

Oral Squamous Cell Carcinoma: Advances in Diagnosis, Therapy, and Salivary Biomarkers

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Abstract

Oral squamous cell carcinoma (OSCC) is one of the most prevalent malignancies of the oral cavity and remains a significant global health concern because of its aggressive progression, potential for regional and distant metastasis, and considerable impact on patients' quality of life. Despite improvements in clinical assessment and therapeutic interventions, delayed diagnosis and disease recurrence continue to present major challenges in effective disease management. This review examines recent advances in the diagnosis, treatment, and identification of salivary biomarkers for OSCC, emphasizing their potential contribution to early detection, accurate disease characterization, and personalized clinical care. Conventional diagnostic approaches, including comprehensive oral examination, histopathological assessment, and tissue biopsy, remain fundamental to establishing a definitive diagnosis. However, emerging technologies, such as advanced imaging techniques, molecular profiling, artificial intelligence-assisted diagnostic systems, and genomic analysis, are expanding opportunities for earlier and more precise identification of malignant lesions. Particular attention is directed toward salivary biomarkers, including proteins, microRNAs, circulating cell-free nucleic acids, metabolites, and inflammatory mediators, which may provide a non-invasive and patient-friendly approach to cancer screening, monitoring, and prognostic evaluation. The review also explores contemporary therapeutic strategies, encompassing surgical resection, radiotherapy, chemotherapy, targeted molecular therapies, and immunotherapy, alongside emerging treatment combinations designed to improve therapeutic response and reduce recurrence. Furthermore, the integration of molecular biomarkers with clinical and pathological findings may facilitate risk stratification, treatment selection, and longitudinal monitoring of disease progression. Nevertheless, the translation of promising biomarkers into routine clinical practice remains constrained by variations in sample collection, analytical methods, patient characteristics, and validation protocols, as well as the limited availability of large-scale prospective studies. Addressing these limitations through standardized methodologies, multicentre investigations, and clinically representative validation studies is essential to establish the diagnostic reliability and practical utility of salivary biomarkers. Overall, integrating technological innovations, molecular diagnostics, and individualized treatment approaches offers considerable potential to improve the early detection and management of OSCC. Continued interdisciplinary research may ultimately support more accessible diagnostic pathways, optimized therapeutic decisions, and improved clinical outcomes for patients affected by this malignancy.

Keywords: Oral squamous cell carcinoma; Early diagnosis; Salivary biomarkers; Targeted therapy; Precision medicine.

Introduction

Oral squamous cell carcinoma (OSCC) represents one of the most clinically significant malignancies of the oral cavity, accounting for the majority of oral cancer cases and presenting a persistent challenge to contemporary healthcare systems. Originating from the squamous epithelial cells lining the oral mucosa, this malignancy can affect several anatomical sites, including the tongue, floor of the mouth, buccal mucosa, gingiva, hard palate, and other intraoral structures. Its development is associated with a complex interaction of environmental exposures, behavioural factors, genetic alterations, and changes in the local tissue microenvironment. Tobacco consumption, including smoking and smokeless tobacco use, excessive alcohol intake, and areca nut or betel quid chewing are well-established risk factors, particularly in regions where these practices remain widespread. Human papillomavirus (HPV) infection is also relevant to selected oral and oropharyngeal malignancies, although its established causal role differs between anatomical sites and should not be generalized to all OSCC cases. In addition to these exposures, advancing age, inadequate oral health, chronic mucosal irritation, nutritional influences, and inherited or acquired molecular susceptibility may contribute to variations in individual risk. The clinical importance of OSCC extends beyond its incidence because the disease can progress rapidly, invade surrounding tissues, involve regional lymph nodes, and compromise essential functions such as speech,

mastication, swallowing, and facial expression. Patients diagnosed at advanced stages may require extensive surgical procedures and multimodal treatment, frequently accompanied by functional limitations, psychological distress, and substantial rehabilitation requirements. Although advances in oncology have improved the understanding and management of oral malignancies, the overall burden of OSCC remains considerable in populations where awareness, preventive services, and timely access to specialist care are limited. These challenges highlight the need for diagnostic and therapeutic approaches that combine clinical examination with molecular investigation and patient-specific risk assessment.

Early and accurate diagnosis is a central determinant of effective OSCC management because the stage of disease at presentation influences treatment selection, functional preservation, recurrence risk, and long-term prognosis. Conventional diagnostic practice relies on visual and tactile examination of suspicious oral lesions, detailed assessment of clinical history, and histopathological evaluation of biopsy specimens. Persistent ulcers, indurated lesions, unexplained mucosal changes, erythroplakia, leukoplakia, and abnormal tissue growth require appropriate clinical assessment, particularly when they fail to resolve within an expected period. Nevertheless, early malignant lesions may resemble benign inflammatory or traumatic conditions, while some potentially malignant disorders exhibit subtle clinical characteristics that complicate differentiation. Histopathology remains the definitive method for confirming OSCC, but tissue biopsy is invasive and may not fully characterize the molecular heterogeneity of a tumour. Advances in diagnostic imaging, optical visualization, digital pathology, and molecular analysis are creating opportunities to complement conventional assessment and improve the characterization of suspicious lesions. Techniques such as autofluorescence imaging, narrow-band imaging, optical coherence tomography, and other emerging optical methods can provide additional information about mucosal abnormalities, although their performance depends on the clinical setting and they cannot independently replace histopathological confirmation. Artificial intelligence and machine learning are also being investigated for image-based lesion classification, automated histopathological analysis, and the identification of patterns that may be difficult to recognize consistently through unaided observation. Their potential value lies in supporting clinical decision-making, prioritizing high-risk lesions, and improving diagnostic consistency, particularly in settings with limited specialist resources. However, variations in image quality, clinical documentation, population characteristics, and validation procedures must be addressed before these systems can be incorporated reliably into routine practice. Accordingly, contemporary OSCC diagnosis increasingly requires an integrated approach in which clinical examination, pathological confirmation, imaging findings, and relevant molecular evidence contribute complementary information to patient evaluation.

Among the emerging approaches to cancer detection, salivary biomarker analysis has attracted considerable interest because saliva can be collected non-invasively, repeatedly, and with relatively limited discomfort to patients. As an oral biological fluid, saliva contains proteins, enzymes, cytokines, metabolites, extracellular vesicles, microRNAs, messenger RNA, and cell-free DNA that may reflect physiological changes, local inflammation, cellular damage, and tumour-associated molecular activity. The close anatomical relationship between oral tumours and salivary secretions creates opportunities to investigate disease-associated molecular signatures without relying exclusively on tissue sampling. Alterations in salivary interleukins, tumour-associated proteins, oxidative stress indicators, nucleic acid profiles, and extracellular vesicle contents have been explored as potential indicators of OSCC development, disease burden, and progression. These biomarkers may eventually support screening strategies, assist in distinguishing selected suspicious lesions, provide information about prognosis, and facilitate monitoring after treatment. Salivary microRNA profiles and tumour-associated genetic alterations are particularly relevant because they may reveal biological changes that are not readily apparent during routine examination. However, the clinical usefulness of any individual biomarker depends on its sensitivity, specificity, reproducibility, and ability to distinguish malignancy from inflammatory disorders and other oral conditions. Salivary composition is influenced by age, hydration, diet, oral hygiene, periodontal disease, medication use, collection time, and sample-handling procedures, all of which can affect analytical measurements. Furthermore, promising results from small or selected patient cohorts do not necessarily translate into reliable performance across diverse populations. Standardized collection protocols, validated analytical platforms, adequately powered clinical studies, and independent multicentre investigations are therefore essential for establishing the diagnostic value of salivary biomarkers. Rather than replacing biopsy-based diagnosis at the present stage, salivary testing is best investigated as a complementary approach that may strengthen clinical risk assessment and longitudinal disease monitoring when supported by appropriate evidence.

Therapeutic advances constitute another major dimension of contemporary OSCC research, particularly as clinicians seek to improve tumour control while preserving oral function and quality of life. Treatment selection depends on several factors, including tumour location and stage, histological characteristics, lymph node involvement, resectability, patient fitness, anticipated functional outcomes, and individual preferences. Surgery remains a principal treatment for many localized tumours, while radiotherapy and systemic therapies are used according to disease extent, pathological risk factors, and treatment objectives. Chemotherapy, targeted agents, and immune checkpoint inhibitors have expanded the therapeutic options available for selected patients, especially in recurrent, unresectable, or metastatic disease. Nevertheless, treatment resistance, tumour heterogeneity, recurrence, treatment-related toxicity, and the development of secondary disease continue to complicate long-term management. Molecular profiling and biomarker research may help clarify the biological mechanisms underlying tumour progression and therapeutic response, potentially supporting more individualized treatment decisions. Integrating these developments with improved diagnostic imaging, digital pathology, and salivary biomarker assessment offers a promising direction for connecting early detection with treatment planning and post-treatment surveillance. Against this background, the present review, titled “Oral Squamous Cell Carcinoma: Advances in Diagnosis, Therapy, and Salivary Biomarkers,” examines the evolving diagnostic landscape, established and emerging therapeutic strategies, and the potential clinical applications of saliva-based molecular indicators. It also considers the methodological, biological, and translational barriers that must be overcome before emerging technologies can deliver consistent benefits in routine healthcare. By bringing these interconnected areas together, the review aims to clarify how advances in molecular science and clinical practice may contribute to earlier recognition, more informed therapeutic decisions, improved monitoring, and better patient outcomes. Ultimately, progress in OSCC management will depend not on a single diagnostic test or treatment modality, but on the coordinated application of evidence-based clinical assessment, validated biomarkers, effective multidisciplinary care, and accessible preventive and diagnostic services.

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Methodology

The methodology for this review is designed to examine the relationship between advances in oral squamous cell carcinoma (OSCC) diagnosis, contemporary therapeutic approaches, and the emerging role of salivary biomarkers in clinical decision-making. Because the research topic encompasses diagnostic technologies, molecular investigations, treatment strategies, and translational applications, an integrative literature review provides a suitable framework for synthesizing evidence from clinical studies, laboratory investigations, systematic reviews, and relevant clinical guidelines. The methodological approach should enable a structured comparison of established diagnostic procedures and emerging technologies while evaluating the clinical relevance of saliva-based molecular indicators. Rather than treating diagnosis, therapy, and biomarkers as independent research domains, the review considers them interconnected components of a comprehensive disease-management pathway. Diagnostic evidence is examined in relation to its capacity to identify suspicious lesions, establish histopathological confirmation, characterize tumour behaviour, and support disease staging. Therapeutic evidence is assessed according to its relevance to tumour control, treatment selection, recurrence prevention, adverse effects, and preservation of oral function. Salivary biomarker studies are evaluated in terms of biological plausibility, analytical reliability, diagnostic performance, prognostic value, and potential applicability in routine clinical practice. The review also distinguishes established clinical practices from technologies that remain investigational, thereby reducing the risk of presenting preliminary findings as confirmed clinical recommendations. To maintain methodological transparency, the final review should report the databases searched, the search period, the exact search strategies, the eligibility criteria, the screening procedure, and the methods used to extract and synthesize evidence. If the paper is intended as a narrative or integrative review, this design should be stated explicitly; a systematic review designation should be used only when the corresponding reproducible procedures have actually been followed.

The literature identification process should cover major biomedical and multidisciplinary databases, including PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library, with supplementary searches of reference lists from relevant publications and authoritative clinical guidelines. The search strategy should combine controlled vocabulary, where available, with free-text keywords related to OSCC, oral cancer diagnosis, histopathology, diagnostic imaging, artificial intelligence, salivary biomarkers, microRNAs, cell-free DNA, proteomics,

metabolomics, surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. Boolean operators should be applied to combine these concepts while adapting syntax to the requirements of each database. For example, a diagnostic search may combine “oral squamous cell carcinoma” with “early detection,” “diagnostic accuracy,” “optical imaging,” or “artificial intelligence,” whereas a biomarker search may combine the disease term with “saliva,” “microRNA,” “extracellular vesicles,” “protein biomarkers,” or “cell-free DNA.” Therapeutic searches should include disease-specific terms alongside treatment modalities and clinical outcomes. The search period must be specified in the completed manuscript, including the final search date, and should be selected to capture foundational studies alongside recent developments. Publications in English may be included when this restriction is justified by the available resources, although the resulting language bias should be acknowledged. Original clinical investigations, diagnostic-accuracy studies, prospective and retrospective cohorts, randomized controlled trials, relevant laboratory studies, systematic reviews, meta-analyses, and professional guidelines may be considered according to their relevance to the research objectives. Editorials, unsupported opinion articles, duplicate records, and studies lacking sufficient methodological information should generally be excluded from the principal evidence synthesis. Preclinical investigations may contribute mechanistic information but should be distinguished from studies demonstrating clinical utility in human populations.

Table 1. Literature search strategy and evidence identification

Research domain	Principal search terms	Evidence of interest
Diagnostic methods	OSCC, biopsy, histopathology, optical imaging, artificial intelligence	Diagnostic accuracy, early detection, tumour classification
Salivary biomarkers	Saliva, microRNA, cell-free DNA, proteins, metabolites, extracellular vesicles	Sensitivity, specificity, reproducibility, prognostic potential
Therapeutic approaches	Surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy	Treatment response, survival, toxicity, recurrence
Molecular characterization	Genomics, transcriptomics, tumour heterogeneity, molecular profiling	Disease mechanisms, risk stratification, therapeutic response
Clinical translation	Validation, screening, clinical utility, standardized protocols	Feasibility, applicability, evidence quality

Following literature identification, the retrieved records should undergo a staged screening process to ensure that the selected publications directly address the review objectives. Duplicate records should first be removed using reference-management software or a documented manual procedure. Titles and abstracts should then be examined to identify potentially relevant studies, followed by full-text assessment against predefined eligibility criteria. Studies should be selected when they provide meaningful evidence concerning OSCC diagnosis, therapeutic management, salivary biomarker discovery, biomarker validation, or the integration of these approaches into clinical practice. Investigations focusing exclusively on unrelated oral diseases should be excluded unless they provide a relevant comparison group or help evaluate the specificity of a proposed biomarker. Studies involving oropharyngeal carcinoma should be interpreted separately when anatomical location, aetiology, or treatment differences limit their direct applicability to oral cavity squamous cell carcinoma. Particular attention should be given to the distinction between healthy-control comparisons and clinically relevant comparisons involving patients with potentially malignant oral disorders, benign inflammatory conditions, and other lesions that may resemble OSCC. This distinction is important because a biomarker that differentiates established cancer from healthy individuals may not perform equally well in the clinical setting where diagnostic uncertainty is greatest. The reasons for excluding full-text publications should be recorded, and the selection process should be summarized using a PRISMA flow diagram if the review follows systematic-review procedures. Where feasible, two independent reviewers should conduct screening and resolve disagreements through discussion or a third reviewer. If independent screening is not undertaken, the manuscript should transparently describe the actual procedure rather than imply that multiple reviewers were involved.

Data extraction should be conducted using a predefined template that captures the characteristics, methods, findings, and limitations of each eligible publication. For clinical studies, relevant information includes publication

year, country, study design, participant number, age distribution, tumour location, disease stage, comparator population, diagnostic criteria, treatment characteristics, and reported clinical outcomes. For salivary biomarker investigations, extraction should additionally cover saliva collection conditions, sample-processing methods, storage temperature, analytical platform, biomarker type, normalization procedure, assay thresholds, and reported measures of diagnostic performance. Information on sensitivity, specificity, area under the receiver operating characteristic curve (AUC), positive and negative predictive values, and confidence intervals should be recorded when available. Predictive values must be interpreted in relation to disease prevalence, whereas sensitivity and specificity should be considered alongside the clinical population in which they were estimated. When studies report multiple biomarkers or combinations of biomarkers, the review should distinguish individual-marker performance from panel-based performance and note whether the findings were validated in an independent cohort. For therapeutic investigations, extracted variables should include treatment modality, disease setting, comparator treatment, follow-up duration, response criteria, recurrence, progression-free survival, overall survival, adverse events, and patient-reported functional outcomes where reported. Missing information should be documented rather than inferred, and differences in study design or outcome definitions should be retained during synthesis to prevent misleading comparisons.

Table 2. Data extraction framework for the three principal research domains

Domain	Variables to extract	Main assessment objective
Diagnosis	Examination method, imaging modality, biopsy findings, diagnostic accuracy	Determine the contribution and limitations of diagnostic techniques
Salivary biomarkers	Biomarker class, collection protocol, assay, sensitivity, specificity, AUC	Evaluate analytical reliability and potential clinical utility
Therapy	Treatment type, stage, response, survival, recurrence, toxicity	Compare clinical effectiveness and treatment-related limitations
Molecular profiling	Genetic alterations, expression patterns, molecular subgroups	Examine disease heterogeneity and potential treatment relevance
Clinical translation	Validation cohort, reproducibility, cost, feasibility, implementation barriers	Assess readiness for practical clinical application

The assessment of diagnostic advances should focus on the methodological validity and clinical applicability of the evidence rather than on technological novelty alone. Conventional oral examination and histopathological confirmation should serve as essential reference points when evaluating newer diagnostic techniques. Studies of optical imaging, computer-assisted analysis, and artificial intelligence should be assessed according to participant selection, reference standards, blinding, external validation, and the possibility of selection or verification bias. Where applicable, the review should consider established diagnostic-accuracy reporting principles, including the STARD framework, and use the QUADAS-2 tool to evaluate the risk of bias and applicability concerns in diagnostic-accuracy studies. For artificial intelligence-based approaches, relevant factors include dataset size, class balance, image acquisition conditions, training and testing separation, independent validation, model interpretability, and performance across different clinical populations. Results obtained from retrospective image datasets should not automatically be interpreted as evidence of effectiveness in prospective clinical screening. Similarly, the performance of an imaging technique should be considered in relation to the additional diagnostic information it provides beyond routine clinical examination. These procedures allow the review to distinguish methods that are promising for clinical support from those that have demonstrated sufficient evidence for routine diagnostic use. Salivary biomarker evidence should be evaluated through a combined assessment of biological relevance, analytical validity, clinical validity, and potential clinical utility. Biological relevance concerns whether a biomarker is plausibly associated with OSCC development, progression, or host response. Analytical validity concerns the reliability of its measurement, including assay precision, detection limits, reproducibility, and susceptibility to sample degradation or contamination. Clinical validity concerns the ability of the marker to discriminate between clinically relevant patient groups, while clinical utility concerns whether its use can improve diagnostic decisions or patient outcomes. Studies involving salivary proteins, microRNAs, cell-free nucleic acids, extracellular vesicles, and

metabolites should therefore be compared with attention to their sampling protocols, assay platforms, control populations, and validation methods. Biomarker panels should be evaluated separately from single-marker tests, particularly when machine-learning algorithms or multivariable statistical models are used to combine multiple molecular features. Where sufficient information is available, the review should examine whether investigators used independent validation cohorts, prespecified thresholds, appropriate statistical adjustments, and clinically representative comparison groups. Risk-of-bias assessment may be informed by QUADAS-2 for diagnostic-accuracy studies and by relevant prognostic-biomarker assessment methods for studies addressing clinical outcomes. Particular caution is necessary when interpreting small exploratory studies, as high reported accuracy may reflect overfitting, limited sample diversity, or differences between cases and controls rather than robust clinical discrimination.

The therapeutic component should synthesize evidence concerning surgery, radiotherapy, systemic chemotherapy, targeted treatment, and immunotherapy, taking into account disease stage and clinical indication. Direct comparisons should be made only when study populations, treatment settings, outcome definitions, and follow-up periods are sufficiently comparable. Randomized trials, observational cohorts, and systematic reviews should be interpreted according to their respective strengths and limitations. For example, randomized controlled trials may provide stronger evidence of comparative treatment effects, whereas observational studies may contribute information about treatment delivery, uncommon adverse effects, and outcomes in routine practice. Relevant endpoints include local and regional control, recurrence, overall survival, progression-free survival, treatment toxicity, postoperative complications, speech and swallowing function, and quality of life. Biomarker-guided treatment should be considered separately from biomarker discovery: identifying a molecular association does not establish that the marker can reliably predict response to a particular therapy. The review should therefore distinguish prognostic biomarkers, which provide information about likely disease outcomes, from predictive biomarkers, which help identify differences in the expected benefit of a treatment. Where evidence is insufficient to establish a treatment-specific predictive effect, the conclusion should remain appropriately cautious. The review should also consider how tumour heterogeneity, treatment resistance, comorbidities, and access to multidisciplinary care influence the translation of research findings into clinical decisions.

Finally, the extracted evidence should be synthesized using a structured narrative approach, with studies grouped by diagnostic modality, biomarker category, therapeutic strategy, and level of clinical validation. A quantitative meta-analysis should be considered only when studies demonstrate adequate comparability in population characteristics, methods, and outcome definitions. If diagnostic-accuracy studies are sufficiently homogeneous, pooled estimates of sensitivity and specificity may be considered using suitable hierarchical statistical models. Heterogeneity should be explored in relation to sample size, disease stage, assay methodology, comparator selection, and validation design. Where quantitative pooling is inappropriate, findings should be presented through comparative tables and a critical narrative synthesis, emphasizing the consistency of results, limitations of the evidence, and gaps requiring further investigation. The overall strength of conclusions should reflect study quality, reproducibility, and clinical relevance rather than the number of publications reporting favourable results. Because the present topic encompasses diverse evidence types, the methodology should acknowledge possible publication bias, language restrictions, inconsistent outcome reporting, and the limited availability of prospective validation studies. The final synthesis should identify which diagnostic technologies and therapeutic strategies are established, which salivary biomarkers remain investigational, and what evidence is needed to support clinical implementation. This approach provides a transparent basis for understanding how advances in diagnosis, therapy, and salivary biomarker research may contribute to more timely detection, individualized management, and improved outcomes in patients with oral squamous cell carcinoma.

Results and Discussion

The results and discussion of this review bring together the major developments in oral squamous cell carcinoma (OSCC) research, focusing on diagnostic accuracy, emerging molecular approaches, therapeutic progress, and the potential contribution of salivary biomarkers to clinical management. The available evidence indicates that OSCC remains a complex malignancy in which early recognition, reliable pathological confirmation, appropriate treatment selection, and continued monitoring are closely interconnected. Conventional oral examination and histopathological assessment remain fundamental to diagnosis, while advances in imaging, digital pathology, and molecular analysis are expanding the range of tools available to clinicians. At the same time, research on salivary

proteins, microRNAs, cell-free nucleic acids, and other tumour-associated molecules has generated interest in less invasive methods for detecting and monitoring disease. These developments should not, however, be interpreted as evidence that a single technology can independently resolve the major clinical challenges associated with OSCC. Differences in study populations, disease stages, diagnostic criteria, laboratory methods, and validation procedures make direct comparisons difficult. Consequently, the findings are best interpreted through a critical synthesis of established clinical practices and emerging approaches, distinguishing technologies supported by routine clinical evidence from those that require further investigation.

Conventional diagnostic procedures continue to provide the foundation for effective OSCC management. Visual and tactile examination enables clinicians to identify suspicious oral lesions, assess their anatomical distribution, and determine whether further investigation is necessary. Histopathological examination of a biopsy specimen remains essential for confirming malignancy and evaluating relevant tissue characteristics. Nevertheless, the effectiveness of this diagnostic pathway depends on lesion recognition, timely referral, appropriate biopsy selection, and access to qualified pathology services. Early lesions may be overlooked when their appearance resembles benign mucosal conditions, while patients in underserved communities may experience delays before obtaining specialist evaluation. Emerging imaging techniques, including autofluorescence imaging, narrow-band imaging, and optical coherence tomography, may provide additional information about tissue abnormalities and help guide the assessment of selected lesions. Artificial intelligence-assisted analysis of clinical photographs and digitized histopathological slides also offers opportunities to improve image interpretation and diagnostic consistency. However, promising performance in controlled datasets does not necessarily establish effectiveness in routine clinical practice. Differences in image acquisition, disease prevalence, lesion characteristics, and patient demographics may reduce model performance when algorithms are applied to external populations. These findings support the complementary use of advanced diagnostic technologies alongside clinical examination and histopathological confirmation rather than their immediate substitution for established procedures.

Salivary Biomarkers: Diagnostic Potential and Clinical Limitations

Salivary biomarker research represents one of the most promising areas of OSCC investigation because saliva can be collected repeatedly without invasive procedures. Published studies have examined inflammatory mediators, tumour-associated proteins, nucleic acids, extracellular vesicles, and metabolic compounds as potential indicators of malignancy. A 2025 systematic review and meta-analysis of 28 studies involving 3,507 patients with OSCC and 3,501 control participants reported pooled sensitivity of 71% and specificity of 69% across salivary protein biomarkers, illustrating both their diagnostic potential and their present limitations.

The findings suggest that no single protein marker should be assumed to provide sufficiently reliable discrimination across all clinical populations. Interleukin-8 (IL-8), interleukin-1 beta (IL-1 β), tumour necrosis factor-alpha (TNF- α), matrix metalloproteinase-9 (MMP-9), and cytokeratin 19 fragment 21-1 (CYFRA 21-1) are among the candidates investigated for their associations with tumour-related inflammation, tissue remodelling, and epithelial cell damage. However, inflammatory biomarkers may also increase in periodontal disease and other inflammatory conditions, potentially reducing their specificity for malignancy. Molecular markers, including salivary microRNAs and cell-free DNA, may provide complementary information about tumour-associated genetic and regulatory changes. Metabolomic investigations have likewise identified candidate compounds associated with altered cellular metabolism, although their clinical relevance requires further confirmation.

The interpretation of salivary biomarker performance must account for differences in sample collection, processing, assay platforms, control populations, and diagnostic thresholds. A 2026 meta-analysis incorporating 18 studies and 1,647 participants reported pooled sensitivity of 64%, specificity of 71%, and an area under the curve of 0.75 across multiple salivary biomarker classes, with substantial heterogeneity between datasets.

These findings reinforce the distinction between identifying a statistically significant biomarker and establishing a clinically dependable diagnostic test. In addition, diagnostic performance measured by comparing established cancers with healthy controls may overestimate the usefulness of a test in patients presenting with ambiguous oral lesions. The most valuable future studies will therefore include clinically representative comparison groups, standardized saliva collection protocols, prespecified thresholds, and independent validation cohorts. Salivary biomarker panels may eventually improve risk stratification when combined with clinical findings and other diagnostic information, but their routine use must be supported by evidence of clinical benefit. An updated 2026 evidence-informed guideline recommends restricting salivary adjunct tests for early oral cancer detection to

research settings, while maintaining clinical examination and biopsy or referral for persistent oral mucosal abnormalities as central elements of care.

Table 1. Principal salivary biomarker categories investigated in OSCC

Biomarker category	Representative candidates	Potential relevance	Main limitation
Inflammatory proteins	IL-8, IL-1 β , TNF- α	Tumour-associated inflammation	Limited specificity in inflammatory oral disease
Tumour-associated proteins	CYFRA 21-1, CD44, MMP-9	Epithelial damage and tissue remodelling	Variable performance between studies
Nucleic acids	MicroRNAs, cell-free DNA	Molecular alterations and disease-associated expression	Assay standardization and validation challenges
Metabolic compounds	Amino acids and other altered metabolites	Changes in cellular metabolism	Dietary, physiological, and sampling influences
Extracellular vesicles	Vesicle-associated proteins and RNA	Intercellular signalling and tumour-related molecular signatures	Isolation and analytical reproducibility

Therapeutic Advances and Individualized Management

The therapeutic evidence indicates that OSCC management increasingly depends on the integration of tumour stage, anatomical location, pathological risk factors, patient fitness, and anticipated functional outcomes. Surgery remains a major treatment option for resectable disease, with radiotherapy and systemic treatment incorporated according to clinical stage and pathological findings. For patients with advanced or recurrent disease, chemotherapy, targeted therapies, and immunotherapy may provide additional treatment options. Immune checkpoint inhibition is particularly relevant to selected patients with recurrent or metastatic disease, although the suitability of individual agents depends on disease characteristics, treatment history, and applicable clinical indications. The development of these approaches reflects an increasing recognition that OSCC is biologically heterogeneous and that patients with apparently similar clinical presentations may respond differently to treatment. Molecular profiling and the evaluation of tumour-associated pathways may help identify clinically relevant differences, while immune-related biomarkers can contribute to treatment selection in appropriate settings. Nevertheless, the identification of a molecular alteration does not automatically establish that targeting it will improve clinical outcomes. Evidence from well-designed clinical trials remains necessary to demonstrate treatment effectiveness, characterize adverse effects, and establish the populations most likely to benefit.

An important consideration in interpreting therapeutic progress is that tumour control alone does not fully represent treatment success. Extensive surgery and combined treatment may affect speech, swallowing, chewing, facial appearance, nutritional status, and psychological well-being. Consequently, treatment evaluation should incorporate functional recovery, rehabilitation requirements, quality of life, and the burden of treatment-related complications alongside recurrence and survival outcomes. Multidisciplinary care involving surgical oncology, radiation oncology, medical oncology, pathology, dentistry, nutrition, and rehabilitation services can support more coordinated treatment planning. Salivary biomarkers may eventually contribute to post-treatment monitoring by identifying molecular changes associated with residual disease or recurrence. Preliminary prognostic research has examined salivary microRNAs, proteins, and metabolites in relation to disease progression and survival, but the evidence remains limited by methodological variation and insufficient external validation.

Accordingly, biomarker-guided surveillance should not replace established clinical follow-up or appropriate imaging and pathological investigation when recurrence is suspected.

Table 2. Relationship between emerging advances and clinical application

Research area	Potential contribution	Evidence required before wider
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		implementation
Artificial intelligence-assisted diagnosis	Support lesion classification and pathology interpretation	External validation and prospective clinical evaluation
Salivary biomarker panels	Complement clinical risk assessment	Standardized assays and independent diagnostic validation
Molecular profiling	Support biological characterization and selected treatment decisions	Evidence linking molecular findings to clinical benefit
Immunotherapy and targeted treatment	Expand options for eligible patients	Comparative trials and treatment-specific selection criteria
Salivary monitoring after treatment	Investigate possible indicators of recurrence or progression	Longitudinal studies with validated clinical endpoints

Source: Critical synthesis of the reviewed research areas; the table summarizes potential applications rather than established outcomes.

Integrated Interpretation and Future Research Directions

Taken together, the literature supports an integrated model in which conventional examination and histopathological confirmation remain central, while imaging technologies, artificial intelligence, molecular profiling, and salivary biomarker research may provide additional information at different stages of the clinical pathway. The principal opportunity lies in combining complementary sources of evidence rather than expecting any single method to overcome all existing diagnostic and therapeutic limitations. However, differences in study design, sample size, population characteristics, analytical methods, and outcome reporting prevent many promising findings from being translated directly into routine clinical practice. Future investigations should prioritize prospective multicentre studies, standardized saliva collection and processing, clinically representative control groups, independent validation, and transparent reporting of diagnostic performance. Research should also examine cost-effectiveness, accessibility, acceptability, and the feasibility of implementing emerging technologies in settings with limited specialist resources. For therapeutic advances, additional attention should be given to treatment resistance, recurrence, long-term functional outcomes, and the identification of biomarkers that genuinely predict treatment benefit rather than merely correlate with disease severity.

In conclusion, advances in OSCC diagnosis, therapy, and salivary biomarker research offer complementary opportunities to improve disease assessment and patient management. Conventional diagnostic procedures continue to provide the essential clinical foundation, while emerging technologies may strengthen lesion characterization, molecular understanding, and individualized care. Salivary biomarkers are particularly attractive because of their non-invasive nature, but their diagnostic reliability and clinical utility remain insufficiently established for routine early-detection use. Therapeutic progress likewise requires continued evaluation of efficacy, safety, patient selection, and quality-of-life outcomes. A coordinated approach combining validated diagnostic procedures, evidence-based treatment, carefully evaluated molecular tools, and multidisciplinary care offers the most credible pathway toward improving OSCC outcomes.

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Conclusion

Oral squamous cell carcinoma remains a significant clinical challenge because of its potential for aggressive progression, late-stage presentation, recurrence, and considerable effects on patients' functional abilities and quality of life. Advances in diagnostic imaging, digital pathology, artificial intelligence, molecular profiling, and therapeutic interventions are expanding opportunities for more accurate disease assessment and individualized management. Nevertheless, conventional oral examination and histopathological confirmation remain central to the diagnostic process, while emerging technologies should be evaluated according to their reliability, clinical relevance, and ability to improve patient outcomes. Contemporary treatment approaches, including surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, provide important options for managing

disease at different stages. Their effectiveness must be considered alongside treatment-related complications, functional recovery, recurrence risk, and long-term patient well-being. Integrating diagnostic innovation with multidisciplinary treatment planning and appropriate follow-up may help improve the overall quality of OSCC care. Salivary biomarkers offer considerable research potential because they enable non-invasive sample collection and may reveal molecular changes associated with tumour development, progression, and treatment response. Proteins, microRNAs, cell-free nucleic acids, metabolites, and extracellular vesicles are promising candidates for future diagnostic and monitoring applications. However, variations in sample collection, analytical techniques, patient characteristics, and validation procedures continue to limit their routine clinical application. Current evidence supports further investigation rather than replacing established diagnostic procedures with salivary testing.

Future research should prioritize standardized protocols, prospective multicentre studies, independent clinical validation, and the identification of biomarkers that provide meaningful information beyond conventional examination and pathology. Greater attention to affordability, accessibility, and implementation in resource-limited healthcare settings is equally important. Ultimately, combining validated diagnostic methods, evidence-based therapeutic strategies, and rigorously evaluated molecular technologies offers a promising direction for advancing early detection, treatment personalization, and long-term outcomes in patients with OSCC.

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