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Clinical utility of liquid biopsy in distinguishing true progression from radiation necrosis and pseudoprogression in malignant brain tumor

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Abstract

Background: Distinguishing true tumor progression from pseudoprogression (PsP) and radiation necrosis (RN) following radiotherapy or radiosurgery for intracranial tumors remains a significant clinical challenge. Conventional imaging modalities, including MRI and PET, often lack sufficient diagnostic accuracy, while histopathological confirmation, although definitive, is invasive and not always feasible. Liquid biopsy (LB) has emerged as a promising noninvasive diagnostic approach.

Methods: A systematic review was conducted across PubMed, Embase, Scopus, and Cochrane databases. A total of 964 records were identified, including PubMed (n = 322), Embase (n = 280), Scopus (n = 297), and Cochrane (n = 65), along with three clinical trials identified from trial registers. After removal of 157 duplicates using Covidence, 807 studies were screened by title and abstract. Of these, 749 were excluded, and 58 articles underwent full-text review. Ultimately, 11 studies met the inclusion criteria and were included in the analysis.

Results: A diverse range of LB-based biomarkers has been investigated, including immune cell-based markers (e.g., HLA-DR^{neg/low} and VNN2⁺ CD14⁺ monocytic myeloid-derived suppressor cells), immune-related proteins (e.g., CXCL11 and MUC-16), circulating tumor cells, cell-free DNA, mitochondrial DNA, B1-SINE elements, microvesicles, and RNA analytes. Plasma was the most used biofluid, with limited evaluation of urine and cerebrospinal fluid. Analytical techniques varied widely, including flow cytometry, PCR-based assays, immunostaining-FISH, and multiplex protein platforms. Several biomarkers showed statistically significant differences among RN, PsP, and tumor recurrence; however, these findings were largely derived from small, heterogeneous cohorts with inconsistent reporting of diagnostic performance metrics. Composite indices, such as the DR-VNN2 index (DVI) and the Necrosis Prediction Index (NPI), showed potential for improving diagnostic differentiation.

Conclusions: LB-based biomarkers show promise for differentiating RN and PsP from tumor recurrence; however, current evidence is limited by small sample sizes, methodological heterogeneity, and lack of standardized diagnostic criteria. Larger prospective studies and validation of composite biomarker models are required to establish their clinical utility.

Clinical trial number: Not Applicable.

Keywords: Biomarkers; Brain metastases; Glioma; Liquid biopsy; Pseudoprogression; Radiation necrosis; Radiosurgery; Radiotherapy; True progression.