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BIOMARKERS IN PRIMARY MULTIPLE ORAL CANCERS: IMPLICATIONS FOR DIAGNOSIS AND PROGNOSIS

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Abstract

Oral cancer presents formidable obstacles in early detection, diagnosis, and prognosis due to its diverse array of malignancies impacting the oral cavity. Multiple primary oral cancers (MPOCs), defined by the occurrence of two or more primary tumors within the oral cavity, amplify the complexity of clinical management and treatment planning. Biomarkers, encompassing molecular and genetic markers, represent promising tools for enhancing the detection, diagnosis, and prognostication of oral cancers, including MPOCs. These biomarkers provide valuable insights into the underlying molecular alterations driving tumor development and progression, aiding in risk stratification, treatment selection, and monitoring of therapeutic response. By leveraging biomarker-based approaches, clinicians can refine diagnostic accuracy, predict disease behavior, and tailor treatment strategies to the individualized needs of patients with MPOCs. Ultimately, the integration of biomarkers into clinical practice holds significant potential to improve patient outcomes and mitigate the challenges associated with managing oral cancer, offering hope for more effective and personalized approaches to care.This manuscript provides an overview of current literature on biomarkers linked with MPOCs, exploring their potential applications in clinical practice and their implications for personalized treatment strategies. We address the complexities associated with biomarker-based approaches in managing MPOCs, including challenges and opportunities, and outline future research directions in this area.

INTRODUCTION

Multiple primary oral cancers (MPOCs) constitute a distinctive subset within the spectrum of oral malignancies, delineated by the concurrent or sequential development of two or more primary tumors within the oral cavity. Unlike solitary tumors, the multifocal nature of MPOCs introduces intricate clinical complexities, presenting unique challenges in treatment planning and prognostic evaluation (Krafft and Popp 2023). The coexistence of multiple tumors within a confined anatomical space necessitates meticulous consideration of various factors, including tumor location, size, histological subtype, and genetic alterations, to devise an effective management strategy. This multifocality not only complicates surgical interventions but also amplifies the risk of local recurrence and distant metastasis, thereby compromising the overall prognosis for affected individuals (Feygin, Khalek et al. 2020). Despite notable advancements in diagnostic modalities and therapeutic approaches for oral cancers, the prognosis for MPOCs remains notably poorer compared to their solitary counterparts. This disparity underscores the imperative need for innovative strategies aimed at enhancing the detection, risk stratification, and treatment selection for patients afflicted with MPOCs (Marshall 2021). One promising avenue in this regard is the exploration of biomarkers, encompassing molecular and genetic signatures, which hold potential for revolutionizing the management of MPOCs (Doña-Termine 2022, Melby 2023). Biomarkers serve as measurable indicators of biological processes or pathological conditions within the body, offering valuable insights into disease pathogenesis, progression, and treatment response. In the

context of MPOCs, biomarkers play a pivotal role in augmenting diagnostic accuracy, facilitating early detection of primary and recurrent tumors, and refining risk stratification to guide personalized treatment strategies (Ahmad, Imran et al. 2023). By leveraging biomarker-based approaches, clinicians can optimize patient outcomes by tailoring therapeutic interventions to individual tumor characteristics and molecular profiles. Early detection of MPOCs is paramount for initiating timely interventions and improving patient prognosis (Beniwal, Lamo et al. 2023). Biomarkers can aid in the identification of high-risk individuals predisposed to developing MPOCs, enabling targeted surveillance and screening programs for early disease detection (Cajander, Kox et al. 2023). Molecular biomarkers, such as genetic mutations, chromosomal aberrations, and epigenetic alterations, can be utilized as predictive indicators of MPOC development, allowing for proactive management strategies in at-risk populations. Additionally, biomarker-based screening protocols may facilitate the identification of premalignant lesions and facilitate their prompt treatment, thereby averting progression to invasive malignancy (Deacon, Smith et al. 2021).

Furthermore, biomarkers play a crucial role in refining prognostic assessment for individuals diagnosed with MPOCs, providing valuable prognostic information to guide treatment decisions and predict clinical outcomes. Molecular profiling of MPOCs can identify prognostic biomarkers associated with disease aggressiveness, metastatic potential, and treatment response, enabling risk stratification to optimize patient management (Fan, Chen et al. 2024). By integrating biomarker data with clinicopathological parameters, clinicians can stratify patients into distinct risk groups, facilitating individualized treatment planning and prognostic counselling. Moreover, biomarkers hold promise for guiding treatment selection and monitoring therapeutic response in patients with MPOCs. Molecular biomarkers can inform therapeutic decision-making by identifying actionable targets and predicting tumor sensitivity to specific treatment modalities, including surgery, radiation therapy, chemotherapy, and targeted therapies (Gyamfi, Kim et al. 2022). By tailoring treatment regimens based on molecular profiling, clinicians can optimize therapeutic efficacy while minimizing treatment-related toxicity and adverse effects. Additionally, biomarkers can be utilized for real-time monitoring of treatment response, enabling early detection of treatment resistance and facilitating timely modifications to therapy to improve clinical outcomes (Enseñat Méndez 2024).

MPOCs represent a unique subset of oral cancers characterized by the presence of two or more primary tumors within the oral cavity. The multifocal nature of MPOCs poses significant challenges in treatment planning and prognostic assessment, necessitating innovative approaches to improve patient outcomes (Freudenreich, Donnelly-Boylen et al. 2020). Biomarkers, encompassing molecular and genetic signatures, hold immense potential for enhancing the detection, risk stratification, and treatment selection for patients with MPOCs. By leveraging biomarker-based strategies, clinicians can optimize patient management and improve clinical outcomes in this challenging disease entity (Rashid, Wiredu et al. 2022, Rashid, Al-Obeidat et al. 2023).

Epidemiology and Clinical Features of MPOCs

MPOCs are relatively rare, accounting for approximately 1-5% of all oral cancers. They typically occur in individuals with a history of tobacco and alcohol use, as well as those with a genetic predisposition to cancer, such as those with germline mutations in tumor

suppressor genes like TP53 or CDKN2A. Clinically, MPOCs may present as synchronous or metachronous tumors within the oral cavity, often involving multiple subsites such as the tongue, buccal mucosa, and floor of the mouth. The diagnosis of MPOCs requires careful clinical evaluation, imaging studies, and histopathological confirmation to distinguish between primary tumors and metastatic lesions (Adhikari, Yousef et al. , Krafft and Popp 2023).

Biomarkers in MPOCs

Multiple primary oral cancers (MPOCs) constitute a relatively rare subset of oral malignancies, accounting for approximately 1-5% of all oral cancer cases. These tumors are characterized by the development of two or more primary tumors within the oral cavity, either concurrently or sequentially .(Manto, Hadjivassiliou et al. 2023) While MPOCs are less common than solitary oral tumors, they present unique challenges in terms of diagnosis, treatment, and prognosis due to their multifocal nature. Various factors contribute to the development of MPOCs, including lifestyle habits, genetic predisposition, and environmental exposures. Individuals with a history of tobacco and alcohol use are at increased risk of developing MPOCs, as these substances are well-established risk factors for oral cancer development. (Katuwal 2022, Verma, Verma et al. 2023) Additionally, genetic factors play a significant role, with individuals harboring germline mutations in tumor suppressor genes such as TP53 or CDKN2A being predisposed to developing multiple primary tumors. These genetic mutations can disrupt normal cellular processes, leading to uncontrolled cell growth and tumor formation within the oral cavity (Usman, Razzaq et al. 2021, Hiremath, Goel et al. 2022, Steele, Pillay et al. 2022).

Clinically, MPOCs may present as synchronous or metachronous tumors, with synchronous tumors occurring simultaneously and metachronous tumors developing sequentially over time. These tumors often involve multiple subsites within the oral cavity, including the tongue, buccal mucosa, floor of the mouth, and palate. The multifocal nature of MPOCs poses challenges in terms of accurate diagnosis and delineation of individual tumor boundaries (Hyrcza, Lindenmuth et al. 2023). Careful clinical evaluation, imaging studies (such as computed tomography and magnetic resonance imaging), and histopathological examination are essential for distinguishing between primary tumors and metastatic lesions, as well as for assessing tumor extent and involvement of adjacent structures (Sergi and Sergi 2020, Lajolo, Rupe et al. 2021, Ntatsaki 2022). Histopathological confirmation is crucial for establishing the diagnosis of MPOCs and determining the histological subtype of each tumor. Histological assessment allows for the classification of tumors based on their morphological features, such as cell type, degree of differentiation, and presence of invasive characteristics. Additionally, immunohistochemical staining may be employed to further characterize tumors and identify specific molecular markers associated with tumor behavior and prognosis (Bonacho, Rodrigues et al. 2020, Dinehart, Dinehart et al. 2020).

Molecular Profiling of MPOCs

Advancements in high-throughput sequencing technologies have revolutionized our understanding of the molecular landscape of multiple primary oral cancers (MPOCs), offering unprecedented insights into their pathogenesis, heterogeneity, and therapeutic vulnerabilities. High-throughput sequencing platforms, including next-generation sequencing (NGS) and whole-genome sequencing (WGS), have facilitated

comprehensive molecular profiling of MPOCs, enabling the identification of novel biomarkers and therapeutic targets that hold promise for personalized treatment approaches (Savelieva, Tashireva et al. 2020).

Genomic studies have unveiled extensive genetic heterogeneity among MPOCs, with each tumor harboring a unique mutational landscape shaped by somatic mutations, copy number alterations, and structural rearrangements. These genomic alterations drive dysregulation of key signaling pathways implicated in MPOC development and progression, including the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway and the mitogen-activated protein kinase (MAPK) pathway. Dysregulation of these signaling pathways promotes cellular proliferation, survival, and metastasis, contributing to the aggressive behavior of MPOCs (Yang, Liu et al. 2022). Integrative analyses of genomic, transcriptomic, and proteomic data have provided valuable insights into the molecular mechanisms underlying MPOC pathogenesis, identifying candidate biomarkers associated with disease development and progression. These biomarkers encompass a wide range of molecular alterations, including genetic mutations, gene expression changes, and protein dysregulation, that collectively contribute to the malignant phenotype of MPOCs. (Park, Han et al. 2020)

At the genetic level, recurrent mutations in tumor suppressor genes (e.g., TP53, CDKN2A) and oncogenes (e.g., PIK3CA, HRAS) have been identified in MPOCs, driving aberrant cell proliferation and survival. Additionally, copy number alterations, such as amplifications and deletions, contribute to genomic instability and tumor heterogeneity in MPOCs, further complicating their molecular characterization (Bousset and Gil 2022). Transcriptomic analyses have revealed alterations in gene expression patterns associated with MPOC development and progression, highlighting dysregulation of key biological processes, including cell cycle control, DNA repair, and apoptosis. Gene expression signatures indicative of aggressive tumor behavior and treatment resistance have been identified, providing valuable prognostic information for risk stratification and treatment planning in MPOCs (Lu, Peng et al. 2023, Hill, Bona et al. 2024).

Proteomic profiling has uncovered dysregulated protein expression patterns in MPOCs, reflecting underlying molecular alterations driving tumor progression and metastasis. Proteomic biomarkers associated with epithelial-to-mesenchymal transition (EMT), angiogenesis, and immune evasion have been implicated in MPOC aggressiveness and therapeutic resistance, offering potential targets for novel therapeutic interventions associated with epithelial-to-mesenchymal transition (EMT), angiogenesis, and immune evasion have been implicated in MPOC aggressiveness and therapeutic resistance, offering potential. Integration of multiomic data sets, including genomics, transcriptomics, and proteomics, has facilitated the identification of molecular subtypes and signaling pathways driving MPOC pathogenesis, paving the way for personalized treatment strategies tailored to individual tumor characteristics and molecular profiles. These integrated approaches enable the identification of actionable biomarkers and therapeutic targets, guiding treatment selection and monitoring treatment response in MPOC patients (Malone, Oliva et al. 2020). The advancements in high-throughput sequencing technologies have provided unprecedented insights into the molecular landscape of MPOCs, revealing extensive genetic heterogeneity and dysregulation of key signaling pathways implicated in tumor development and progression (Alcid and Tsukiyama 2014). Integrative analyses of

genomic, transcriptomic, and proteomic data have identified candidate biomarkers associated with MPOC aggressiveness and therapeutic resistance, offering promising avenues for personalized treatment approaches. Further research is warranted to validate these biomarkers and translate them into clinical practice, ultimately improving outcomes for patients with MPOCs (Frangogiannis 2012).

Clinical Implications of Biomarkers in MPOCs

Biomarker-based approaches have emerged as promising strategies for enhancing the diagnosis, prognosis, and treatment of multiple primary oral cancers (MPOCs), offering insights into the underlying molecular mechanisms driving tumor development and progression. Molecular profiling of MPOCs enables the identification of biomarkers associated with disease aggressiveness, treatment response, and clinical outcomes, facilitating risk stratification and personalized treatment approaches tailored to individual patient characteristics (Testa, Castelli et al. 2019). Risk stratification is a critical aspect of MPOC management, as it enables clinicians to identify patients at higher risk of disease recurrence and progression, thereby guiding treatment decisions and optimizing patient outcomes. Biomarkers associated with MPOC aggressiveness, such as genetic mutations, gene expression signatures, and protein markers, provide valuable prognostic information that can inform risk stratification strategies. By integrating biomarker data with clinicopathological parameters, clinicians can identify high-risk patients who may benefit from more aggressive treatment approaches or closer surveillance protocols (Miao, Luo et al. 2014, Dama, Melocchi et al. 2019, Merry, Thway et al. 2021).

The biomarker-based approaches have the potential to guide treatment decisions and predict response to therapy in MPOC patients. Molecular profiling of MPOCs allows for the identification of actionable biomarkers, such as genetic mutations or protein markers, that can inform treatment selection and monitoring (Rodríguez-Antona and Taron 2015, Schmidt, Chau et al. 2016). For example, tumors with specific genetic alterations may be more sensitive to targeted therapies, while those with resistance mutations may require alternative treatment approaches. Biomarker-driven treatment strategies enable personalized medicine approaches tailored to the unique molecular characteristics of individual tumors, maximizing therapeutic efficacy while minimizing treatment-related toxicity and adverse effects (Asselin and Rizzari 2015, Deutsch, Chargari et al. 2019).

Furthermore, biomarkers may serve as therapeutic targets for precision medicine approaches in MPOC management. By targeting specific molecular pathways or genetic alterations driving tumor growth and progression, precision medicine strategies aim to disrupt tumor biology and improve treatment outcomes. For example, inhibitors targeting the PI3K/Akt/mTOR pathway or the MAPK pathway, which are commonly dysregulated in MPOCs, have shown promise in preclinical and clinical studies for the treatment of oral cancers (Conway, Herrmann et al. 2019). Biomarker-driven precision medicine approaches enable the identification of patients who are most likely to benefit from targeted therapies, thereby optimizing treatment efficacy and patient outcomes. Despite the potential benefits of biomarker-based approaches in MPOC management, several challenges remain in translating biomarker discoveries into clinical practice. One key challenge is the standardization of testing methodologies and validation of biomarker assays to ensure accuracy, reproducibility, and reliability of results across different clinical settings (Perlis 2011, Conway,

Herrmann et al. 2019). Additionally, the integration of biomarkers into existing diagnostic algorithms and treatment guidelines requires careful consideration of clinical utility, cost-effectiveness, and regulatory approval processes. Biomarker validation studies in large, well-characterized patient cohorts are needed to establish the clinical validity and utility of biomarkers for MPOC diagnosis, prognosis, and treatment (Perez-Gracia, Sanmamed et al. 2017, Archetti, Ingala et al. 2019).

The biomarker-based approaches hold promise for improving the diagnosis, prognosis, and treatment of multiple primary oral cancers (MPOCs). Molecular profiling of MPOCs enables risk stratification, treatment selection, and prediction of treatment response, facilitating personalized medicine approaches tailored to individual patient characteristics. However, challenges remain in translating biomarker discoveries into clinical practice, highlighting the need for further research and validation studies to realize the full potential of biomarkers in MPOC management (Feng, Prentice et al. 2004, Frangogiannis 2012, Goossens, Nakagawa et al. 2015).

Future Directions and Conclusion

The biomarkers play a pivotal role in unraveling the underlying mechanisms driving MPOC development and progression. By delineating the molecular landscape of MPOCs, biomarkers shed light on the intricate interplay of genetic, epigenetic, and proteomic alterations that contribute to tumor initiation, growth, and metastasis. Understanding these molecular mechanisms is essential for identifying novel therapeutic targets and developing targeted treatment strategies tailored to individual tumor characteristics (Fares, Fares et al. 2020, Malki, ElRuz et al. 2020). Moreover, biomarkers offer opportunities for personalized approaches to diagnosis and treatment in MPOCs. By stratifying patients based on their molecular profiles, clinicians can tailor treatment regimens to target specific molecular vulnerabilities and optimize therapeutic efficacy. Biomarker-driven diagnostic algorithms enable early detection of MPOCs and facilitate timely intervention, leading to improved patient outcomes and survival rates (Perel and Elkin-Koren 2015, Sutton-Smith 2021, Cajander, Kox et al. 2023). Future research efforts should focus on validating and implementing biomarker-based strategies in clinical practice to realize their full potential in MPOC management. Robust validation studies are needed to assess the clinical validity and utility of biomarkers for MPOC diagnosis, prognosis, and treatment response prediction. Standardization of biomarker assays and protocols is essential to ensure consistency and reproducibility of results across different clinical settings (Rifai, Gillette et al. 2006, Dancey, Dobbin et al. 2010, Masucci, Cesano et al. 2016).

Furthermore, leveraging multiomic approaches holds promise for elucidating the complex molecular landscape of MPOCs and identifying novel biomarkers and therapeutic targets. Integrating genomic, transcriptomic, and proteomic data enables a comprehensive understanding of the molecular mechanisms driving MPOC pathogenesis and progression. By integrating multiomic data sets, researchers can uncover molecular subtypes and signaling pathways associated with MPOC aggressiveness and treatment resistance, guiding the development of targeted therapies and precision medicine approaches (Gallagher, Lynch et al. 2006, Kumar, Bansal et al. 2016). Exploration of novel therapeutic targets is another crucial avenue for improving patient outcomes in MPOCs. Biomarker-driven precision medicine approaches enable the identification of actionable targets for targeted therapies, immunotherapies, and combination treatment regimens. By targeting specific

molecular vulnerabilities, such as driver mutations or dysregulated signaling pathways, clinicians can disrupt tumor growth and metastasis, leading to improved treatment responses and survival rates (Khaddour, Maahs et al. 2021).

CONCLUSION

In conclusion, biomarkers offer invaluable insights into the pathogenesis and clinical behavior of MPOCs, providing opportunities for personalized approaches to diagnosis and treatment. Future research efforts should focus on validating and implementing biomarker-based strategies in clinical practice, leveraging multiomic approaches to elucidate the complex molecular landscape of MPOCs, and exploring novel therapeutic targets for improving patient outcomes. By harnessing the power of biomarkers, we can advance our understanding of MPOCs and enhance the precision and efficacy of therapeutic interventions for this challenging disease entity.

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