Review Article

Imaging and Liquid Biopsy for Distinguishing True Progression From Pseudoprogression in Gliomas, Current Advances and Challenges

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Rationale and Objectives: Gliomas are aggressive brain tumors with a poor prognosis. Assessing treatment response is challenging because magnetic resonance imaging (MRI) may not distinguish true progression (TP) from pseudoprogression (PsP). This review aims to discuss imaging techniques and liquid biopsies used to distinguish TP from PsP.

Materials and Methods: This review synthesizes existing literature to examine advances in imaging techniques, such as magnetic resonance diffusion imaging (MRDI), perfusion-weighted imaging (PWI) MRI, and liquid biopsies, for identifying TP or PsP through tumor markers and tissue characteristics.

Results: Advanced imaging techniques, including MRDI and PWI MRI, have proven effective in delineating tumor tissue properties, offering valuable insights into glioma behavior. Similarly, liquid biopsy has emerged as a potent tool for identifying tumor-derived markers in biofluids, offering a non-invasive glimpse into tumor evolution. Despite their promise, these methodologies grapple with significant challenges. Their sensitivity remains inconsistent, complicating the accurate differentiation between TP and PSP. Furthermore, the absence of standardized protocols across platforms impedes the reliability of comparisons, while inherent biological variability adds complexity to data interpretation.

Conclusion: Their potential applications have been highlighted, but gaps remain before routine clinical use. Further research is needed to develop and validate these promising methods for distinguishing TP from PsP in gliomas.

Key Words: Gliomas; True progression; Pseudoprogression; Imaging; Liquid biopsy.

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INTRODUCTION

Gliomas are the most common and aggressive primary brain tumors, accounting for approximately 80% of all malignant brain cancers (1). The standard of care for gliomas, especially high-grade gliomas such as glioblastoma, involves maximal surgical resection followed by chemoradiation and/or immunotherapy (2). However, the prognosis of glioma patients remains poor, with a median survival of less than 15 months (3).

One of the major challenges in the management of glioma is the accurate assessment of treatment response and disease progression. Conventional magnetic resonance imaging (MRI) is the mainstay for monitoring gliomas, but it has limitations in distinguishing true progression (TP) from pseudoprogression (PsP). TP refers to the actual growth and invasion of tumor cells into the surrounding brain tissue, whereas PsP refers to the transient increase in contrast enhancement and edema caused by treatment-induced inflammation and necrosis (4). Both phenomena can appear similar on MRI scans, leading to misdiagnoses and inappropriate clinical decisions.

Differentiating TP from PsP in gliomas is crucial for determining the optimal treatment strategy and predicting

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patient outcomes. Therefore, there is a need for more reliable and sensitive methods for evaluating tumor response and evolution. In this review, we discuss the current advances and challenges in the use of imaging techniques and liquid biopsy to distinguish TP from PsP in gliomas. We also highlight the potential applications and future directions of these methods in clinical practice.

Imaging techniques, such as MRI and computed tomography (CT), can provide detailed images of the brain and the tumor, but they may not be able to distinguish between tumor growth and inflammation caused by treatment (5). Therefore, advanced imaging techniques, such as magnetic resonance diffusion imaging (MRDI) and perfusion weighted imaging (PWI) MRI, are required to measure the blood flow and microstructure of the tumor tissue. These techniques can help distinguish TP from PsP by showing different patterns of perfusion and diffusion in the tumor.

Liquid biopsy is a less invasive method that samples tumor-derived material from biofluids such as blood and cerebrospinal fluid (CSF) (6). Liquid biopsy can detect circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and extracellular vesicles (EVs), which carry tumor-specific molecular markers (7). However, liquid biopsy is hampered by technical and biological problems such as low concentrations of tumor-derived DNA in the bloodstream of patients (8).

Distinguishing TP from PsP post-glioma treatment remains a focal challenge in the current radiological research. Previous studies have extensively discussed this issue. This study aimed to provide a comprehensive overview of current techniques, including imaging and liquid biopsy, and discuss their merits and limitations. The goal was to offer clinically meaningful insights into practice and future research.

PSEUDOPROGRESSION OF GLIOMA

PsP of glioma is a condition in which MRI demonstrates worsening lesions not caused by actual tumor growth (9). PsP most commonly occurs within 12 weeks following radiation therapy in patients with high-grade gliomas (HGGs), although it may manifest from the first few weeks to 6 months post-treatment (10). Biopsy reveals PsP as a consequence of inflammation, cell death, or, rarely, an immune response. PsP does not indicate tumor dissemination but is a side effect of therapy (11). PsP often resolves spontaneously without additional intervention. The precise etiology and mechanisms underlying PsP remain poorly defined. PsP may arise from an exaggerated treatment response. Both radiotherapy and chemotherapy elicit increased levels of intracranial tumor necrosis factor-alpha (TNF-α), disturbing brain homeostasis, vasculature, and the blood-brain barrier (BBB) (12,13). An association between PsP and isocitrate dehydrogenase 1 (IDH1) mutations in glioma patients has been proposed. Li et al. identified IDH1 mutations as a risk factor for PsP development in 145 glioblastoma patients, with IDH1 demonstrating 34.2% sensitivity and 97.3% specificity for PsP diagnosis, suggesting its utility as a predictive biomarker. The basis of this relationship is yet to be elucidated (14,15). In certain instances, MRI interpretation can be challenging, with PsP lesions potentially mistaken for TP. Accordingly, a reliable, non-invasive approach is imperative for distinguishing TP from PsP when evaluating ambiguous intracranial lesions via neuroimaging.

IMAGING TECHNIQUES FOR DISTINGUISHING TRUE PROGRESSION FROM PSEUDOPROGRESSION IN GLIOMAS

Imaging detection remains the predominant method for distinguishing TP from PsP in gliomas. However, the efficacy of conventional imaging techniques in distinguishing this distinction is challenging. The demand for more precise and dependable imaging modalities that can accurately differentiate between TP and PsP in gliomas is evident (16). Recently, several advancements have been made in this domain, employing a variety of imaging modalities, including, but not limited to, conventional MRI, advanced MRI, CT scans, and positron emission tomography (PET) scans. Despite these advancements, numerous challenges and limitations have persisted, necessitating further research and development. In this section, we provide a comprehensive review of the current state-of-the-art imaging techniques and discuss potential future directions for improving the differentiation of TP from PsP in gliomas **(**Fig 1**)**.

Conventional Magnetic Resonance Imaging

Conventional MRI is difficult to distinguish between TP and PsP using conventional MRI in most cases, but considering that conventional MRI is a routine examination technique in most hospitals, we have also summarized some conventional MRI features that may help distinguish TP from PsP. Conventional MRI is instrumental in evaluating TP and PsP in gliomas. It offers invaluable anatomical data, aiding in the assessment of alterations in tumor size, morphology, and enhancement patterns (17). In the early 1990 s, Macdonald et al. proposed criteria for assessing the treatment response in HGGs based on conventional MRI (18). These criteria primarily consider the extent of lesion enhancement on MRI, in conjunction with clinical symptoms and steroid use, to determine glioma progression. However, the limitations of this approach include the fact that post-treatment contrast enhancement may not be related to tumor activity but rather to BBB (19,20). Furthermore, the increased incidence of PsP following concurrent temozolomide chemoradiation, as well as the use of antiangiogenic agents, has made the deficiencies of the Macdonald criteria more apparent. Consequently, the Response Assessment in Neurooncology (RANO) working group introduced the RANO criteria, which incorporate additional measures, such as T2/FLAIR, to the assessment, emphasizing that the non-enhancing tumor component

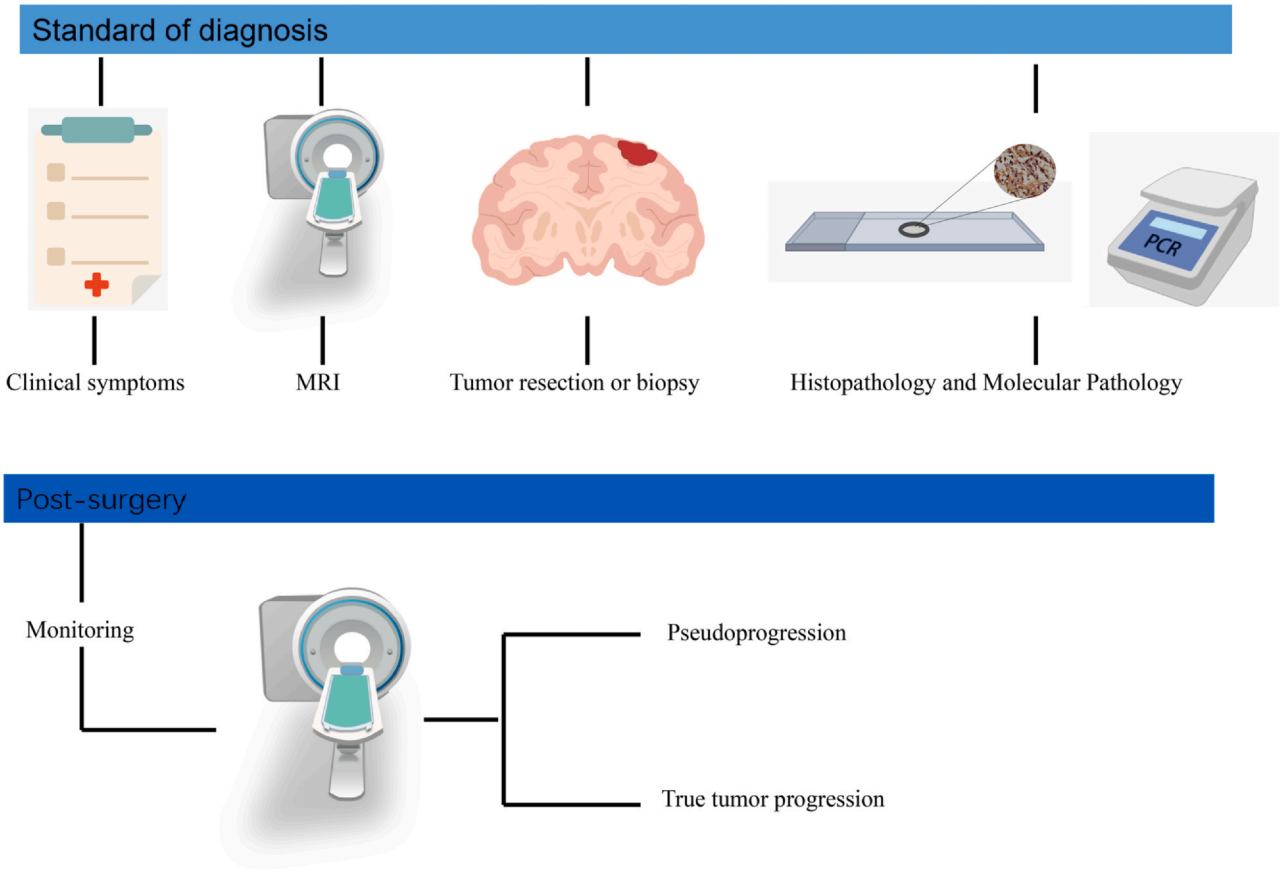

Figure 1. The imaging techniques are applied to differentiate TP from PsP.

should also be evaluated for decision-making (21). Currently, certain traditional MRI features may assist in distinguishing PsP from TP. For instance, the presence of a solitary lesion within the resection cavity or lesions with mass effect and progressive enhancement involving the corpus callosum may suggest TP; in contrast, PsP is typically characterized by "Swiss cheese-like" enhancement (13) and involvement of subependymal enhancement (22). In a study of 93 patients, subependymal enhancement on MRI was identified as a unique indicator of TP, with a sensitivity of 38.1%, specificity of 93.3%, and negative predictive value of 41.8% (23). However, it may be difficult to differentiate or coexist these features.

To address these limitations, the incorporation of advanced imaging techniques such as MRDI, PWI, and magnetic resonance spectroscopy (MRS) can provide supplementary information (19). These techniques can evaluate blood flow, vascular permeability, microstructural alterations, and metabolic changes, thereby enhancing differentiation accuracy (24,25).

Advanced Magnetic Resonance Imaging Technique

Advanced MRI techniques refer to various MRI methods that can provide more information on the structure and function of the brain than conventional MRI. The most common advanced MRI techniques currently available for differentiating TP from PSP in gliomas include MRDI, MRS, PWI, among others (26,27). Although each of these techniques holds a certain value in their application, they also have limitations. Therefore, summarizing the application of these techniques in glioma treatment is of significant importance.

Magnetic Resonance Diffusion Imaging Technique

MRDI is an MRI technique that reflects the microstructure and function of tissues based on the diffusion of water molecules (28). MRDI includes diffusion-weighted imaging (DWI) and Diffusion tensor imaging (DTI). DWI can reflect the degree of diffusion and restriction of water molecules in tissues and lesions and is the only non-invasive method for detecting water molecule diffusion (29). DTI can reflect the direction and anisotropy of water molecule diffusion and perform brain white matter fiber tract imaging (30). The main difference between DWI and DTI is that DWI only needs to apply a diffusion gradient in one direction and can image quickly; however, it cannot reflect the diffusion direction and anisotropy of water molecules. DTI requires the application of a diffusion gradient in at least six directions and

can obtain more information and a higher spatial resolution, but has a longer imaging time and is more affected by motion artifacts (31).

Diffusion Weighted Imaging

A commonly used MRDI technique is DWI, which reflects the diffusion of water molecules within relevant tissues by utilizing multiple diffusion gradients to measure the magnitude of random water molecule movement (32). The most widely used quantitative parameter is the Apparent Diffusion Coefficient (ADC), which is inversely proportional to cell density (33). In patients with tumor recurrence, the ADC value tends to decrease because of restricted water molecule diffusion within the tumor (34). Conversely, PsP of a tumor is associated with higher ADC values (35). Studies suggest that among the currently used ADC values, including the mean ADC, relative ADC, and fifth percentile value, the fifth percentile value is considered more suitable for distinguishing TP from PsP. The sensitivities were 90% and 80%, the specificities were 90% and 80%, and the Area Under Curve(AUC) was 0.880 and 0.840, respectively (36). Another study demonstrated that diagnostic accuracy was enhanced when employing the subtracted histogram mode within a multiparametric framework compared to a uniparametric approach, achieving a higher AUC of 0.877, with a sensitivity of 81.8% and a specificity of 100% (37). However, using the mean ADC value to differentiate TP from PSP has certain limitations, as the ADC values of cystic and necrotic areas are higher than those of solid tumors (38). Overall, although ADC values have a good diagnostic value, the practicality of these different ADC parameters requires further research. Moreover, the interpretation of ADC values can be confounded by the overlapping characteristics of the different tissue types. For instance, inflammation or infection can also lead to restricted diffusion, mimicking the ADC characteristics of a tumor (39). This can lead to false positives in the detection of tumor recurrence. Furthermore, the presence of edema, which is common in post-treatment brain tissues, can artificially elevate ADC values, potentially leading to false-negatives. In addition, the real-world clinical validity of these techniques is further complicated by the heterogeneity of patient populations and multifactorial nature of disease progression and treatment response.

Another commonly used diffusion imaging technique is DTI, which utilizes anisotropic diffusion of water molecules for imaging. Fractional Anisotropy (FA) images can display the structure and anisotropy of white matter fibers in the brain and evaluate their treatment effects (40). In conclusion, MRDI techniques have a certain sensitivity in distinguishing TTP from PSP, but their specificity is not strong, necessitating a combination of multiple methods for accurate differentiation.

Diffusion Tensor Imaging

DTI serves as a pivotal tool in distinguishing TP from PsP in gliomas, offering insights into the structural integrity and organization of white matter tracts (41). In TP, gliomas display increased cellularity and invasiveness, disrupting the adjacent white matter tracts. DTI visualizes these alterations through parameters such as FA, with decreased FA values within the tumor region indicating disrupted tracts, which may suggest TP (42–43). Conversely, PsP, characterized by transient increases in contrast-enhancing regions on MRI scans due to treatment effects, can be differentiated by DTI through assessment of white matter tract integrity (44). Preserved or minimally changed FA values compared to baseline scans suggest that contrast enhancement is due to treatment effects rather than TP (45). Wang et al. integrated DTI with Dynamic Susceptibility Contrast (DSC) suggesting that a diagnostic model combining both can distinguish TP from non-TP (PsP and mixed). This model comprises FA, the linear anisotropy coefficient, and the maximum relative cerebral blood volume, resulting in an AUC of 0.905 (46).

Nonetheless, the interpretation of DTI results should consider its limitations. PsP can exhibit decreased FA values owing to inflammation, edema, or treatment-induced changes affecting white matter integrity, which can mimic the DTI appearance of TP. The location and extent of white matter involvement, with certain regions inherently having lower FA values, should be considered (47). Comparisons with baseline scans and correlation with clinical findings are crucial for improving differentiation accuracy. Technical limitations of DTI, such as susceptibility artifacts and variability in protocols across different centers, can impact data quality and comparability, potentially limiting the generalizability of the study results to broader clinical practice. Agarwal's study, which included 46 patients, concluded that morphological MRI features and DTI play a limited role in differentiating between PsP and TP. Thus, while DTI is a promising tool for distinguishing glioma progression, its definitive utility may require integration with other imaging modalities and parameters to enhance its accuracy and reliability, as well as the development of standardized protocols to ensure consistency across different clinical environments.

Magnetic Resonance Spectroscopy

MRS utilizes the phenomenon of magnetic resonance chemical shifts to ascertain the molecular composition of a substance. It is capable of measuring the concentration of various metabolites in the brain tissue and tumors, thereby reflecting the distribution of metabolites within the brain tissue and facilitating the evaluation of tumor treatment efficacy (48). The characteristic manifestation of tumor tissue in MRS is attributed to an increase in cell density and overall cell membrane, resulting in elevated choline (Cho) levels, whereas a decrease in neurons leads to a reduction in N-acetylaspartate (NAA) (49). Typical proton magnetic resonance spectroscopy (1 H-MRS) exhibits an increase in the Cho/NAA and Cho/Cr ratios, with the NAA/Cr ratio either remaining normal or decreasing (50).

However, the signal-to-noise ratio and image quality of MRS can be influenced by factors such as susceptibility artifacts, motion artifacts, and partial-volume effects. These factors can potentially impact the interpretation and comparison of MRS ratios, which are also subject to the selection of regions of interest, threshold choices, and variability of normal values. Despite these challenges, a meta-analysis suggested that MRS, among advanced MRI techniques, distinguishes between treatment-related changes and tumor recurrence. With sensitivity and specificity of 91% and 95%, respectively, MRS demonstrates superior diagnostic performance (51). However, it is important to note that these figures may not be universally applicable because they can vary depending on the technical setup and expertise of the interpreting radiologists. A study published in Nature Reviews Clinical Oncology suggests that MRS holds a very broad prospect for identifying postoperative glioma TP or PsP following temozolomide chemotherapy and radiotherapy (52). Thust and colleagues' research posits that MRS's capability to recognize PsP exceeds that of the Perfusion MRI technique, which will be discussed later (53). Nonetheless, the real-world application of MRS is limited by its availability in clinical settings and the need for standardization in the interpretation of its results. Overall, the use of MRS to evaluate early treatment effects during glioma therapy has yielded positive results, but further studies are required to establish its role in routine clinical practice and to determine its effectiveness across diverse patient populations.

Perfusion Weighted Imaging

PWI often provides grading and prognostic information and can distinguish between TP and PsP (54). PWI includes techniques such as DSC MRI, Dynamic contrast-enhanced perfusion imaging (DCE) MRI, arterial spin labeling (ASL), and multiparametric combinations to differentiate between the conditions. Among them, DSC and DCE-MRI are the two most common techniques.

Dynamic Susceptibility Contrasts Magnetic Resonance Imaging

DSC Perfusion Imaging is a valuable technique for evaluating TP and PsP in gliomas by assessing cerebral blood flow and microvascular characteristics. It provides information regarding the relative cerebral blood volume (rCBV), which can aid in distinguishing between these two conditions (55).

In TP, gliomas exhibit increased angiogenesis and neovascularization, leading to elevated rCBV values. The growth of malignant tissue requires a rich blood supply, and as the tumor progresses, new blood vessels are formed to support its growth. DSC perfusion imaging can detect these changes by tracking the passage of a contrast agent through the brain (56,57). The regions with increased rCBV values indicated areas of active tumor growth and angiogenesis, suggesting TP. PsP, on the other hand, refers to the transient increase in contrast-enhancing regions on conventional MRI scans due to treatment-related effects rather than actual tumor growth (58). In PsP, the extent of angiogenesis and neovascularization is typically less pronounced than in TP, resulting in lower rCBV values. As a result, DSC perfusion imaging may show lower rCBV values in PSP than in TP (59,60). The current study confirms the significant value of DSC imaging in differentiating TP from PsP. Taylor et al.'s systematic review and meta-analysis, comparing various advanced MRI diagnostic techniques, identified DSC as the most clinically promising for high-grade glioma progression, with an AUC of 0.93, and sensitivity and specificity of 0.88 (26). Similarly, another study reported strong sensitivity (0.84) and specificity (0.78) for distinguishing TP from PsP in high-grade gliomas, with an AUC of 0.85 (61). However, there are constraints to be considered when using DSC perfusion imaging to differentiate TP from PsP. First, interpretation should consider the timing of the imaging study because contrast enhancement patterns can vary at different time points after treatment. Additionally, other factors, such as inflammation, treatment-induced changes, and ischemic effects can also affect rCBV values, leading to potential false interpretations (62). Moreover, DSC perfusion imaging relies on the accurate measurement of the arterial input function and assumes a linear relationship between contrast agent concentration and signal intensity. Technical factors, such as susceptibility artifacts, partial volume effects, and contrast agent leakage, can introduce errors and affect the reliability of rCBV measurements.

In summary, DSC perfusion imaging plays a significant role in distinguishing TP from PsP in gliomas by assessing the rCBV. While it provides valuable information, careful interpretation of the clinical context, temporal patterns, and potential confounding factors is essential. Integration with other imaging modalities and clinical data can enhance the accuracy of differentiation and guide appropriate management. Furthermore, the generalizability of DSC perfusion imaging findings is limited by variability in imaging protocols and post-processing techniques across different institutions, which necessitates the establishment of standardized procedures to ensure consistent and reliable results.

Dynamic Contrast-Enhanced Perfusion Imaging

DCE perfusion imaging, an advanced MRI technique, measures vascular permeability based on the shortening of the T1 relaxation time by gadolinium contrast agents. It quantifies parameters, such as Ktrans, extravascular extracellular volume fraction (v_e), and vascular plasma volume fraction (v_p). and the initial area under the contrast uptake curve(iAUC), which reflects various aspects of the BBB and extracellular extravascular space (EES) (63). In TP, increased BBB disruption and leakage lead to elevated Ktrans, v_e, v_p, and iAUC, whereas in PsP, decreased BBB permeability and leakage resulted in reduced values of these parameters (64,65). Qiu et al.'s meta-analysis of DCE imaging indicated that it effectively differentiated glioma TP from PsP, with a sensitivity of 0.792, specificity of 0.779, and AUC of 0.846 (66). Similarly, another meta-analysis published in Neuro-

Oncology in 2017 reported that DCE imaging has a sensitivity of 88% and a specificity of 85% for discerning progression in high-grade gliomas (67). Thus, DCE perfusion imaging can differentiate TP from PsP by comparing the changes in these parameters within the tumor region and surrounding tissue.

However, the availability and feasibility of DCE may vary across different centers and scanners, and it requires the injection of a contrast agent and postprocessing. The signal-to-noise ratio and image quality may be compromised by susceptibility artifacts, motion artifacts, and partial-volume effects. The interpretation and comparison of DCE parameters may be affected by the choice of region of interest, threshold selection, and variability of normal values. The specificity and sensitivity of DCE perfusion imaging for differentiating TP from PsP may also depend on glioma type and grade, treatment timing and modality, and the presence of confounding factors such as inflammation, infection, or hemorrhage. Despite these challenges, DCE perfusion imaging, when combined with other imaging modalities and parameters, holds promise in improving the accuracy and reliability of distinguishing TP from PsP in gliomas. Furthermore, similar to other advanced MRI techniques, the real-world application of DCE imaging is contingent upon the standardization of protocols and calibration of equipment across institutions to ensure consistent and reproducible results.

Positron Emission Tomography-Computed Tomography

Positron emission tomography-computed tomography (PET-CT) is a metabolic functional imaging technique that detects positrons emitted from intravenously injected radioactive tracers and analyzes their accumulation and distribution patterns in the body (27). In the oncological context, PET provides valuable physiological information beyond what traditional MRI and CT imaging can offer, and is commonly used for tumor staging, treatment response evaluation, and guiding therapy. The most widely used radioactive tracer is β-2-[18 F]-Fluoro-2-deoxy-D-glucose (18 F-FDG), a glucose analog that directly measures metabolic rate (68). Standardized uptake values can be compared between tumor regions and reference regions for the semi-quantitative measurement of metabolic activity, thereby distinguishing low-grade and high-grade tumors. This method also has some limitations, as the brain inherently has relatively high glucose metabolism, especially in the gray matter. Measurements may not reflect the true lesion if they are located close to the cortical gray matter.

Due to increased proliferative activity and amino acid transfer in malignant brain tumors, as well as relatively low uptake levels of amino acids in normal brain tissue, the clinical use of amino acid radiotracers can better delineate tumors to some extent (69). Several amino acid-based radiotracers have been developed, including ^{11}C-methionine positron emission tomography (^{11}C-MET PET) and O-(2-[18 F]fluoroethyl)-l-tyrosine (18 F-FET). These two tracers have shown comparable performance in differentiating TP from PsP; however, ^{11}C-MET PET is less commonly used because of its complex synthesis (70–72). With the gradual development of PET/MRI, the combination of PET and MRI takes full advantage of MRI's excellent soft tissue contrast and multi-parametric evaluation capabilities of MRI. Studies have demonstrated the potential of PET/MRI in evaluating treatment response in glioblastoma; however, its ability to monitor immunotherapeutic response in glioblastoma warrants further investigation (27). Eddie et al. demonstrated that FET-PET CT has strong diagnostic performance for glioma recurrence (sensitivity 93%, specificity 100%, accuracy 96%) (73). Another FET-PET study corroborated the high diagnostic capability of PET for glioma TP (sensitivity, 100%; negative predictive value, 100%) (74). A study involving 58 glioma cases indicated that combined PET/MR with ASL and [18 F]DOPA-PET map analysis effectively differentiated between TP and PsP (specificity 100% and sensitivity 94.1%) (75).

Since the advent of PET technology, the debate comparing PET/CT and PET/MRI modalities has been ongoing. However, to date, there is a paucity of research specifically addressing the differentiation between glioma TP or PsP using PET/CT or PET/MRI. In the majority of oncological applications, the diagnostic performance of PET/MRI is comparable to that of PET/CT, yet PET/MRI appears to have a superior edge in the detection of head, neck, and pelvic tumors, and in identifying tumor recurrence (76). Data from a Single-Center Observational Study on 1003 Sequential Examinations suggest that PET/MRI facilitates staging on par with PET/CT and enhances lesion detectability in selected malignancies, potentially aiding in the acceleration of comprehensive local and systemic staging in a single procedure, particularly when additional MRI is advised. Moreover, the reduced radiation dose associated with PET/MRI may confer benefits to younger patients (77). Additionally, given MRI's superior capability of MRI in delineating neuroanatomical details and its broader selection of imaging sequences, PET/MRI may hold more promise than PET/CT for distinguishing PsP from TP. However, it is noteworthy that integrating two distinct imaging modalities makes PET/MRI technically more challenging.

Amide Proton Transfer Imaging

Amide Proton Transfer (APT) is a type of chemical exchange saturation transfer imaging and derivative technique for magnetization transfer. The APT technique selectively presaturates the signal from the amide protons of free proteins and polypeptides and detects subsequent signal changes in the surrounding free water after exchange with the amide protons. By collecting signals before and after free water saturation, the APT signal value was indirectly obtained (78). Compared to normal cells, tumor cells proliferate abnormally

and are metabolically active with increased protein content, leading to elevated amide proton concentrations and, thus, higher APT signals. Hence, the APT signal intensity within a lesion reflects the protein concentration (79).

Multiple studies have shown that on APT-weighted imaging, patients with recurrent tumors demonstrate higher signal intensity, while patients with PsP exhibit only mildly increased signal intensity (80). A clinical study involving 38 patients indicated that APT imaging technology can differentiate between TP and PsP with mean and maximum intensity values of 2.42% (sensitivity, 85.0%; specificity, 100%) and 2.54% (sensitivity, 95.0%; specificity, 91.7%), respectively (81). Another meta-analysis revealed that for distinguishing TP from PsP, individual APT imaging parameters had a combined sensitivity of 0.85 and specificity of 0.88. In contrast, multiparametric MRI that includes APT showed a combined sensitivity of 0.92 and specificity of 0.83 (82). These findings suggest that APT imaging can provide valuable diagnostic information for distinguishing between tumor progression and treatment-related changes.

However, the interpretation of APT imaging findings must be approached with caution. The APT signal is not only influenced by protein content, but can also be affected by other factors, such as pH changes, tissue temperature, and water content, which may vary in different pathological conditions. Furthermore, the specificity and sensitivity reported in the literature can be influenced by the heterogeneity of patient populations, variability in treatment protocols, and differences in APT image acquisition and processing across different institutions. These factors can potentially limit the generalizability of APT imaging findings to broader clinical practice (83).

Artificial Intelligence Enhances Imaging Diagnostic Precision

The advent of artificial intelligence (AI) in neuro-oncology has ushered in a new era of precision in the diagnosis of glioma progression. AI-assisted imaging, particularly through machine learning and deep learning algorithms, has significantly improved the differentiation between TP and PsP in patients with glioma. Deep learning automated segmentation models trained on extensive datasets have demonstrated high reproducibility in extracting features from DWI and PWI MRI. This reproducibility is crucial for the reliability of radiomics features across different institutions, which in turn enhances the robustness of predictive modeling for glioma progression.

AI models that utilize multiparametric MRI data and integrate DTI, DSC-PWI, and T1-weighted contrast-enhanced imaging (T1CE) have shown superior diagnostic accuracy. Hu et al. attempted to use an optimized classifier to perform machine learning on post-gadolinium T1, T2, and FLAIR data of 31 glioblastoma patients, achieving an AUC of 0.9434 for PsP differentiation, with a sensitivity of 89.91% and a specificity of 93.72%. Another study integrating multiple MRI parameters for quantitative machine learning found that the accuracy of PsP prediction reached 87% with an AUC of 0.92. These models leverage the complex interplay of the tumor microenvironment captured in high-dimensional imaging data, offering a more nuanced analysis than traditional imaging techniques. For example, convolutional neural network models combined with recurrent neural network architectures outperform conventional convolutional neural network models. They effectively harness temporal and spatial information from various MRI sequences, thereby enhancing the accuracy of differentiating between TP and PsP.

Moreover, the integration of AI with clinical data has led to more comprehensive models that outperform those based solely on imaging or clinical data. This holistic approach not only aids in clinical decision-making, but also addresses the challenges of limited data availability and the need for interpretability in clinical settings. Patel et al. reported that incorporating a machine learning-based approach with data such as O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, T1CE, T2WI, and ADC can effectively differentiate TP in glioblastoma patients, with an AUC of 0.8, sensitivity of 78.2%, and specificity of 66.7%. AI-assisted imaging has also been instrumental in refining the treatment response criteria. The RANO criteria have been enriched by incorporating AI tools, such as radiomics, radiogenomics, and radiopathomics, alongside advanced neuroimaging techniques. In a machine learning model involving 44 glioblastoma patients, Kebir et al. confirmed that the AUC for predicting PsP, as defined by RANO criteria, could reach up to 93%. This integration aims to provide a more objective and quantifiable assessment of the treatment response, which is particularly valuable in the early post-treatment phase.

In summary, owing to the BBB, conventional MRI is limited in distinguishing between TP and PsP. Even the more advanced MRI techniques currently used clinically cannot completely differentiate between them. Among the advanced techniques, MRS appears to have superior diagnostic performance, with good sensitivity and specificity, compared to other techniques. However, it is important to note that the diagnostic accuracy of MRS can be influenced by the choice of the spectral region of interest, experience of the operator, and quality of the equipment used, which may limit its generalizability across different clinical settings. Clinically, a multi-parametric approach combining DWI and perfusion MRI with rCBV and ADC values is preferred, as diagnosis based on multiple parameters is more accurate than that based on single parameter methods. This approach achieved a sensitivity of 82% and specificity of 100%, with rCBV being the best predictor for TP. Nevertheless, reliance on high-quality imaging and the need for expert interpretation are critical factors that can affect the reproducibility of these results in different clinical environments. The emergence of AI is a landmark development in the medical sector, particularly in pathology and imaging diagnostics, the emergence of AI is a landmark development. Integrating AI into imaging diagnostics enhances the precision and speed of discerning true TP from PsP, offsetting the occasional

TABLE 1. The Advantages and Disadvantages of Various Imaging Techniques in Distinguishing TP From PsP

Imaging Technique	Advantages	Disadvantages
Conventional MRI	Provides invaluable anatomical data, aiding in the assessment of alterations in tumor size, morphology, and enhancement patterns.	The imaging characteristics of TP and PsP can overlap, complicating the differentiation based solely on morphological changes.
DWI	Reflects the diffusion of water molecules within the relevant tissues, providing insights into cell density and structure.	The ADC values of cystic and necrotic areas are higher than those of solid tumors, which can complicate interpretation.
DTI	Offers insights into the structural integrity and organization of white matter tracts.	PsP can exhibit decreased FA values due to inflammation, edema, or treatment-induced changes affecting white matter integrity.
MRS	Measures the concentration of various metabolites in brain tissue and tumors, reflecting the distribution of metabolites within the brain tissue.	The signal-to-noise ratio and image quality of MRS can be influenced by factors such as susceptibility artifacts, motion artifacts, and partial volume effects.
DSC	Assesses cerebral blood flow and microvascular characteristics, providing information about the rCBV.	Interpretation should consider the timing of the imaging study, as contrast enhancement patterns can vary at different time points after treatment.
DCE	Measures vascular permeability based on the shortening of T1 relaxation time by gadolinium contrast agents.	Its availability and feasibility may vary across different centers and scanners, and it requires contrast agent injection and post-processing.
PET-CT	Provides valuable physiological information beyond what traditional MRI and CT imaging can offer and is commonly used for tumor staging, treatment response evaluation, and guiding therapy.	Measurements may not reflect the true lesion if located close to the cortical gray matter.
APT	Reflects protein concentration, providing insights into cell proliferation and metabolic activity.	The interpretation and comparison of APT signals may be influenced by the choice of regions of interest, threshold selection, and variability of normal values.

inaccuracies of subjective human interpretations. This integration is critical for optimizing patient management and tailoring treatment strategies. However, the effectiveness of AI applications is contingent upon the availability of large annotated datasets for training, and the algorithms' performance may vary depending on the heterogeneity of the data and the complexity of the cases encountered in real-world settings. As AI technology advances, it is necessary to redefine postoperative care for neuroglioma patients, leading to more personalized and adaptive therapeutic approaches. However, clinical adoption of AI is still in its infancy, and further validation studies are required to establish its utility and reliability across diverse populations and healthcare systems. Finally, the advantages and limitations of each imaging technique are summarized in Table 1.

LIQUID BIOPSY FOR DISTINGUISHING TRUE PROGRESSION FROM PSEUDOPROGRESSION IN GLIOMAS

Liquid biopsy is another promising technology to differentiate TP from PsP in gliomas. Liquid biopsy is a technique that analyzes tumor-derived materials obtained from biofluids, such as blood and CSF. Liquid biopsy can detect CTCs, cell-free ctDNA, circulating cell-free microRNAs and EVs carrying tumor-specific biomarkers (84).

Compared to conventional tissue biopsy, liquid biopsy has several advantages, including being minimally invasive, more accessible, allowing serial sampling, and better capturing intratumoral heterogeneity. Liquid biopsy can also provide information on tumor presence, molecular profiling, clonal evolution, therapeutic response, and prognosis (85).

Liquid biopsy can aid in distinguishing TP from PsP in gliomas by detecting changes in the levels and molecular profiles of tumor-derived materials in biofluids (86). For instance, increased ctDNA or CTCs counts may indicate TP, whereas decreased or stable levels suggest PsP. Similarly, alterations in the expression or mutations of tumor-specific genes or microRNAs can differentiate TP from PsP.

However, liquid biopsy also faces some challenges and limitations, such as low concentrations of tumor materials in glioma patient bloodstreams, technical variability and sensitivity of detection methods, lack of standardization and validation of biofluid collection/analysis protocols, and

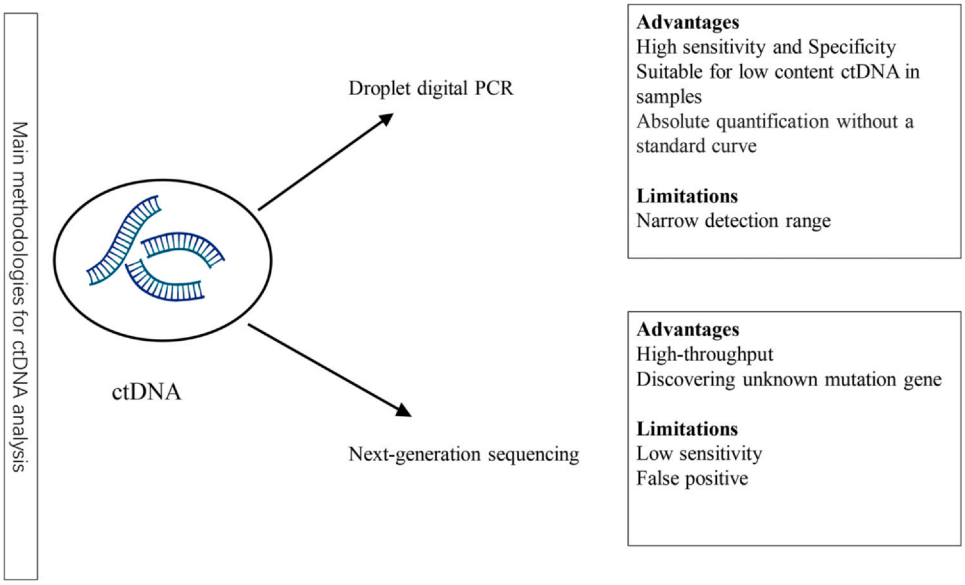

Figure 2. Droplet digital PCR vs Next-generation sequencing. Schematic illustration of main methodologies for ctDNA analysis. Advantages and limitations for each methodology are indicated.

biological complexity and heterogeneity of tumor-derived materials (87,88).

Biology of Circulating ctDNA

Cell-free DNA (cfDNA) comprises short DNA fragments detectable in plasma, urine, and other bodily fluids, whereas ctDNA represents a subset of cfDNA stemming from tumor cells or their microenvironment (89,90). Crucially, ctDNA is more readily discernible in fluid biopsies than in CTCs, which are scarce and challenging to isolate. Over the past two decades, numerous ctDNA mutations and detection techniques have been identified and developed for diverse cancer types, including gliomas, in blood and CSF (91,92). Consequently, ctDNA has seen escalating utility as a non-invasive means of diagnosis, residual disease monitoring, and treatment efficacy assessment in oncology. Biologically, ctDNA serves as a vector that conveys the genetic profile of solid tumors to peripheral circulation or bodily fluids, mirroring tumor heterogeneity and evolution. Owing to its tumor cell origin, ctDNA indicates tumor presence and relative burden; however, profiling remains problematic due to limited quantities, high fragmentation, and low mutation frequencies in the normal cfDNA background. Thus, diagnosis via ctDNA currently occurs at advanced stages with a high tumor burden and ctDNA levels (93). Advances in platforms such as next-generation sequencing (NGS) and digital PCR (dPCR) now permit the accurate detection of plasma ctDNA alterations (94). Figure 2 shows the differences between dPCR and NGS results. Serum or fluid ctDNA levels correlate with stage, size, residual tumor post-treatment, recurrence/progression, and survival (95). Moreover, the association between short ctDNA half-life and tumor cell turnover produces sharp declines in response to radiotherapy, chemotherapy, or targeted therapy (96). Additionally, ctDNA enables the detection of minimal residual disease (MRD), which is strongly linked to recurrence and prognosis (97). In summary, ctDNA has emerged as a promising noninvasive biomarker for longitudinal tumor management.

Detection Technology of ctDNA

ctDNA comprises a minute fraction of cfDNA, often less than 0.01%. Thus, ctDNA detection requires ultrasensitive technologies that are capable of identifying rare somatic variants with abundant normal cfDNA. NGS and dPCR are the two predominant ctDNA detection platforms (Fig 2) (98). NGS, the most common deep sequencing technique, provides extensive genomic coverage through millions of reads and can identify various ctDNA alterations in plasma, including single nucleotide variants (SNVs), insertions/deletions (indels), copy number variations (CNVs), and structural variants (SVs). However, limitations exist, including high cost, long turnaround times, complex data analysis, and low sensitivity for rare mutations (99). dPCR, the most advanced PCR technique, enables the highly sensitive mutant quantification and genotyping of ctDNA. Emulsion-based droplet dPCR (ddPCR) and chip-based dPCR comprise two main dPCR varieties. dPCR quantifies DNA amplification via a Poisson distribution of positive and negative partitions, furnishing absolute quantification without calibration (100,101). Compared to NGS, ddPCR offers superior sensitivity, speed, and reliability for MRD tracking. As an effective liquid biopsy ctDNA detection method, ddPCR is suitable for low ctDNA content samples and provides sensitive and specific ctDNA mutation identification (102,103). In summary, both platforms have advantages

and disadvantages for ctDNA analysis, with the optimal choice depending on the clinical context and the available resources.

Clinical Application of ctDNA in Glioma

CtDNA analysis is a non-invasive alternative to biopsy for diagnosing glioma tumor properties. CtDNA reveals heterogeneity and evolution, detecting mutations across multiple tumor deposits in one sample (104). Genomic ctDNA profiles closely match tumor tissues, suggesting their utility in glioma diagnosis and treatment personalization. As ctDNA is released constantly with a short half-life, it enables the early detection of recurrence after therapy.

ctDNA from the blood and CSF has advantages for monitoring tumor burden, identifying molecular subtypes, detecting resistance, and predicting prognosis. However, the BBB limits the passage of tumor cells and DNA from the brain to the circulation, so CSF may provide more sensitive and specific glioma information than blood (105). Overall, ctDNA is a promising non-invasive tool for glioma monitoring and treatment guidance.

Application of Blood ctDNA in Glioma Monitoring

Blood ctDNA detection technology is very mature and widely used for tumor monitoring. ctDNAs are DNA fragments derived from malignant cells that may contain cancer-specific mutations. Some common mutations and epigenetic alterations in glioma patients are IDH, Telomerase reverse transcriptase(TERT), phosphatase and tensin homolog (PTEN), MGMT, and Alu (106,107). In 2013, Majchrzak-Celińska et al. analyzed the methylation status of MGMT, RASSF1A, p15INK4B, and p14ARF in serum ctDNA of 33 patients with newly diagnosed central nervous system (CNS) tumors, including 17 gliomas, six meningiomas, and 10 metastatic malignancies. They found that glioma patients were characterized by a higher frequency of gene hypermethylation, suggesting that DNA methylation is one of the most promising biomarkers for glioma diagnosis (108). Mutation and methylation of these genes are important hallmarks of glioma and could serve as guidance for specific treatments and monitoring of treatment efficacy. Noroxe et al. reported that the level of ctDNA is principally a function of two factors: tumor bulk and tumor cell turnover, which results in an increase in serum ctDNA in glioma TP (109). As the level of ctDNA correlates with disease progression, the quantitation of ctDNA is clinically important. However, only low amounts of ctDNAs originating from brain tumors are present in the plasma because of the BBB. The BBB ensures that the CNS maintains a high degree of homeostasis by strictly controlling the exchange of endogenous and exogenous substances between the brain and the external environment (88). These low concentrations of ctDNA are among the main challenges in liquid biopsy for the diagnosis of gliomas. Recent developments in sequencing technologies have made the detection and quantification of ctDNAs feasible and practical for translation into routine clinical practice. For example, Florent Mouliere et al. developed a technology in which differences in fragment lengths of circulating DNA could be exploited to enhance the sensitivity for detecting the presence of ctDNA and for non-invasive genomic analysis of glioma (110). Carme et al. found that methylated MGMT, p16, DAPK, and RASSF1A were present in serial ctDNA of glioblastoma patients, and there was a good correlation between serial ctDNA and primary tumor tissue (111). A study including 70 samples confirmed that serum ctDNA can be used as a noninvasive approach for the detection of genetic/epigenetic alterations in different grades of glioma during disease (112). In addition, serum ctDNA was confirmed to be informative for both loss of heterozygosity and aberrant gene promoter methylation analysis during glioma progression, with moderate sensitivity and high specificity for both low- and high-grade tumors. Gong et al. found that ctDNA isolated from plasma had high concordance with MGMT and ALU methylation alterations observed in primary tumors (113).

Compared to methylation detection, the use of ctDNA for the detection of mutations in gliomas has been more challenging. Bettegowda et al. employed dPCR to identify ctDNAs in 640 patients with various types of cancer. They found that ctDNA was detectable in > 75% of patients with advanced pancreatic, ovarian, colorectal, bladder, melanoma, and head and neck cancer but was detectable in only < 10% of patients with gliomas (n = 27) (114). With improvements in detection technology, the detection rate of ctDNA mutations in the blood of patients with glioma is increasing. Mair et al. reported that the dPCR detection of plasma tumor mitochondrial DNA (tmtDNA), an alternative to the detection of nuclear ctDNA, improved the plasma DNA detection rate (82% vs 24%), and allowed detection in CSF and urine (115). Jonathan et al. developed a technology of INtegration of VAriant Reads (INVAR) pipeline, which combines custom error-suppression methods and signal-enrichment approaches based on biological features of ctDNA (116). Using this approach, the ctDNA mutation detection limit in each sample can be estimated independently based on the number of informative reads sequenced across multiple patient-specific loci. Using NGS technology, Liang et al. detected multiple mutations in the blood ctDNA of 47.6% of glioma patients, including 1p/19q, MDM2, ERBB2, IDH1, CDKN2A, CDK4, PDGFRA, CCNE1, and MET (117). Pacia et al. developed focused ultrasound (FUS) - enabled liquid biopsy technology, which improved the diagnostic sensitivity of brain tumor-specific genetic mutations compared to conventional blood-based liquid biopsy (118). Furthermore, studies have reported that a high concordance exists between detection of mutations in tissue tumors and serum ctDNA, such as IDH, TERT, and H3K27M mutations (119,120). Santiago et al. used bead, emulation, amplification, and magnetics (BEAMing) technology to evaluate the concordance between ctDNA and tissue NGS in glioma patients with paired sequencing. BEAMing

detected IDH1 mutations in the plasma of patients with gliomas with modest clinical sensitivity (true positivity rate) but 100% clinical specificity, with complete agreement between the mutant loci detected in tumors and plasma (118). Moreover, if ctDNA is present after curative treatment, the risk of relapse increases significantly. In addition, Pan et al. found a significant decrease in H3K27M plasma ctDNA agreed with MRI assessment of tumor response to radiotherapy in 83% (10/12) of brainstem glioma patients (121). In 2021, Muralidharan et al. developed a novel ddPCR assay that incorporates features to improve sensitivity and allows for the simultaneous detection and longitudinal monitoring of two TERT promoter mutations (C228T and C250T) in ctDNA from the plasma of patients (122). This study was based on novel ddPCR technology to verify that peripheral TERT-mutant allele frequency reflects the clinical course of the disease, with levels decreasing after surgical intervention and therapy and increasing with tumor progression (123).

Overall, the detection of hallmark ctDNA mutations or methylation is of great significance in the detection of blood ctDNA in TP gliomas. Due to the low abundance of ctDNA in the blood, more accurate sequencing technology is required to improve the detection sensitivity of blood ctDNA.

Application of CSF ctDNA in Glioma Monitoring

Currently, the CSF tumor DNA enables selective profiling of glioma molecular subtypes at the first clinical presentation (124). Meanwhile, the RANO group suggested CSF ctDNA to monitor residual disease after surgery, distinguish progression from PSP, and predict the outcome (125). Owing to the existence of the BBB as a unique physiological barrier, the CSF should theoretically contain higher levels of ctDNA, particularly for primary tumors of the nervous system, such as gliomas. The presence of the BBB may filter out potentially diagnostic macromolecules from the blood. However, CSF collection is more invasive than blood collection and may be associated with risks and complications. Compared to the tissue gold standard, the sensitivity and specificity of serum biomarkers for detecting gene methylation were 50% and 100%, respectively. The low concentration of tumor-specific ctDNA in the serum is likely responsible for the relatively poor sensitivity of these nucleic acid biomarkers for detecting intracranial tumors and suggests that CSF analysis may improve false-negative rates given the difference in concentrations. The presence of tumor DNA in CSF was first reported in 1995 by Rhodes et al., who used allele-specific PCR to detect tumor-derived p53 DNA in the CSF of a glioblastoma patient (126). In 2015, Pan et al. extracted ctDNA from the CSF of seven patients with solid brain tumors, six (85.7%) of whom had detectable tissue-concordant mutations in at least one of the following genes: NF2, AKT1, BRAF, NRAS, KRAS, and EGFR. They demonstrated that the concentration of ctDNA from brain tumors was higher in the CSF than in the serum. This implies that CSF ctDNA can be used to detect mutations in brain tumors (127). Another study isolated ctDNA from the CSF of 12 patients with brain tumors and found that the mutant allelic frequency was significantly higher in CSF than in serum (128). However, mutations in EGFR, PTEN, ESR1, IDH1, ERBB2, and FGFR2 were readily detected in CSF ctDNA with a sensitivity of 58%, compared to 0% for serum (129). Wang et al. identified detectable levels of CSF ctDNA in 74% of the cases (130). All medulloblastomas, ependymomas, and HGGs abutting the CSF space were detectable (100% of 21 cases), whereas no CSF ctDNA was detected in patients whose tumors were not directly adjacent to a CSF reservoir (131). In medulloblastoma, CSF ctDNA can predict TP before it is radiographically detected (132). These results suggest that CSF ctDNA has the potential to distinguish between TP and PsP in patients with glioma.

Similarly, ctDNA detection can be effectively used for glioma diagnosis. In 2016, Pentsova et al. sequenced 341 cancer-associated genes in cfDNA from CSF obtained through routine lumbar puncture of 53 patients with suspected or known CNS involvement in cancer (133). This study found that the examination of ctDNA extracts from gliomas uncovered patterns of tumor evolution, including temozolomide-associated mutations. In 2019, Pan et al. detected CSF ctDNA in 57 patients with brainstem glioma, and found that at least one tumor-specific mutation was detected in over 82.5% of CSF ctDNA samples. In cases with primary tumors harboring mutations, alterations were identified in the CSF ctDNA in 97.3% of the cases (36/37). In over 83% (31/37) of the cases, all primary tumor alterations were detected in the CSF, and in 91.9% (34/37) of the cases, at least half of the alterations were identified. Among the 10 patients found to have primary tumors that were negative for mutations, 30% (3/10) had detectable somatic alterations in their CSF. However, mutation detection using plasma ctDNA is less sensitive than that using CSF ctDNA sequencing (38% vs 100%, respectively) (134). In the same year, another group identified H3K27M in the CSF and plasma of 88% of patients with diffuse midline glioma, with CSF being the most enriched for ctDNA (121). In 2021, Fujioka et al. established a novel, non-invasive molecular diagnostic method using a chip-based dPCR system targeting ctDNA derived from CSF with high sensitivity and specificity (135). This study detected either of the diagnostic mutations in tumor DNA samples from 28 of 34 patients and precisely diagnosed WHO grade 3 or 4 diffuse gliomas using lumbar CSF obtained from six (87%) of seven patients with tumors harboring any mutation. These studies suggest that CSF ctDNA can provide valuable information for glioma diagnosis, especially for tumors that are difficult to biopsy or have low mutation rates in the plasma ctDNA.

Therefore, CSF ctDNA monitoring could be a useful biomarker for glioma recurrence and PsP. Fujita et al. confirmed that the IDH1 p.R132H mutation by ddPCR and increased D-2-hydroxyglutarate (D-2HG) levels in the CSF may help identify IDH-mutant gliomas. In addition, this study also suggested that the D-2HG level and D/L-2HG ratio correlate with tumor volume in patients with IDH-mutant gliomas and could

TABLE 2. The Advantages and Disadvantages of Traditional Biopsy and ctDNA in Blood and CSF

Biopsy Type	Advantages	Disadvantages
Traditional biopsy		
	1. Mature technical method 2. The gold standard for tumor diagnosis	1. Special parts are not suitable for aspiration biopsy 2. Some patients are unsuitable for surgery 3. Clinical risks in aspiration biopsy
Blood-ctDNA biopsy		
	1. Convenient sampling, noninvasive 2. Realize dynamic monitoring 3. Suitable for special parts, avoiding repeatedly aspiration biopsy	1. CtDNA abundance is low and the detection means are limited 2. Low accuracy 3. No corresponding targeted drugs for the mutations detected 4. Lack of unified criteria
SCF-ctDNA biopsy		
	1. Convenient sampling, minimal invasive 2. Realize dynamic monitoring 3. High ctDNA abundance, high sensitivity and specificity 4. Suitable for special parts, avoiding secondary surgery	1) No corresponding targeted drugs for the mutations detected 2) Lack of unified criteria

be used as surrogate markers for tumor burden and response to treatment (136). This study revealed that it is possible to monitor glioma volume and progression using CSF. In 2019, Li et al (137). demonstrated that the overall minor allele frequency of CSF ctDNA was associated with earlier stages of glioblastoma compared to that of plasma ctDNA when the tumor burden was immediately released through surgical resection. Furthermore, disease status can be tracked by monitoring key mutations in cells representing the tumor burden of the CNS, MRD, or both. In 2020, Zhao et al. reported that CSF ctDNA mutations in PTEN and TP53 are commonly detected in patients with recurrent gliomas. Furthermore, IDH mutations were detected in most CSF ctDNAs derived from IDH-mutant diffuse astrocytomas, whereas CSF ctDNA mutations in RB1 and EGFR were found in IDH-wild-type glioblastoma (128). Recently, Miller et al. sequenced the ctDNA of patients with CNS tumors of different types and ages, including glioma, and confirmed that ctDNA from CSF can be used as an effective auxiliary means for monitoring tumor prognosis and therapeutic effects (138). In summary, these studies indicate that CSF-derived ctDNA assays are highly sensitive for tumor tissue genotyping. ctDNA analysis demonstrates usability in dynamic monitoring procedures because ctDNA can be repeatedly obtained even after resection of the primary tumor. Compared to blood ctDNA, analysis of ctDNA in the CSF may be more appropriate for the early detection of gliomas that harbor specific oncogenic mutations **(**Table 2 **and** Fig 3**).**

Application of miRNAs and Extracellular Vesicles in Glioma Monitoring

Circulating miRNAs are 18–25 nucleotide non-coding RNAs that regulate tumor growth and immune invasion. miRNAs can cross the BBB and stably exist in the peripheral blood, making them ideal glioma biomarker candidates (139). Although miRNAs have been widely studied as diagnostic and postoperative monitoring biomarkers in glioblastoma, research on distinguishing PsP from TP is limited.

One study found no change in serum miR-320e levels in two glioblastoma patients with possible PsP on MRI, suggesting that miR-320e reflects glioblastoma volume, but not PsP inflammation and edema (139). However, the small sample size limits reliability, necessitating larger validation studies.

EVs are small membrane-bound particles released by cells into the extracellular environment. EVs can carry various molecules such as proteins, lipids, and nucleic acids, which reflect the characteristics and status of the parent cells. Compared to PsP, TP patients have a higher plasma EVs content (140). For example, microvesicles (MVs) are 100–1000 nm EVs formed by cell membrane budding. MVs are significantly elevated in the blood of patients with TTP versus PSP patient blood (141). However, EV quantification lacks specificity for tumor-derived EVs, limiting their diagnostic utility (142).

A digital SWARM algorithm demonstrated higher tumor-educated platelet (TEP) scores in suspected TP versus PsP glioblastoma patients, potentially related to the platelet-immune axis in glioblastoma progression, although the mechanism is unclear (143). Overall, liquid biopsies have limited sample sizes and specificity, cannot replace standard imaging, and lack CSF research to distinguish PsP from TP. Further clinical studies and biosamples are needed to identify reliable liquid biopsy techniques involving miRNAs, EVs, and other molecules.

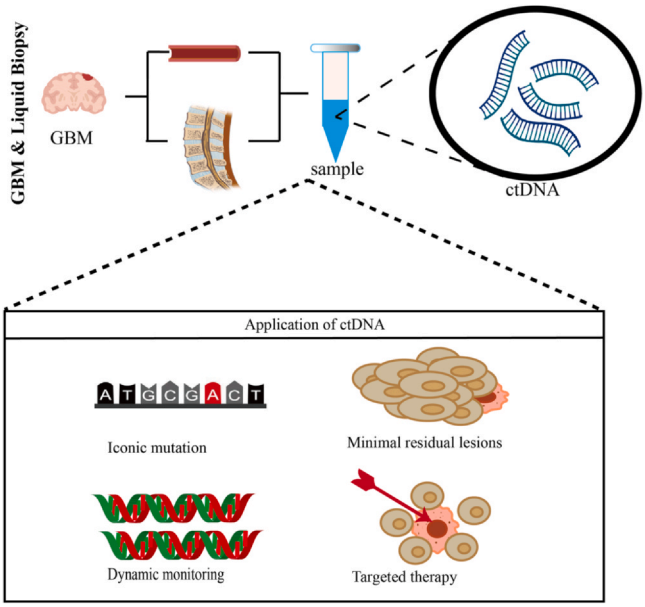

Figure 3. Liquid biopsy. A schematic representation of the application of ctDNA from blood and cerebrospinal fluid of patients with glioblastoma.

Insights From Combined Imaging and Liquid Biopsy in Glioma Management

The confluence of imaging and liquid biopsy in cancer patient management is an area ripe with potential, yet research is scant at present. Drawing from current studies on other cancer types, we aim to shed light on therapeutic management for glioma patients. A 2023 study on leukemia, which involved 84 patients with Follicular Lymphoma, highlighted the efficacy of tracking mutated gene expression levels via liquid biopsy in tandem with PET/CT imaging and Deauville scoring. This approach successfully identified patients who were undergoing disease progression during treatment, with a sensitivity of 88% and a perfect specificity of 100% (144). The study highlighted the significance of continuous, personalized monitoring of mutated genes through liquid biopsy coupled with PET/CT for tracking patient diseases. Further research, including studies on 102 patients with metastatic castration-resistant prostate cancer (145) and 84 patients with advanced non-small cell lung cancer (68), corroborated that monitoring total ctDNA levels alongside PET/CT imaging could accurately reflect patient treatment responses, enabling prognostic scoring or risk stratification for tailored patient management. Thus, whether it involves mutation-based monitoring or total ctDNA level assessment, their integration with imaging techniques positively affects the evaluation of cancer treatment effects or outcomes. Given that these studies were predominantly conducted in patients with systemic metastatic malignancies, where PET/CT is crucial, and that gliomas seldom metastasize beyond the CNS, the prospect of combining advanced MRI with liquid biopsy is expected to be particularly promising.

CONCLUSION

The advantages and challenges in the utilization of imaging techniques and liquid biopsy for distinguishing TP from PsP in gliomas are the focus of this review. Imaging modalities such as conventional MRI, advanced MRI, CT, and PET offer detailed visualization of the brain and tumor. Among the relevant imaging technologies, particular attention should be paid to MRS, DTI, DSC, and PET. In the current literature, these modalities have demonstrated higher sensitivity and specificity in differentiating glioma progression, especially when used in conjunction with other MRI parameters, which can significantly enhance the diagnostic accuracy. Liquid biopsy, a less invasive approach, involves sampling tumor-derived material from biofluids, such as blood and CSF. It enables the detection of ctDNAs, CTCs, and EVs that carry tumor-specific molecular markers. The most common targets for testing are MGMT methylation, IDH1 status, p53 mutation, and the genetic markers EGFR, TERT, 1p/19q co-deletion, and PTEN. However, technical and biological challenges, such as low concentrations of tumor-derived DNA in the bloodstream of glioma patients, technical variability and sensitivity of detection methods, lack of standardization and validation of biofluid collection and analysis, and biological complexity and variability of tumor-derived materials, impede its application.

Both imaging and liquid biopsy have advantages and disadvantages in the diagnosis of glioma, TP, and PSP. Imaging techniques, such as advanced MRI technologies, are widely accessible in most hospitals equipped with MRI machines, circumventing the need for additional investment in equipment. The synergy of different MRI modalities can enhance the accuracy of TP versus PSP for gliomas. On the other

hand, liquid biopsy, owing to the unique nature of the CNS, demands higher technical and equipment standards, including dPCR platforms. However, the current state of liquid biopsy is predominantly single-center studies with a lack of a uniform genetic testing scope and standardized criteria, which significantly hampers its development.

Although imaging and liquid biopsy differ in their accessibility and reliability, they also face common challenges in the interpretation of results. Conversely, while imaging diagnostics have established protocols, the interpretation of results poses a challenge because of the variability in professional backgrounds (e.g., radiologists vs neurosurgeons) and the individual expertise and experience of diagnosing physicians, which can lead to divergent interpretations of imaging data. By contrast, liquid biopsies often rely on changes in gene expression levels or binary positive results, theoretically offering higher objectivity and reproducibility. This is considered to be a major advantage of liquid biopsy over imaging. AI is emerging as a transformative force in this field, with the capability to learn and analyze complex imaging data through algorithms, thereby reducing the variability of physicians' subjective interpretations, and potentially revolutionizing the imaging diagnosis of glioma TP and PSP.

However, the future of glioma diagnostic technology is not an 'either/or' scenario. The convergence of imaging and liquid biopsy techniques to improve the diagnostic accuracy for glioma TP and PSP represents a trend of future advancements. The integration of these modalities, supported by AI, could lead to a more comprehensive and precise diagnostic approach, ultimately benefiting patient outcomes through tailored and timely therapeutic intervention.

In conclusion, although imaging and liquid biopsy hold promise for distinguishing TP from PsP in gliomas, further development and refinement are necessary before their widespread adoption in routine clinical practice. This review aims to offer a comprehensive overview and insight for researchers and clinicians interested in this topic, and to stimulate further research and innovation in this field.

DECLARATION

The revised version of this article has purchased the language polishing service Paperpal, which is recommended by the American Association for Cancer Research.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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