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# LIQUID BIOPSY IN ORAL CANCER: A REVIEW

Dental Science

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## ABSTRACT

Liquid biopsy is a revolutionary non-invasive diagnostic technique that has transformed the way cancer is monitored. By analysing specific genetic biomarkers present in bodily fluids, such as blood, saliva, or urine, liquid biopsies provide valuable insights into the genetic characteristics of cancer and its potential treatment response. This advanced method utilizes circulating tumour DNA (ctDNA), circulating tumour cells (CTCs), and exosomes containing DNA fragments to detect genetic biomarkers that can predict, disclose, and monitor cancers. Liquid biopsies can provide predictive genetic predisposition information for specific cancers, including oral squamous cell carcinomas (OSCC). One of the key advantages of liquid biopsies is their dynamic nature, enabling real-time monitoring of treatment response to chemotherapy or radiotherapy, as well as the detection of cancer recurrence following surgical excision. Unlike traditional tissue biopsies, which are invasive and carry a degree of morbidity, liquid biopsies are non-invasive. They can be repeated frequently, making them a safer and more accessible option for cancer monitoring. This review comprehensively overviews liquid biopsy and its importance in oral cancer.

## KEYWORDS

Liquid biopsy, oral cancer, saliva, blood

## INTRODUCTION

Head and Neck Carcinoma, mainly squamous cell carcinomas, is ranked as the sixth most common cancer worldwide and is linked to high morbidity and low survival rates.[1] Oral cancer includes cancers of the tongue, buccal mucosa, lip, soft and hard palate, gums, and mouth base. [2] According to the Global Cancer Observatory (GCO), 377,713 new cases of OSCC were reported globally in 2020, with the highest number of cases occurring in Asia (248,360), followed by Europe (65,279) and North America (27,469). [3,4]

Oral carcinogenesis is a multifaceted process involving a multitude of genetic anomalies that disrupt various cellular functions such as signalling, growth, survival, motility, angiogenesis, and cell cycle regulation. The emergence and progression of oral cancer are linked to the dysregulation of critical oncogenes and tumor suppressor genes including CCND1, EGFR, RAS, VEGF, p53, CDKN2A, STAT3, and Rb. These genes play pivotal roles in the development and progression of oral cancer. [5–7] Early detection is crucial for successfully preventing and treating oral cancer, particularly oral squamous cell carcinomas (OSCC). Unfortunately, most cases are not diagnosed until the disease has progressed to advanced stages, significantly reducing the effectiveness of treatment and leading to a poorer prognosis.[8-9] While tissue biopsy remains the gold standard for oral cancer diagnosis, it is invasive, expensive, time-consuming, and potentially harmful. Furthermore, conventional biopsies are limited in capturing the full extent of heterogeneity within the tumor, providing only a brief snapshot of a single region.[10]

Early detection of aggressive tumors is critical for better treatment outcomes. Identifying these tumors at an earlier stage allows for more effective interventions, which can significantly improve the quality of life for cancer patients and also increase their chances of survival. As the disease progresses, surgical options become less effective, and treatments such as radiotherapy and chemotherapy may become more necessary, leading to potential increased toxicity. Delays in diagnosis can lead to poorer patient outcomes and significantly escalate medical expenses related to medications, home and clinical care, and in-hospital treatments as the cancer advances. [11,12,13]

Currently,there is a strong emphasis on finding innovative, non-intrusive techniques to understand and diagnose tumor genomic structure. These methods aim to track the evolution of tumors and assess their response to treatment in real-time. [14,15]

The field of liquid biopsy has become a game-changer in various aspects of oncology and the advancement of personalized medicine for tumors. Liquid biopsy serves as a non-invasive method for diagnosis, relying on identifying circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) and circulating tumor RNA (ctRNA), proteins, and exosomes. [14,16,17] The key point is that a liquid biopsy can be performed using bodily fluids like urine, saliva, seminal plasma, pleural effusions, cerebrospinal fluid, sputum, and stool samples in addition to blood.[18]

Non-invasive cancer screening and detection play a crucial role in modern medical practices. By utilizing less intrusive procedures, non-invasive methods make cancer diagnostics more patient-centric and readily accessible. Furthermore, they facilitate regular monitoring of the disease's progression and the effectiveness of therapies. Liquid biopsies, in particular, have the potential to significantly transform clinical protocols. These advanced biopsies provide invaluable insights into the diversity, evolution, and genetic characteristics of cancer. This, in turn, allows for the development of tailored, individualized treatment plans that can significantly improve patient outcomes.[19]

Liquid biopsies offer several advantages over traditional surgical tissue biopsies. They have lower procedural costs,[20,21] can be easily repeated, and are considered to be more reliable.[22] These factors make liquid biopsies a potentially more suitable and accessible option for use in low- and middle-income countries. In addition, since surgical tissue biopsies can be too risky for some cancers, liquid biopsies provide a safer alternative. Liquid biopsies also avoid the issue of sample heterogeneity, which can lead to misdiagnosis with surgical biopsies.[23] Unlike tissue biopsies, liquid biopsies are not contaminated from the use of preservatives, providing a fresh and reliable source of tumor-derived components and materials.[24] Furthermore, liquid biopsies can swiftly provide genomic, proteomic, and metabolomic information and are less invasive than tissue biopsies.[21,24,25]

### Circulating tumor cells

Circulating tumor cells, known as CTCs, were initially described by Ashworth in 1869 [26].These cells are shed by primary tumors and enter the bloodstream or lymphatic system, enabling them to disseminate to distant sites within the body. This process gives rise to the potential for the formation of secondary tumors, a phenomenon known as distant metastasis. [20,21,26] At first, liquid biopsy applications in cancer research were primarily centered on circulating tumor cells (CTCs). CTCs exhibit diverse molecular markers based on the specific type of cancer. However, a universal epithelial molecular marker known as EpCAM is utilized for the detection of CTCs. EpCAM expression levels vary across different cancer types and are particularly relevant for cancers such as breast and prostate, which exhibit strong EpCAM expression.[27,28]

### Cell-free DNA/circulating tumor DNA

Cell-free DNA (cfDNA) refers to the DNA that has been released from cells into the bloodstream and other bodily fluids. It originates from various cell processes such as programmed cell death (apoptosis), accidental cell death (necrosis), and active secretion from tumors. This fragmented DNA can be found in bodily fluids including blood (plasma and serum), urine, saliva, and cerebrospinal fluid, and is present in both healthy and diseased individuals. [11,29-31]

When the fragmented DNA originates from tumor cells in the bloodstream, it is referred to as circulating tumor DNA (ctDNA). CtDNA accounts for about 1 to 2% of the total cfDNA in individuals with cancer. It differs from normal cfDNA fragments due to the presence of tumor-specific methylation markers and somatic mutations, making it possible to distinguish between the two. [32-34]

However, the disadvantage of ctDNA is its short half-life and generally low levels, which can make detection quite challenging.

### Extracellular vesicles

Extracellular vesicles (EVs) are tiny membrane-bound particles present in various bodily fluids, with a significant presence in blood. EVs are crucial in facilitating communication between different cells, influencing a wide range of normal and disease-related biological processes. These EVs are classified into three main categories - exosomes, microvesicles (MVs), and apoptotic bodies - based on differences in size, contents, functions, release mechanisms, and how they are formed. [35]

### Tumor educated platelets

Platelets are small, disc-shaped, non-nucleated cell fragments generated by megakaryocytes and located in the blood and spleen. Compared to other blood-based biosources, the advantages of using TEPs are their abundance, ease of isolation, and their capability to process RNA in response to external signals. [36,37]

## CONCLUSION

Liquid biopsies capable of early cancer detection will enhance patient prognosis and survival. The current definition of a liquid biopsy needs to be expanded to encompass both tumor and non-tumour-related data. The leading approach in the early cancer detection liquid biopsy market involves genetic testing of biomarkers derived from tumors, such as cfDNA. However, the majority of existing liquid biopsy methods lack the required detection capability for early-stage cancers. It is essential to focus research efforts on conducting comprehensive, large-scale studies across multiple centres to explore the role of CTCs, ctDNA, and exosomes in oral cancer.

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