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Review Article

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Decoding Brain Tumors with Liquid Biopsies: A Narrative Review of a Silent Sentinel in Neuro-Oncology

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Abstract

Traditionally, diagnosing brain tumors has relied on tissue biopsies, which are considered the gold standard. However, these invasive procedures come with drawbacks, including the possibility of sampling errors resulting from the heterogeneous nature of tumors. Furthermore, they are not ideal for continuous monitoring. In contrast, liquid biopsies offer a promising, minimally invasive alternative by analyzing tumor-derived substances found in biofluids. The goal of this review is to consolidate current research on the role of liquid biopsies in the field of neuro-oncology. Specifically, we will explore their applications in diagnosis, tumor classification, treatment monitoring, and the identification of minimal residual disease, while also acknowledging the challenges faced and outlining future directions for this promising technology. Essential elements, such as circulating tumor DNA, circulating tumor cells, and extracellular vesicles, provide critical genetic and molecular insights. Notably, cerebrospinal fluid is often a superior biofluid to blood for brain tumors, as it directly contacts the central nervous system and bypasses the filtering effect of the blood-brain barrier (BBB), yielding higher concentrations of tumor-derived material. Liquid biopsies offer several essential advantages, including the ability to capture tumor heterogeneity more effectively and facilitate real-time monitoring of treatment responses. However, their clinical adoption is currently hindered by issues, such as low concentrations of biomarkers in blood, the absence of standardized protocols, and the challenges posed by the BBB. Liquid biopsies have the potential to advance personalized care in neuro-oncology significantly. To move these techniques into routine clinical use, future efforts should prioritize technological advancements, the establishment of standardized assays, and the integration of these approaches with artificial intelligence and advanced imaging techniques. This will enhance our ability to tailor treatments more effectively and improve patient outcomes in neuro-oncology.

Key words: Biomarkers, Brain Neoplasms, Circulating Tumor DNA, Glioma, Liquid Biopsy

Introduction

Conventional tissue biopsies have long been considered the gold standard for diagnosing and molecularly characterizing brain tumors (1). Despite their established role, these invasive procedures come with considerable risks, including such complications as hemorrhage, infection, and the potential for new neurological deficits. These risks are particularly pronounced when lesions occur in eloquent or deep-seated regions of the brain (2, 3). Another significant drawback is that tissue biopsies provide only a limited snapshot of the tumor's overall characteristics; they sample just a small portion of the lesion and cannot be easily repeated to track changes in response to treatment or to understand evolving resistance mechanisms (4, 5). Consequently, the discomfort and risks associated with multiple surgical interventions make them impractical for effective long-term management of the disease.

In contrast, liquid biopsies have emerged as a game-changing, non-invasive option in oncology.

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This innovative technique involves examining various tumor-derived components, including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and extracellular vesicles (EVs), which are released into biofluids. A key consideration in neuro-oncology is the choice of biofluid.

Although blood is the most common and readily available, the blood-brain barrier (BBB) significantly limits the passage of brain tumor-derived material into the bloodstream. Consequently, cerebrospinal fluid (CSF), which is in direct contact with the central nervous system, often contains a higher concentration of these biomarkers, providing a more sensitive window into the tumor's biology, albeit requiring a more invasive procedure like a lumbar puncture for collection (6, 7).

By providing a comprehensive genetic overview of the tumor burden, liquid biopsies offer an invaluable tool for early detection and profiling tumor heterogeneity, and monitoring treatment response in real-time. They also enable earlier detection of minimal residual disease (MRD) or recurrence, compared to standard imaging methods (8, 9).

The primary aim of this review is to critically assess the current applications of liquid biopsies in the field of neuro-oncology. We seek to answer the pivotal question: How can liquid biopsies address the shortcomings of traditional tissue biopsies to enhance the diagnosis, monitoring, and management of brain tumors? In doing so, this review collates evidence regarding the analytical validity and clinical efficacy of various components of liquid biopsies, while also discussing the challenges that remain, and the future directions needed for their integration into standard clinical practice.

Methods

Search Strategy

This comprehensive narrative review provides a clear overview of the current research on liquid biopsies for brain tumors. To achieve this, a thorough search of the literature was conducted across several electronic sources databases, namely PubMed/MEDLINE, Scopus, and Web of Science. Our search focused on articles published from January 2014 to July 2024, allowing us to capture the latest developments in this rapidly advancing area of research.

Our search strategy employed a combination of specific keywords and Medical Subject Headings (MeSH) terms, including: ("Liquid Biopsy" OR "Circulating Tumor DNA" OR "ctDNA" OR "Circulating Tumor Cells" OR "CTC" OR "Extracellular Vesicles" OR "Exosomes") AND ("Brain Neoplasms" OR "Glioma" OR "Glioblastoma" OR "Neuro-oncology").

Inclusion Criteria

To ensure relevance and quality, the selection was limited to articles published in English, considering both original research studies and review articles. This dual approach allowed for a well-rounded perspective on the topic.

Exclusion Criteria

Exclusion criteria were:

- Articles not available in full text.
- Case reports with fewer than 5 patients.
- Studies not directly related to central nervous system tumors.
- Non-English publications.

Article Screening

The relevant articles were then carefully selected based on their titles and abstracts, and their full texts were obtained for thorough analysis and interpretation.

Data Extraction, Collection, and Synthesis

A structured approach was employed to extract and synthesize data from the included studies. Key information was collected using a standardized template, capturing:

- Study characteristics (author, year, design)
- Patient population and sample size
- Type of biofluid analyzed (blood, CSF)
- Biomarker class (ctDNA, CTCs, EVs, miRNAs)
- Analytical methodology
- Primary clinical application
- Main findings and limitations

Data were thematically synthesized to address the review's objectives: evaluating the role of liquid biopsies in diagnosis, molecular classification, treatment monitoring, and detection of minimal residual disease in brain tumors. Emphasis was placed on identifying consensus findings, methodological challenges, and emerging trends. The synthesis aimed to provide a coherent, critical overview of the field while highlighting gaps for future research.

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Results

Components of Liquid Biopsies

Liquid biopsies have significantly transformed the aspect of cancer diagnostics by offering a non-invasive method to analyze tumor-derived components found in biofluids. These components, such as ctDNA, CTCs, exosomes, and microRNAs (miRNAs), each provide unique insights into the cancer phenotype. However, their application in neuro-oncology presents unique challenges and considerations, primarily due to the BBB.

ctDNA refers to particles of DNA shed by tumor cells into the bloodstream. These particles often exhibit genetic mutations that mirror those in the primary tumor, providing valuable insights into the tumor's genetic landscape. Recent advancements in technologies, such as next-generation sequencing and digital PCR, have significantly enhanced our ability to detect ctDNA, establishing it as a key player in precision oncology. Clinically, ctDNA is utilized for identifying genetic alterations, monitoring treatment responses, and assessing the presence of minimal residual disease (1-3). In neuro-oncology, the detection of ctDNA in blood is challenged by the BBB, which limits its release; however, CSF has proven to be a much richer source of brain tumor-derived ctDNA, offering high sensitivity for mutation detection and tumor monitoring.

CTCs are intact cancer cells that have separated from the primary tumor and entered the bloodstream. They provide essential information regarding the tumor's genetic and phenotypic characteristics. Innovative techniques, including immunoaffinity capture and microfluidic devices, have enhanced the isolation and analysis of CTCs, making them invaluable for monitoring disease progression, evaluating treatment efficacy, and studying metastatic potential (3-6). For brain tumors, CTCs are exceptionally rare in peripheral blood due to the BBB and the predominantly locally invasive nature of gliomas (10). Their detection remains a significant technical challenge, though they may have greater relevance in the context of leptomeningeal disease or metastatic brain tumors.

Exosomes, small extracellular vesicles released by cancer cells, encapsulate DNA, RNA, proteins, and lipids. These vesicles are pivotal in intercellular communication. Their inherent stability within biological fluids positions them as promising candidates for early cancer detection and for monitoring treatment responses. Recent technological advancements in the isolation and characterization of exosomes have significantly expanded their applications in clinical settings (7-9). Exosomes are particularly promising in neuro-oncology because they can actively cross the BBB (11). This makes them more readily detectable in blood than ctDNA or CTCs, providing an accessible window into the brain tumor's molecular makeup for diagnosis and tracking therapeutic response.

miRNAs are small non-coding RNA molecules that play a crucial role in gene regulation. Their presence in body fluids makes them important markers for diagnosing cancer, predicting its progression, and assessing the effectiveness of treatment. Given their stability and capability to reflect molecular changes in tumors, miRNAs have emerged as promising candidates for incorporation into liquid biopsies (12, 13). Specific miRNA signatures in both blood and CSF have been associated with different brain tumor types and grades (14). Their stability in biofluids makes them robust analytes. However, distinguishing tumor-specific miRNAs from those released by other tissues or inflammatory processes remains an area of active research in neuro-oncology.

The utilization of these components in clinical practice enables us to gain a deeper understanding of how tumors function, ultimately leading to improved patient outcomes. This marks a significant improvement in cancer diagnostics and personalized treatment. For brain tumors, the choice of analyte and biofluid is critical, with CSF often providing a more direct and sensitive correlate of tumor activity.

Applications in Brain Tumors

For Diagnosis and Tumor Classification

Liquid biopsies are redefining how we approach the diagnosis and molecular classification of brain tumors. This technique analyzes a specific topic in a new way with ctDNA, CTCs, and EVs found in biofluids. By studying these specific biomarkers, clinicians can identify critical genetic mutations that are essential for accurately categorizing brain tumors. Among the well-documented mutations are H3F3A K27M and BRAF, which have significant implications for both diagnosis and treatment strategies (1-3). One of the standout advantages of using ctDNA extracted from cerebrospinal fluid is its exceptional sensitivity and specificity. This

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makes CSF ctDNA an invaluable tool not just for the early detection of brain tumors but also for precise tumor classification. The ability to detect molecular characteristics at such an early stage enhances the prospect for timely and targeted therapeutic interventions (4, 5).

For Treatment Response Monitoring and Tracking Progression

Liquid biopsies represent a significant advancement in oncology, particularly for the real-time assessment of how tumors respond to treatment and how they evolve. This innovative approach allows healthcare professionals to monitor a tumor's genetic profile without the need for repeated and invasive procedures, thereby minimizing patient discomfort and risk. By examining changes in ctDNA, CTCs, and EVs, clinicians can acquire essential insights into tumor behavior. These analyses are necessary to distinguish between real tumor growth and pseudo-progression, which can complicate treatment decisions. Accurately identifying these differences is crucial, as it empowers clinicians to make more informed and timely adjustments to treatment plans. This can ultimately lead to improved patient outcomes and enhanced efficacy of therapeutic strategies (3-5, 14).

For Checking Minimal Residual Disease and Recurrence

The application of liquid biopsy has emerged as a transformative tool in oncology, particularly due to its remarkable sensitivity in detecting MRD and predicting cancer recurrence well ahead of traditional diagnostic methods. By analyzing ctDNA found in blood and other biofluids, liquid biopsies can identify residual tumor cells that standard imaging techniques may miss.

This early detection capability is vital because it enables timely interventions that can significantly improve long-term survival outcomes for patients. Research has shown that changes in ctDNA levels are closely associated with tumor burden, offering clinicians insight into anticipating recurrence even before it becomes evident on imaging studies (6, 7, 15, 16). This proactive strategy not only enhances disease management but also substantially increases the likelihood that patients will achieve more favorable outcomes. The regular use of liquid biopsy in healthcare facilitates a more personalized and practical approach to cancer treatment.

Advantages Over Traditional Biopsies

Liquid biopsies provide several benefits compared to traditional tissue biopsies for brain tumor management:

Liquid biopsies represent a significant leap forward in the field of neuro-oncology, offering a non-invasive method to analyze components derived from tumors found in biofluids. When it comes to brain tumors, the biofluids of most significant relevance include blood plasma and CSF, with CSF often yielding a more abundant array of central nervous system-specific biomarkers. The advantages of liquid biopsies over traditional surgical tissue biopsies are profound. Surgical biopsies require invasive procedures that not only pose considerable risks to the patient but also can be uncomfortable and traumatic. In contrast, liquid biopsies are minimally invasive, allowing clinicians to collect samples safely and repeatedly with little risk to the patient. This capability fosters continuous monitoring of tumor dynamics through various stages of the disease, providing invaluable insights for both clinicians and patients. Moreover, the ease of access to biofluids means that healthcare teams can regularly assess how a tumor is evolving and how the patient is responding to treatment, all while prioritizing the individual's comfort and safety. By decreasing the necessity for multiple surgeries, liquid biopsies open the door to a more personalized approach to patient management, ultimately contributing to better outcomes in the management of brain tumors. This innovative technique not only enhances our understanding of tumor behavior but also empowers patients by keeping them more engaged and informed throughout their treatment journey (20, 21).

Liquid biopsies represent a significant advancement in our ability to understand and treat cancer, primarily because they capture the complexities of tumor heterogeneity in a way that traditional tissue biopsies cannot. While tissue biopsies typically focus on a small portion of a tumor, liquid biopsies analyze biomarkers circulating in the bloodstream from various tumor sites. This method gives a broader understanding of the tumor's genetic variations, revealing important information about different mutations. Such insights are essential, as they can identify specific alterations that therapies may target to address. By employing this comprehensive approach, we can gain a deeper understanding of a patient's unique cancer profile. This understanding helps us create

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more personalized and effective treatment plans. Liquid biopsies not only enhance our knowledge of cancer but also promise to improve patient care through targeted treatments (22, 23).

Liquid biopsies mark a significant leap forward in the field of oncology, offering a unique and non-invasive approach to track the neoplasm genome in real time. This innovative approach enables healthcare providers to assess a patient's response to treatment and track the tumor's progression. By examining circulating tumor DNA and various biomarkers present in bodily fluids, clinicians can glean essential insights into the changing molecular landscape of a patient's cancer. This real-time information is invaluable, as it empowers medical professionals to make prompt and informed adjustments to treatment strategies, thereby enhancing the overall effectiveness of care. Moreover, liquid biopsies play a crucial role in distinguishing between actual tumor progression and pseudo-progression, a vital consideration that can profoundly influence patient management and clinical outcomes. As we continue to integrate liquid biopsy technology into routine practice, we are moving toward more personalized and effective cancer treatments. This evolution not only aims to improve survival rates but also seeks to enhance the well-being of individuals affected by this challenging illness (24, 25).

Liquid biopsies have become an innovative tool in neuro-oncology, offering the potential for less invasive cancer diagnosis and monitoring. However, their full implementation is hindered by several noteworthy challenges that need to be addressed:

Low Biomarker Concentration

One major challenge in using liquid biopsies is that tumor markers are often present in very low amounts in body fluids, such as blood and cerebrospinal fluid. These biomarkers are essential for accurate cancer diagnosis and ongoing monitoring. Their low numbers necessitate the development of sensitive and advanced methods for detecting them. This will help accurately identify and measure these essential indicators. Such advances are crucial for enabling clinicians and researchers to gain meaningful insights into tumor presence and progression (1, 2, 5).

Standardization Issues

Another significant challenge lies in the lack of standardized protocols for collecting biofluids and analyzing biomarkers. The absence of uniformity can significantly impact the reproducibility and clinical utility of liquid biopsies. Variations in sample collection and processing may lead to inconsistent outcomes, thereby undermining the reliability of these diagnostic tests. To enhance the accuracy and trustworthiness of liquid biopsies, consistent protocols must be developed and adopted across the field (3, 5).

Blood-Brain Barrier

The BBB poses a formidable barrier in the quest to detect tumor biomarkers in neuro-oncology. This protective shield selectively regulates the passage of substances between the bloodstream and the brain, thereby restricting the release of critical biomarkers into the circulatory system. Overcoming this obstacle is essential for the successful application of liquid biopsy techniques in detecting brain tumors. Innovative strategies to bypass the BBB are crucial for enabling earlier and more precise diagnoses, and integrating these approaches helps create personalized treatment strategies, leading to better outcomes for patients. This improvement stems from a deeper understanding of tumor biology and the ability to track changes at the molecular level in real-time.

The integration of imaging techniques with artificial intelligence (AI) presents a transformative opportunity for precision medicine in the field of neuro-oncology. By combining liquid biopsies with advanced imaging methods, such as diffusion tensor imaging and magnetic resonance spectroscopy, healthcare providers can significantly enhance their ability to distinguish between tumor progression and changes induced by therapeutic interventions. The use of AI-driven algorithms, particularly convolutional neural networks, allows for the analysis of complex data derived from both liquid biopsies and imaging studies. This not only enhances diagnostic accuracy but also minimizes variability among different observers. Bringing together these elements leads to personalized treatment plans that improve patient outcomes. This occurs because we gain a deeper understanding of tumor biology, allowing us to track changes at the molecular level in real-time.

In parallel, we need to develop new biomarkers and tests to enhance the clinical utility of liquid biopsies. Emerging biomarkers, including ctDNA, CTCs, and EVs, offer critical insights into the genetic composition and molecular alterations of tumors. Innovative assays, including digital PCR and next-generation sequencing, have greatly enhanced the sensitivity and specificity needed to

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detect these biomarkers. Ongoing research is imperative for identifying and validating new biomarkers that offer more accurate and comprehensive information regarding tumor heterogeneity, treatment responses, and disease process.

Moreover, the applications of liquid biopsies in clinical trials are expanding rapidly, with their use encompassing early diagnosis, monitoring the effectiveness of treatments, detecting even tiny remnants of disease, and predicting recurrence. By integrating liquid biopsies into clinical trials, researchers gain access to real-time data concerning tumor dynamics, which enables more precise and timely modifications to treatment protocols. This approach also helps identify patients who are likely to benefit from targeted therapies and immunotherapies, ultimately enhancing the overall effectiveness of clinical trials.

Conclusions

In summary, liquid biopsies hold remarkable promise for transforming how we diagnose, monitor, and treat brain tumors. By providing a non-invasive and reproducible approach, they enable us to capture the diverse characteristics of tumors and track molecular changes as they occur. However, for liquid biopsies to become a routine tool in neuro-oncology, we must tackle several challenges. These challenges include the typically low concentrations of biomarkers, the lack of standardized methodologies, and the obstacles imposed by the blood–brain barrier.

Ongoing research is crucial to improving the sensitivity and specificity of liquid biopsy techniques. It is also essential to develop standardized protocols for the collection and analysis of biofluids, as well as strategies to navigate the complexities introduced by the BBB. As our understanding and technology in this area progress, we may see liquid biopsies play an integral role in clinical practice, paving the way for more personalized treatment approaches and ultimately leading to better outcomes for patients facing brain tumors.

Ethics Approval and Consent to Participate

Not applicable, as this is a narrative review of existing literature and does not involve human participants or original data collection.

Consent for Publication

Not applicable.

Data Availability Statement

No datasets were generated or analyzed during the current study.

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Authors' Contribution

MM had done Conceptualization, Study design with Writing review and editing, and MGh had done Literature search and resources with Writing original drafts.

Conflict of Interest

The authors declare that they have no competing interests.

Declaration of Generative Artificial Intelligence (AI) in Scientific Writing

All scientific content, reasoning, and conclusions in this manuscript are the sole responsibility of the authors.

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