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Review Article

Salivaomics as a Diagnostic Potential Tool in Oral Squamous Cell Carcinoma (OSCC): A Comprehensive View

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Abstract

Saliva is a promising biological fluid which contains a dynamic mixture of biomolecules, including DNA, RNA, proteins, metabolites, microorganisms and extracellular vesicles, many of which reflect the molecular alterations associated with oral carcinogenesis. Oral Cavity Squamous Cell Carcinoma (OSCC) is one of the most common cancers worldwide. The poor outcome of OSCC patients is principally ascribed to the fact that this disease is often advanced at the time of diagnosis, suggesting that early detection of OSCC is urgently needed. Analysis of cancer-related body fluids is one promising approach to identify biomarker candidates of cancers. Advances in high-throughput technologies and molecular diagnostics have enabled the identification and validation of salivary biomarkers with diagnostic, prognostic and predictive value. Compared with conventional diagnostic procedures such as tissue biopsy and serum assays, salivary diagnostics offer several advantages, including non-invasive collection, low cost, patient comfort and feasibility for repeated sampling. However, challenges such as variability in sample collection, lack of standardized protocols and the need for large-scale clinical validation remain barriers to full clinical integration. This review highlights the biological basis, technological advancements, current evidence, challenges and future prospects of saliva as a diagnostic tool in oral cancer.

Keywords: Saliva; Oral Cancer; Biomarkers; Oral Squamous Cell Carcinoma; Non-invasive Diagnosis; Salivary Diagnostics and Molecular Markers

Introduction

Oral Squamous Cell Carcinoma (OSCC) is a malignant neoplasm that arises from the mucosal epithelium of the oral cavity and exhibits varied squamous differentiation. It is a cancerous growth of squamous cells that exhibit different levels of keratinisation. Squamous Cell Carcinoma (SCC) accounts for more than 90% of malignancies in the oral cavity. Patients' overall 5-year survival rate is less than 50% [1]. Traditional diagnostic methods rely heavily on clinical examination followed by surgical biopsy, which, although accurate, is invasive, time-consuming and unsuitable for mass screening. The ability to monitor health status, disease onset and progression and treatment outcome through noninvasive means is a highly desirable goal in health care promotion and delivery [2]. These limitations have prompted the exploration of non-invasive diagnostic alternatives. Saliva, a readily available oral fluid, has emerged as a promising medium due to its simple collection, cost-effectiveness and the presence of diverse biomarkers that mirror pathophysiological changes in the oral cavity and the body. By examining genes, proteins and cells in saliva, it provides insights into cancer development and progression through genomic, transcriptomic, proteomic, metabolomic and microbiomic studies [3,4]. This article provides a comprehensive review of salivaomics role as a diagnostic tool in oral cancer, emphasizing its biological basis, biomarker types, technological advancements, challenges and future perspectives.

Advantages of Saliva for Diagnostic Tool
1. Non-invasive collection-easy, painless, patient-friendly
2. Cost-effective-no specialized equipment needed
3. Repeatable sampling-ideal for monitoring disease progression
4. Safety-lower infection risk compared to blood collection
5. High patient compliance-suitable for children, elderly and anxious patients

Categories of Salivary Biomarkers in OSCC
1. *Genomic and Transcriptomic Markers*
- Altered expression of genes such as MMP1, IL1RN, MAL, FN1, PLAU, SPARC, KRT4, KRT13, TGM3 has been reported in OSCC tissue and saliva
- RT qPCR studies confirm diagnostic potential, with MMP1, MAL and IL1RN showing high sensitivity and specificity (>90%)
- MicroRNAs (miR 125a, miR 200a, miR 31) are consistently dysregulated in OSCC saliva samples
2. *Proteomic Markers*
- Elevated levels of cytokines (IL 8, IL 6), CD44 and matrix metalloproteinases detected in saliva
- Proteomic profiling identifies cancer specific protein signatures useful for early detection
3. *Metabolomic Markers*
- Alterations in metabolites such as polyamines, amino acids and oxidative stress markers have been linked to OSCC
- Metabolomics provides insights into tumor metabolism and progression
4. *Microbiome Alterations*
- Dysbiosis in oral microbiota, with increased abundance of Fusobacterium nucleatum and Porphyromonas gingivalis, has been associated with OSCC
- Microbiome profiling may complement molecular diagnostics
5. *Extracellular Vesicles (Exosomes)*
Salivary exosomes carry tumor-derived molecules including miRNAs, DNA and proteins, offering highly specific diagnostic information.

Technological Advances in Salivary Diagnostics
Recent technological developments have significantly improved the sensitivity and specificity of saliva-based tests.

PCR-Based Assays
Used for detecting DNA mutations, methylation and RNA transcripts.

Next-Generation Sequencing (NGS)
Allows comprehensive genomic and transcriptomic profiling of saliva.

Proteomic Analysis
Techniques include mass spectrometry and ELISA-based assays.

Metabolomics Platforms
Using NMR and LC-MS to detect metabolic signatures.

Lab-on-a-Chip and Point-of-Care Devices
Portable devices that enable rapid detection of salivary biomarkers in clinics or even at home.

Clinical Applications of Salivary Diagnostics in Oral Cancer
- Risk screening: High-risk groups (tobacco use, betel quid, alcohol, chronic mucosal lesions) can benefit from periodic salivary screening to flag early malignancy

- Adjunct to clinical exam: Use salivary panels to triage suspicious lesions for biopsy, especially when clinical features are equivocal

- Surveillance: Post-treatment follow-up using salivary biomarker trajectories can detect recurrence earlier and reduce invasive procedures

Limitations and Future Directions
- Specificity challenges: Inflammation and infection can elevate cytokines; panel-based and multi-omic approaches help distinguish cancer-specific signals
- Standardization gap: Harmonized protocols for collection, processing and reporting are needed to enable cross-study comparability and clinical adoption
- Validation and regulation: Large, prospective, multicenter studies with predefined endpoints are required to establish clinical utility, cost-effectiveness and regulatory approval for routine care
- Emerging frontiers: Exosome-derived miRNAs, methylation signatures and AI-enhanced multi-omic integration are poised to improve accuracy and deliver point-of-care diagnostics for oral cancer

Practical Takeaways
- Use multimarker panels: Combine cytokines (e.g., IL-6, IL-8) with miRNAs and proteomic markers for more reliable screening and diagnosis
- Standardize sampling: Control preanalytical variables to reduce noise and improve test performance
- Pilot and validate locally: Build workflows in high-risk clinics, gather local performance data and iterate toward a deployable, cost-effective tool

Discussion

The findings from the reviewed literature indicate that salivomics has emerged as a highly promising non-invasive approach for detecting OSCC. Because saliva directly interacts with tumour surfaces and contains a wide range of molecular constituents-including proteins, cytokines, nucleic acids and microRNAs-it serves as a valuable diagnostic medium that reflects tumour behaviour more accurately than many conventional body fluids.

Early transcriptomic studies provided the first evidence that tumour-related gene alterations can be reliably identified in saliva. Lallemant, et al., demonstrated that genes such as MMP1, IL1RN and MAL exhibit significant dysregulation in OSCC, achieving high diagnostic accuracy in both tissue and saliva samples. Their work further highlighted MMP1 as a particularly promising marker, although improvements in detection sensitivity were recommended for routine clinical application [8]. These initial insights paved the way for deeper omics-based exploration.Advances in proteomic technologies strengthened the diagnostic potential of salivary analysis. Using iTRAQ-based mass spectrometry, Chu, et al., identified elevated levels of CFH, FGA and SERPINA1 in OSCC patients and noted that these proteins correlated with disease stage. Their findings reinforce the value of the salivary proteome in distinguishing malignant from non-malignant conditions and in reflecting disease progression [9].

Proteomic profiling thus offers a sensitive platform for screening and risk stratification. Cytokine based salivomics has added another dimension to OSCC diagnostics. A 2024 network meta-analysis by Huang, et al., confirmed significant elevation of cytokines such as TNF-α, IL-6, IL-8, IL-1β and IL-10 in OSCC patients. Notably, TNF-α showed the strongest diagnostic performance, with high sensitivity and specificity, positioning it among the most reliable single salivary biomarkers for OSCC detection [10]. These findings support the concept that inflammation-related molecular changes captured in saliva can reflect tumour burden.

In recent years, salivary microRNAs have gained considerable attention due to their stability and tumour specificity. The systematic review by Osan, et al., highlighted dysregulated microRNAs such as miR-21, miR-34a and miR-320a, which were consistently associated with the transition from potentially malignant disorders to OSCC. Their involvement in regulating key cancer-related pathways underscores their usefulness as early indicators of malignant transformation and as potential tools for monitoring high-risk lesions [11].

Comprehensive multi-omics analyses further support the integration of saliva-based diagnostics. Starska-Kowarska emphasized that combining proteomic, transcriptomic, metabolomic and microbiomic markers can substantially improve diagnostic precision, making saliva a versatile and informative diagnostic medium. The review also underscored saliva's practical

advantages-ease of collection, patient comfort and suitability for repeated testing-qualities that are especially beneficial in population-level screening [12]. Additionally, the 2025 IJCRT review found that biomarker panels (e.g., IL-6, IL-8, TNF-α, MMP-9, VEGF and miRNA-21) outperform individual biomarkers, reinforcing the value of multiplex assays for OSCC screening and early diagnosis [13].

Despite encouraging evidence, important challenges remain. Variations in saliva collection methods, lack of standardized laboratory protocols and differences in analytical platforms contribute to inconsistent findings. Many biomarkers still require validation through large, multicentre studies before they can be integrated into routine clinical practice. Addressing these gaps will be essential to transform salivomics from a research tool into a reliable diagnostic modality.

Collectively, the reviewed data suggest that salivomics holds substantial potential for the early detection, risk prediction and monitoring of OSCC. Its non-invasive nature, combined with the molecular richness of saliva, positions it as an attractive complementary tool alongside traditional diagnostic procedures. As standardization improves and biomarker panels are validated across populations, salivomics is likely to become a cornerstone of future OSCC detection and personalised disease management.

Conclusion

Salivaomics represent a rapidly evolving frontier in the early detection and management of Oral Squamous Cell Carcinoma (OSCC). As a non-invasive, cost-effective and patient-compliant medium, saliva provides a unique reservoir of molecular biomarkers-including genomic, transcriptomic, proteomic, metabolomic and microbiome signatures-that mirror both local tumor biology and systemic alterations. The integration of salivary biomarker profiling with advanced analytical platforms such as PCR, ELISA, proteomics and next-generation sequencing has demonstrated promising sensitivity and specificity in identifying OSCC at its incipient stages. Moreover, saliva-based assays hold potential for real-time monitoring of disease progression, therapeutic response and recurrence, thereby supporting precision oncology and personalized treatment strategies. Despite these advantages, challenges such as biomarker validation, inter-individual variability and the need for standardized protocols remain critical barriers to clinical translation. Addressing these limitations through multicenter trials, technological innovation and harmonized methodologies will be essential. Ultimately, saliva as a diagnostic tool offers transformative potential to improve early detection, enhance patient outcomes and reduce the global burden of OSCC.

Conflict of Interest

The authors have declared that no conflict of interest exists.

Ethical Approval

Not applicable.

Author Contributions

All authors contributed to the study conception and design. HN, HA, SSAB and VKB performed material preparation, data collection and analysis. SSAB wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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