-time to scan OSCC lesions. The images gave detailed, cross-sectional views that looked a lot like traditional histology, making it possible to spot key changes in tissue structure like the loss of normal layers seen in cancer. OCT also showed promise for identifying lesion edges and getting a better picture of tissue architecture. But since

this was a small pilot study, it didn't include full diagnostic stats like sensitivity or specificity, which makes it harder to directly compare its performance to other methods. (33).

In contrast, a more recent meta-analysis published in 2023 gives a deeper statistical evaluation of the accuracy of OCT's. pooling data across multiple studies. This review showed OCT had promising diagnostic accuracy, with both sensitivity and specificity consistently exceeding 90% AUC of nearly 95%. Even more notably, the increased negative predictive value highlighted how effective OCT could be for detecting disease in screening contexts (69).

There's also an important difference in how image interpretation was approached in the two sources. While the pilot study relied on clinicians manually analyzing the images, the meta-analysis highlighted that artificial intelligence (AI) and automated interpretation systems outperformed human readers, particularly in terms of sensitivity. This matters because OCT produces a huge amount of imaging data, and AI tools can help conclude general interpretation and reduce the further variability between different clinicians, an advantage not covered in the smaller-scale clinical study (33, 69).

The meta-analysis showed that OCT works better for detecting confirmed cancer than for spotting early, pre-cancerous changes. It's good at picking up clear signs of cancer but may miss the more subtle ones. That aspect wasn't really addressed in the pilot study either, which focused only on confirmed OSCC (69).

OCT performance has been explored with artificial intelligence showing sensitivity ranges from approximately 75% to 100% and specificity between 70% and 100%. The best results came from AI-assisted image, underscoring how OCT, could really change how we approach OSCC diagnosis. (70).

In summary, while the pilot clinical study and the two reviews back up OCT's potential as a diagnostic tool, they state it in different ways. The clinical study shows practical insight into how OCT pathways can be used in clinical life, while the systematic reviews offer more comprehensive data on its diagnostic strengths and technological developments. What really stands out is that combining OCT with AI seems to be the way forward bringing consistency, improving accuracy, and ultimately helping clinicians catch OSCC earlier and more confidently. Still, large clinical trials and protocol standardization are going to be needed to prove if OCT can reach its full potential in everyday clinical use (33, 69, 70).

7.6 Breath Analysis

In a prospective study conducted in Germany breath samples were examinate using gas chromatography ion mobility spectrometry (GC–IMS). By combining this technology with machine learning methods 90% accuracy was achieved in distinguishing cancer patients from healthy individuals based on unique volatile organic compound (VOC) patterns (34).

Higher levels of volatile sulfur compounds (VSCs) in the breath are often found in OSCC patients. Using a simple gas chromatography method with logistic regression, one study reached an AUC of above 70% showing that even basic breath tests can help with non-invasive diagnosis. (71) . Adding to this, a 2017 pilot study analyzed breath samples from OSCC patients before and after surgery. They found a pattern of several VOCs linked to the tumor three of which disappeared completely after surgery. This suggests breath analysis could help both with OSCC's diagnosis and tracking treatment progress. (72)

Moreover, several VOCs such as dimethyl undecane and benzaldehyde were consistently associated with cancer presence. Breath biopsy techniques show high accuracy, sensitivity, and specificity, but emphasized the need for further research to validate and standardize protocols. (73)

Breath analysis still being an emerging technique, it consistently shows potential as a safe, painless, (34) and accessible method for the early diagnosis and monitoring of OSCC (71). As technology advances and more standardized research is conducted, breath analysis may become an integral part of future screening and follow-up strategies for patients at risk of or recovering from OSCC (72,73).

Although some models show good accuracy, results can be influenced by diet, inflammation, and environmental factors highlighting the need for controlled protocols and better VOC profiling. (74)

7.7 Artificial Intelligence

Artificial intelligence (AI) has rapidly become a cornerstone in medical imaging and diagnostic technology, particularly through image-based analysis (16)

Recent progress in deep learning, especially with convolutional neural networks (CNNs), has shown great promise in spotting OSCC from clinical images. One study trained a CNN on over 6,000 oral cavity photos and achieved good results detecting early-stage OSCC impressive results. (36)

Similarly, another study introduced a deep learning-based diagnostic model (DL-OSCDC), which combines NASNet and a Deep Belief Network. This system achieved a diagnostic accuracy of 95% and a sensitivity of 94%, reinforcing the robustness of AI models in classifying cancerous and non-cancerous lesions from biomedical images (35)

Smartphone-based AI tools are also showing real promise, especially in places with limited resources. Models like DenseNet-196 could accurately classify OPMDs and OSCC using just smartphone photos, reaching AUCs as high as 1.00. This kind of tech could make screening much more accessible. (75)

Findings pooled sensitivity and specificity values around 92%. This supports AI's promise as a frontline tool for early OSCC detection, potentially reducing diagnostic delays and improving outcomes (76)

AI is also helping automate histopathology. Using deep learning with techniques like stimulated Raman histology (SRH), it’s possible to classify OSCC tissue with around 90% accuracy showing that real-time, stain-free analysis could be a practical option with AI support. (77)

In clinical use, AI helps reduce human error and differences between observers, making diagnoses more consistent. It also improves tools like autofluorescence, OCT, and hyperspectral imaging by making it easier to spot lesion edges and classify tissue. (70)

Although, there are still challenges. AI models need large, diverse, and well-labeled datasets to work well for everyone. It’s also important to standardize how images are taken and to test these models in real clinical settings before they can be widely used. (36)

Also, without standard ways to take images, results can vary and affect how accurate and reliable AI tools are. That’s why multicenter studies and real-world clinical trials are needed to properly test these models and help get them approved for regular use. (35).

In parallel, there are ethical issues to consider: Protecting patient data, being clear about how AI makes decisions, and avoiding biases in the data used to train these systems. Most importantly, AI should support doctors, not replace them, so that human judgment stays at the heart of patient care.

7.8 Salivary and Serum Biomarkers in OSCC Diagnosis

Inflammatory markers like IL-6, IL-8, and TNF-α are frequently elevated in OSCC patients, highlighting tumor-induced immune responses. Chemerin, linked to cancer progression, has also shown strong salivary sensitivity (78)

MMP-9, involved in extracellular matrix breakdown, is another promising marker, with its salivary levels correlating with OSCC invasiveness (79)

Of particular interest are salivary miRNAs. For example, miR-136 and miR-27b are differentially expressed in OSCC saliva, supporting their diagnostic potential (80)

3-miRNA panel (miR-106b-5p, miR-423-5p, miR-193b-3p) showed good accuracy of highlighting the ability of salivary miRNA to distinguish OSCC patients from healthy individuals with remarkable precision. (38). Also, proteomic profiling of saliva could serve as a complementary tool in OSCC diagnosis, particularly for monitoring disease progression (37).

In addition to salivary biomarkers, circulating microRNAs (miRNAs) in serum or plasma are gaining attention as minimally invasive diagnostic tools, capable of noting tumor signals in OSCC (42).

Blood-based markers like IL-6, SCC antigen, and CYFRA 21-1 have been studied for detecting OSCC, but their accuracy is only moderate (39). Their strength may lie more in monitoring treatment response rather than primary diagnosis, and they may work best when combined with other screening tools. (81)

In contrast, saliva-based tests using miRNA and protein panels have shown much better accuracy. Since they're also non-invasive and easy to collect, they're a more practical option for routine screening, especially on a larger scale (39).

Moreover, one of the most exciting advances in the detection of OSCC is the fusion of salivary biomarker analysis with artificial intelligence (AI). Artificial intelligence methods have been shown to enhance diagnosis accuracy by processing big data with high accuracy (35, 36).

Generally, saliva used for diagnosis is an affordable, simple, and efficient means of OSCC screening, particularly in at-risk populations (38, 42). As further research and development are done, salivary biomarkers have the potential to be a crucial element in the standard programs for cancer screening and change the way OSCC detection, evaluation, and treatment will be managed in the future. With the evolution of AI-based diagnostic algorithms, the integration of salivary biomarkers with advanced imaging and computational analysis is likely to bring forth a paradigm shift in OSCC detection and monitoring (36, 41).

7.9 DNA Methylation Biomarkers

Researchers are exploring less invasive ways to catch oral cancer early, and one promising method is testing for DNA methylation tiny changes that happen at the molecular level before visible signs appear. These changes can switch off tumor-suppressor genes, allowing cancer to grow (82).

Recent studies have shown that methylation patterns could help diagnose and predict the outlook for OSCC. One study found seven key genes linked to cancer severity and survival. A risk model using four of these genes may help spot high-risk patients early by combining methylation and gene expression data for a fuller picture of the disease (83).

A clinical study used oral swabs to detect gene methylation in OSCC patients and found high accuracy. PAX1 stood out as well, with high sensitivity and specificity. In people without common risk factors like smoking or alcohol use, accuracy was also high. This makes it a promising, non-invasive, and low-cost screening option even in remote areas (84).

Circulating miRNAs look like a promising non-invasive way to detect OSCC, but there are still some challenges. Different lab methods and no set testing standards make it hard to compare results or develop a reliable test (85). While miRNA tests often show good specificity, they can possibly miss some early-stage cases due to lower sensitivity. Factors as Inflammation or how samples are handled can also affect the results. To make these tests reliable for real-world use, we need larger studies and more well- defined consistent testing methods. (86).

Future in the field of OSCC diagnosis

Although biopsy followed by histopathological analysis is still considered the gold standard for diagnosing oral squamous cell carcinoma (OSCC), it comes with clear limitations (20). The procedure is invasive, can cause patient discomfort, and is not practical for routine screening or follow-up in large populations (22). Additionally, interpretation of histopathological samples can be time-consuming and may vary between professionals, especially in borderline cases or when grading dysplasia (3). In contrast, conventional visual examinations using white light alone often fail to detect early-stage or subtle lesions (48). Their effectiveness is highly dependent on the clinician's experience, which introduces an element of subjectivity (5). Even structured screening programs that rely on visual and tactile examination show inconsistencies in technique and areas assessed, making standardization a challenge (6). Tools like chemiluminescence and autofluorescence have been introduced to help, but they lack the specificity needed to replace

conventional methods and often generate false positives (7). This not only adds unnecessary stress for patients but can also lead to avoidable biopsies. Unfortunately, these limitations often mean that OSCC isn't diagnosed until later stages, despite the well-established link between early detection and better survival outcomes (8).

Recent literature highlights a key challenge in OSCC detection: despite advancements, there is still no widely accepted, non-invasive alternative that matches the diagnostic accuracy of a biopsy while offering greater practicality in routine clinical use (9). Delays in diagnosing high-risk OPMDs are common, driven by cultural barriers and the limitations of early detection methods (10). To overcome this, there's growing interest in digital health technologies particularly artificial intelligence that could help clinicians detect early-stage OSCC with greater precision and consistency (11).

7.10 Overview Table

Diagnostic Method	Type	Invasiveness	Advantages	Limitations
Reflectance Confocal Microscopy (RCM)	Optical Imaging (real-time)	Non-invasive	High-resolution imaging, good histological correlation	Operator-dependent, limited depth, not suitable for all oral anatomy, cost
Narrow Band Imaging (NBI)	Optical Imaging (vascular pattern)	Non-invasive	Detects microvascular patterns, real-time lesion differentiation	Reduced visibility in hyperkeratotic or bleeding lesions
Fluorescence Visualization (FV)	Autofluorescence Imaging	Non-invasive	Simple, high patient compliance, real-time assessment	Variable sensitivity/specificity,cost, subjective interpretation
Autofluorescence Imaging (AFI)	Wide-field optical imaging	Non-invasive	Enhances lesion margin detection, improves sensitivity	High false positives, affected by tissue inflammation, needs experienced clinicians
Optical Coherence Tomography (OCT)	Cross-sectional Imaging	Non-invasive	Good structural imaging, matches histology, real-time scan	Shallow imaging depth, motion artifacts, limited availability
Salivary/Serum Biomarkers	Molecular diagnostics	Non-invasive	Early detection, ease of collection, personalized risk assessment	Variability in results, need for validation and standardization
AI/Deep Learning Models	Computational Diagnostics	Non-invasive	High accuracy, reproducibility, fast large-scale screening	Requires large datasets, bias risk, interpretability challenges
DNA Methylation Analysis	Epigenetic Profiling	Minimally invasive (swab/saliva)	Strong diagnostic potential	Experimental, requires standardized protocols

8. CONCLUSION:

Oral squamous cell carcinoma (OSCC) continues to represent a significant global health burden, primarily due to its frequent diagnosis at advanced stages. While biopsies remain the gold standard, they are invasive and not practical for regular monitoring. The growing range of screening methods like optical imaging, saliva-based biomarkers, breath analysis, and AI-supported diagnostics offers real hope for earlier, and more accurate detection. These technologies not only reduce patient discomfort but also make repeated screening more achievable, especially in high-risk and underserved populations. However, for them to become part of everyday clinical practice, further and larger studies are still needed. Looking ahead, one promising direction is the integration of these innovative tools into smarter, hybrid diagnostic systems. By combining their strengths, we can move toward a more coordinated and effective approach to OSCC detection. With continual advances in technology and stronger collaboration between clinicians and researchers, prompt detection of OSCC is now becoming a realistic and expected part of everyday clinical care.

9. SUSTAINABILITY

This project supports a more sustainable approach to healthcare by looking at non-invasive ways to detect oral squamous cell carcinoma (OSCC) early on. Tools like Reflectance Confocal Microscopy (RCM), Narrow Band Imaging (NBI), and Fluorescence Visualization (FV) help reduce the need for repeated biopsies. That means less use of single-use medical supplies and fewer materials ending up as waste.

From a social point of view, these tools offer better convenience for patients. They cause less discomfort, reduce anxiety, and are quicker to use, creating a more comfortable overall experience. They also make early diagnosis more accessible, especially in places where resources are limited. Detecting cancer early doesn't just improve treatments outcome , it can also save lives.

Economically, while technology might be a big investment at first, it pays off in the long run. By helping detect problems earlier, we avoid the high costs of late-stage treatment. Plus, with artificial intelligence being added to these systems, diagnosis could become even faster, more accurate, and less demanding for doctors.

All in all, this project contributes to better health outcomes and promotes the development of smarter and more efficient healthcare systems.

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