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## A REVIEW ON LIQUID BIOPSY IN OMFS

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### ABSTRACT :

Liquid biopsy is emerging as a transformative, non-invasive diagnostic approach in oral and maxillofacial surgery (OMFS), particularly for managing oral squamous cell carcinoma (OSCC). By analyzing circulating biomarkers like tumor DNA (ctDNA), tumor cells (CTCs), and extracellular vesicles in body fluids, liquid biopsy enables early diagnosis, real-time monitoring, and personalized treatment planning, providing a viable alternative to traditional tissue biopsies. Its benefits include reduced patient discomfort, dynamic tumor tracking, and the potential for cost-effectiveness in certain clinical settings. However, challenges persist, including low biomarker sensitivity, lack of protocol standardization, high costs, and technical complexities. Future research aims to address these limitations and integrate liquid biopsy with other diagnostic tools for enhanced accuracy. Overall, liquid biopsy holds the promise to significantly improve OMFS outcomes in oral cancer care through minimally invasive, individualized diagnostic solutions.

**Keywords:** Liquid Biopsy, Oral Squamous Cell Carcinoma, Oral And Maxillofacial Surgery, Circulating Tumor DNA, Non-Invasive Diagnostics

### Introduction :

Oral and maxillofacial surgery (OMFS) frequently involves the management of malignant conditions, particularly oral squamous cell carcinoma (OSCC), a common and aggressive form of oral cancer. Historically, the diagnosis and prognosis of such malignancies have depended on traditional tissue biopsies. While effective, tissue biopsies are invasive, often uncomfortable for patients, and may not always capture the full heterogeneity of the tumor. These limitations can impact both diagnostic accuracy and treatment planning.<sup>1</sup> Liquid biopsy, a cutting-edge diagnostic technique, is transforming the landscape of OMFS by offering a minimally invasive, real-time method of assessing tumor-derived biomarkers present in bodily fluids such as blood and saliva. Through liquid biopsy, clinicians can access circulating biomarkers, including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and other molecular components.<sup>2</sup> These biomarkers hold crucial information about the genetic and molecular profile of the tumor, enabling early detection, ongoing monitoring, and individualized treatment assessment in patients with oral cancers like OSCC. This non-invasive approach provides several advantages over conventional biopsies. Liquid biopsy offers a practical, less invasive option that is generally more comfortable for patients and can be performed multiple times over the course of treatment, allowing for dynamic monitoring of tumor progression or recurrence.<sup>3</sup> Additionally, it presents a more cost-effective and accessible alternative to tissue biopsy in some contexts, reducing both the financial and logistical burdens associated with cancer diagnosis and follow-up care. In the context of OMFS, liquid biopsy represents a potentially revolutionary tool for improving outcomes in oral cancer care. By enabling more precise diagnosis, enhancing the ability to monitor tumor dynamics over time, and providing insights that can help tailor therapies to the individual patient, liquid biopsy promises to elevate the standards of cancer care in OMFS.<sup>4</sup> This article provides a comprehensive overview of liquid biopsy in oral and maxillofacial surgery.

### The Relevance of Liquid Biopsy in Oral and Maxillofacial Surgery

Liquid biopsy is a transformative, noninvasive diagnostic approach that utilizes body fluids, such as saliva and blood (serum/plasma), to facilitate the early diagnosis, staging, and monitoring of malignancies relevant to oral and maxillofacial surgery (OMFS). Particularly valuable for detecting and managing oral squamous cell carcinoma (OSCC) and other potentially malignant oral disorders, liquid biopsy leverages key biomarkers that can be analyzed without the need for invasive tissue sampling. The primary components of liquid biopsy include circulating tumor cells (CTCs), circulating extracellular vesicles (ctEVs), and circulating nucleic acids, such as DNA and RNA, which are essential for providing insights into the molecular and genetic characteristics of the tumor.<sup>5</sup> Tumor-specific epigenetic changes—such as aberrant DNA methylation and promoter hypermethylation—and genetic alterations, including mutations in circulating tumor DNA (ctDNA), enable clinicians to differentiate between cancerous and non-cancerous tissues. These molecular changes are crucial for early cancer detection, and specialized biomarker panels, including those that identify gene mutations, DNA methylation patterns, circulating RNA (ctRNA), and ctEVs, have demonstrated promising diagnostic and prognostic potential in OSCC.<sup>6</sup> However, significant challenges remain in implementing liquid biopsy in routine clinical practice within OMFS. Among these are low sensitivity and specificity due to the variability and often low concentrations of biomarkers in early stages, along with a lack of standardized protocols for sample handling and analysis, which can affect the consistency and accuracy of results. Additionally, the high cost of advanced technologies required for biomarker analysis limits accessibility and integration into OMFS practices.<sup>7</sup> Furthermore, the heterogeneity of CTCs, primarily due to the process of epithelial-mesenchymal transition (EMT), complicates their detection, as CTCs undergo changes that reduce their visibility and distinctiveness in liquid

biopsy samples. While liquid biopsy holds substantial promise for enhancing cancer care in OMFS by providing a dynamic, less invasive approach to tumor assessment, these challenges underscore the need for further research and technological advancement to optimize its efficacy and application in oral and maxillofacial oncology.<sup>8</sup>

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### **Principles and Techniques of Liquid Biopsy in Oral and Maxillofacial Surgery**

Liquid biopsy is an innovative diagnostic approach that identifies molecular biomarkers released by tumors into bodily fluids, providing critical insights for oral and maxillofacial surgery (OMFS). Among the key components analyzed are circulating tumor cells (CTCs), which are shed from the primary tumor into the bloodstream and can indicate metastatic activity; circulating tumor DNA (ctDNA), consisting of DNA fragments from cancer cells that carry mutations reflective of the tumor's genetic makeup; exosomes and extracellular vesicles (EVs), small particles that transport DNA, RNA, and proteins and serve as indicators of tumor characteristics; and microRNA (miRNA), which are small, non-coding RNAs with expression patterns that can help distinguish malignant from benign tissues.<sup>9</sup> Several advanced techniques have been developed to detect and quantify these biomarkers. Next-generation sequencing (NGS) allows for high-throughput sequencing to identify genetic mutations within ctDNA, while droplet digital PCR (ddPCR) provides highly precise quantification of these mutations.<sup>10</sup> Additionally, flow cytometry and immunomagnetic separation techniques are used to isolate and identify CTCs, and exosomal RNA analysis measures RNA levels within exosomes, aiding in tumor profiling. Collectively, these principles and techniques underscore the utility of liquid biopsy in OMFS for understanding tumor biology, enhancing early detection, and informing personalized treatment approaches.<sup>11</sup>

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### **Advantages and Applications of Liquid Biopsy in Oral and Maxillofacial Surgery**

Liquid biopsy offers several significant advantages, particularly in oral and maxillofacial surgery (OMFS), through its non-invasive nature, early detection capabilities, and real-time monitoring. Using bodily fluids such as saliva or blood, liquid biopsy reduces the discomfort and risks that accompany traditional invasive procedures, providing a patient-friendly diagnostic option.<sup>12,13</sup> This method is especially valuable for the early diagnosis of oral squamous cell carcinoma (OSCC), a critical benefit given the high morbidity rates associated with late-stage OSCC detection (Gupta et al., 2024; Keerthivasan et al., 2023).<sup>2,10,14</sup> By enabling continuous monitoring of tumor dynamics, liquid biopsy supports timely adjustments in treatment strategies to optimize patient outcomes (Gupta et al., 2024; Swarup et al., 2024).<sup>2,15</sup> Within OMFS, liquid biopsy has applications across various stages of cancer management. For early detection and diagnosis, it can identify tumor-specific mutations in circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) in patients at high risk for OSCC, with biomarker detection in saliva offering a non-invasive and practical approach due to its direct relevance to oral cancers.<sup>16</sup> For prognostic evaluation, liquid biopsy helps categorize patients based on disease aggressiveness, as higher ctDNA levels or certain mutations are associated with poorer prognoses, which aids in personalized treatment planning. Additionally, for treatment monitoring and recurrence detection, liquid biopsy enables the real-time tracking of ctDNA or CTCs, allowing for early identification of minimal residual disease and recurrence, which is particularly beneficial in high-risk OSCC cases with elevated recurrence rates. Liquid biopsy also facilitates therapeutic guidance by allowing for genetic profiling of tumors to support personalized treatment. For example, detecting EGFR mutations in ctDNA may indicate a need for targeted therapies that inhibit specific tumor growth pathways, aligning with precision medicine approaches.<sup>17</sup>

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### **Challenges and Limitations of Liquid Biopsy in Clinical Practice**

While liquid biopsy holds great promise, several challenges and limitations affect its integration into routine clinical practice. One major issue is the lack of standardized protocols for sample collection and biomarker analysis, which hampers reproducibility and reliability across different laboratories and studies.<sup>18</sup> The process of extracting and analyzing biomarkers like circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) is technically complex, requiring sophisticated technology and specialized expertise, resources that may not be readily available in all clinical settings. Sensitivity and specificity also pose challenges, as low levels of biomarkers, particularly in early disease stages, can reduce detection accuracy.<sup>19</sup> Moreover, technical standardization is essential to address variations in assay sensitivity and sample handling procedures, as these differences can significantly impact results. Tumor heterogeneity further complicates interpretation; disparities between the molecular profiles of primary tumors and liquid biopsy findings may arise, complicating diagnostic clarity. Additionally, the high costs associated with advanced liquid biopsy technologies limit accessibility, especially in low-resource settings, restricting the broader adoption of this promising approach.<sup>20</sup>

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### **Conclusion :**

While liquid biopsy does represent promising advancement in oral cancer diagnostics, several challenges that constitute realities have to be addressed before its whole potential can be realized in the clinical practice of the future. Future research should thus include enhancing sensitivity of assays and validation in clinical trials of the efficacies of liquid biopsy. Perhaps, liquid biopsy may best be used in conjunction with imaging or other diagnostic modalities toward a more holistic approach for diagnosis. Further biomarkers and technologies may be developed in the future that can further increase the precision and usability of liquid biopsies in OMFS. Then, through this, a shift emerges of liquid biopsy as a revolutionary tool in oral and maxillofacial surgery as a practical tool in the diagnosis, prognosis, and monitoring of treatment for malignancies such as OSCC, despite the many challenges which already exist. Liquid biopsy stands poised to have an exponentially positive impact on the outcome in patients being treated for OMFS, which is the main key area of ongoing research and innovation.

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