Review Article

Molecular Biomarkers in Early Detection and Prognosis of Oral Squamous Cell Carcinoma: A Comprehensive Review

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Abstract

Introduction

Oral squamous cell carcinoma (OSCC) accounts for over 90% of oral cancers and remains a leading cause of cancer-related morbidity and mortality globally. The five-year survival rate has stagnated below 60%, largely owing to late-stage diagnosis. Molecular biomarkers offer a non-invasive and sensitive strategy for early detection and prognostic stratification. This review consolidates current evidence on salivary, serum, epigenetic, and microRNA-based biomarkers relevant to OSCC.

Important Results/Observations

Salivary transcriptomic markers including IL-8 and H3F3A mRNA demonstrate sensitivity and specificity exceeding 85% in distinguishing OSCC from healthy controls. Serum markers such as squamous cell carcinoma antigen (SCCA) and vascular endothelial growth factor (VEGF) correlate with tumor stage and lymph node metastasis. Epigenetic alterations, particularly promoter methylation of p16 and DAPK, are detectable in early-stage lesions. MicroRNAs—notably miR-21, miR-31, and the miR-200 family—are dysregulated in OSCC tissue and body fluids, making them attractive candidates for liquid biopsy.

Discussion (including Conclusions)

Transition from single-marker assays to multi-marker panels has substantially improved diagnostic accuracy. Salivary diagnostics are particularly appealing owing to non-invasive sample collection, though standardization of protocols remains a critical unmet need. Prospective validation studies are essential before clinical translation. Molecular biomarkers represent an indispensable component of future precision oncology frameworks for OSCC management.

Keywords: oral squamous cell carcinoma; molecular biomarkers; early detection; prognosis; salivary diagnostics

Introduction

Oral squamous cell carcinoma (OSCC) is the most prevalent malignancy of the oral cavity, constituting over 90% of all oral cancers. It ranks among the ten most common cancers worldwide, with particularly high incidence in South and Southeast Asia, where tobacco use, betel nut chewing, and alcohol consumption are endemic (Bray et al., 2018). Despite advances in surgical techniques, radiation protocols, and targeted therapies, the five-year survival rate has remained stagnant at approximately 50–60% over the past three decades. This unfavorable prognosis is largely attributed to delayed diagnosis, with the majority of cases presenting at advanced stages when locoregional spread is already established.

The oral cavity is uniquely accessible for clinical examination, yet OSCC frequently goes undetected in early stages due to subtle clinical presentation and inadequate patient awareness. Traditional diagnostics—clinical inspection, exfoliative cytology, and tissue biopsy with histopathological evaluation—remain the gold standard but are limited by subjectivity, invasiveness, and inability to characterize molecular heterogeneity. There is therefore an urgent clinical imperative to identify reliable molecular biomarkers that facilitate earlier diagnosis, accurate prognostic stratification, and therapeutic monitoring.

Molecular biomarkers are measurable biological molecules—including nucleic acids, proteins, and metabolites—whose aberrant expression or modification is associated with a pathological process. In OSCC, these markers may be identified in tumor tissue, blood serum, or saliva, which directly bathes the oral mucosa and offers a non-invasive sampling medium. Advances in genomics, transcriptomics, and epigenomics have considerably expanded the repertoire of potential biomarkers (Wong et al., 2006). This review examines salivary, serum, epigenetic, and microRNA-based biomarkers in OSCC with emphasis on diagnostic and prognostic performance.

Salivary Biomarkers

Saliva represents a diagnostically rich biofluid that mirrors the molecular milieu of the oral cavity. Wong et al. (2006) identified a salivary transcriptomic signature—including IL-8, H3F3A, OAZ1, S100P, and SAT mRNA—that achieved 91% sensitivity and 91% specificity in distinguishing OSCC patients from healthy controls. Salivary interleukin-8 and interleukin-1β are consistently elevated in OSCC and correlate with tumor burden, reflecting local inflammatory activity at the tumor-host interface (Rhodus et al., 2005).

DNA methylation status in saliva provides additional diagnostic value. Promoter hypermethylation of tumor suppressor genes such as p16/CDKN2A and DAP kinase (DAPK) has been detected in the saliva of OSCC patients at significantly higher frequency than in controls, suggesting a role in field cancerization (Carvalho et al., 2011). Salivary microRNAs—particularly miR-200a, miR-31, and miR-21—are differentially expressed in OSCC, with area under the curve (AUC) values exceeding 0.85, positioning them as viable candidates for saliva-based liquid biopsy (Park et al., 2009).

Serum and Plasma Biomarkers

Serum-based biomarkers offer systemic insight into tumor biology. Squamous cell carcinoma antigen (SCCA), a serine protease inhibitor overexpressed in squamous epithelial tumors, demonstrates elevated serum levels in OSCC that correlate with lymph node metastasis, tumor size, and disease recurrence (Kato & Torigoe, 1977). Cyfra 21-1, a cytokeratin 19 fragment, shows approximately 65–70% sensitivity and 85–90% specificity for OSCC, with levels correlating with clinical stage. VEGF is significantly elevated in OSCC patients, and higher levels are associated with advanced disease, nodal involvement, and reduced survival (Smith et al., 2000).

Circulating tumor DNA (ctDNA) in plasma, harboring tumor-specific mutations or methylation patterns, represents an emerging frontier in OSCC liquid biopsy with high specificity (Bettegowda et al., 2014). Additional markers of interest include matrix metalloproteinase-9 (MMP-9) and soluble E-cadherin, both of which reflect tumor invasiveness and metastatic potential. The development of multi-analyte serum panels holds potential for significantly improving diagnostic sensitivity over any single circulating marker in isolation.

Epigenetic Biomarkers

Epigenetic modifications—particularly aberrant promoter methylation—are among the earliest and most consistent molecular events in oral carcinogenesis. Several tumor suppressor genes, including p16/CDKN2A, DAPK, E-cadherin (CDH1), and RASSF1A, are frequently methylated in OSCC tissue and potentially dysplastic precursor lesions (Manikandan et al., 2012). Detection of these methylation events in saliva or serum enables early identification of field defects and malignant transformation, providing an opportunity for intervention at a pre-invasive stage (Carvalho et al., 2011).

Global loss of H4K16 acetylation and H4K20 trimethylation are recognized epigenetic hallmarks of human cancers including OSCC (Fraga et al., 2005). Long non-coding RNAs (lncRNAs) such as HOTAIR and MALAT1, which mediate epigenetic regulation of gene networks, are increasingly recognized as both biomarkers and functional drivers of OSCC progression and metastasis, adding another dimension to the epigenetic biomarker landscape.

MicroRNA Biomarkers

MicroRNAs (miRNAs) are short (~22 nucleotide) non-coding RNAs that post-transcriptionally regulate gene expression and are frequently dysregulated in cancer. In OSCC, miR-21 is among the most consistently overexpressed oncogenic miRNAs, promoting tumor proliferation, invasion, and resistance to apoptosis by targeting PTEN and PDCD4. Conversely, miR-200 family members are downregulated in OSCC and correlate with epithelial-to-mesenchymal transition (EMT), lymph node metastasis, and reduced survival (Manikandan et al., 2012). miR-31 overexpression is associated with nodal involvement and serves as an independent predictor of recurrence.

miR-375 downregulation is a frequently reported event correlating with advanced clinical stage and poor prognosis. Importantly, miRNAs exhibit remarkable stability in biological fluids and can be reliably measured in saliva and serum, reinforcing their appeal as minimally invasive biomarkers for OSCC screening and longitudinal monitoring (Mitchell et al., 2008). Panel-based miRNA assays integrating salivary and serum miRNA profiles are under active investigation as combined diagnostic tools.

Discussion

The molecular landscape of OSCC is highly complex, and no single biomarker has yet achieved sufficient sensitivity, specificity, and reproducibility for widespread clinical adoption. Multi-marker panels integrating salivary mRNA, miRNA, protein, and methylation data have consistently demonstrated superior diagnostic accuracy, with several studies reporting AUC values above 0.90 (Wong et al., 2006; Park et al., 2009). The biological rationale for multi-analyte approaches reflects the multistep nature of oral carcinogenesis, wherein distinct molecular events contribute cumulatively to malignant transformation.

Saliva stands out as a particularly attractive diagnostic medium given its non-invasive accessibility and proximity to the tumor microenvironment. However, critical challenges remain—including standardization of saliva collection methods (stimulated versus unstimulated), pre-analytical variables affecting biomarker stability, and lack of validated reference ranges. These methodological heterogeneities partly explain variability in sensitivity and specificity across studies and necessitate rigorous standardization before clinical translation.

From a prognostic perspective, VEGF and miR-200 family members have demonstrated independent prognostic value in multivariate analyses (Smith et al., 2000). Liquid biopsy platforms encompassing ctDNA hold particular promise for real-time monitoring of tumor dynamics and early detection of minimal residual disease (Bettegowda et al., 2014). Collaborative data initiatives such as The Cancer Genome Atlas Head and Neck Squamous Cell Carcinoma dataset have contributed substantially to population-level molecular characterization (Cancer Genome Atlas Network, 2015), enabling discovery of novel prognostic signatures.

A significant challenge in biomarker translation remains the paucity of large-scale, prospective validation studies. Most evidence derives from small single-center retrospective cohorts with limited ethnic and geographic diversity, constraining generalizability. Standardized platforms and analytical pipelines are essential to ensure inter-laboratory reproducibility and facilitate regulatory approval of diagnostic assays.

Conclusion

Molecular biomarkers hold immense potential for transforming early detection, prognostication, and therapeutic monitoring of OSCC. The convergence of salivary diagnostics, epigenomics, miRNA profiling, and serum-based assays with advanced bioinformatic tools is enabling the development of multi-dimensional biomarker signatures that transcend the limitations of individual markers. Clinical translation requires rigorous prospective validation, methodological standardization, and integration into accessible point-of-care platforms—particularly for resource-limited settings where OSCC burden is highest.

Multicenter studies enrolling diverse populations are essential to establish normative reference ranges and validate biomarker panels across different disease stages and risk profiles. As precision oncology advances, molecular biomarkers will occupy a central role not only in diagnosis and prognosis but also in guiding targeted therapies, predicting immunotherapy response, and enabling individualized surveillance protocols. A concerted interdisciplinary effort uniting clinicians, molecular biologists, bioinformaticians, and regulatory scientists will be indispensable in realizing the full clinical potential of biomarker-based OSCC management.

Source of Support: Nil

Conflict of Interest: Nil

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