Journal of Clinical Neuroscience
Volume 152, October 2026, 112202

Review article

Prognostic utility of tumor grade and IDH-mutation status for immunotherapy response in high grade glioma: a systematic review and meta-analysis

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Received 5 May 2026, Accepted 12 July 2026, Available online 20 July 2026, Version of Record 20 July 2026.

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Abstract

Introduction

Survival outcomes among patients with World Health Organization grade III gliomas and IDH-mutant (IDHmt) gliomas treated with immunotherapy (IT) remain understudied, with most research focusing on grade IV (G4) glioblastomas or IDH wild-type (IDHwt) tumors.

Methods

A systematic literature search was conducted in PubMed/MEDLINE, SCOPUS, Embase, Google Scholar, and Science Direct databases following PRISMA guidelines. A random-effects *meta-analysis* was conducted to assess overall survival and 5-year mortality. Outcomes were compared across IT treatments and between historically designated grade III versus grade IV/GBM cohorts and explicitly reported IDHmt versus IDHwt glioma cohorts within each included study.

Results

A total of 21 studies involving 207 patients with grade III gliomas and 11 studies involving 115 patients with IDHmt gliomas were included. IT agents studied included dendritic cell and peptide vaccines (32 grade III, 45 IDHmt), immune checkpoint inhibitors (1 grade III, 39 IDHmt), oncolytic viruses (10 grade III, 20 IDHmt), modified lymphocyte therapies (1 grade III, 11 IDHmt), cytokine immunotherapy (47 IDHmt) and radioimmunotherapy (110 grade III). Most treated grade III (65.6%) and IDHmt (72.7%) gliomas were recurrent tumors. Across all immunotherapy agents, recurrent and newly diagnosed grade III glioma did not exhibit significant differences in overall survival (21.90 versus 29.71 months, p=0.237), 5-year mortality (77.10% versus 60.89%, p=0.481), or overall mortality at last follow-up (78.91% versus 70.37%, p=0.553). Newly diagnosed IDHmt glioma had significantly greater overall survival than recurrent IDHmt glioma (43.13 versus 19.57months, p=0.005) and significantly lower 5-year mortality (10.26% versus 59.78%, p<0.001). Between immunotherapy modalities, grade III glioma did not exhibit differences in overall survival compared to GBM in equivalent treated cohorts (p=0.123). However, dendritic cell and peptide vaccines had a higher overall survival compared to all other immunotherapy agents in IDHmt glioma (p=0.002), including when compared to IDHwt glioma in equivalent treatment arms (p=0.044).

Conclusion

Our study summarizes reported survival outcomes among patients with historically designated grade III and IDHmt gliomas treated with immunotherapy. Observed differences by histological grade, IDH status, and recurrence status are consistent with the established prognostic importance of these tumor features, and should not be interpreted as evidence that immunotherapy caused improved survival. Survival outcomes appeared more favorable in newly diagnosed IDHmt glioma and in IDHmt cohorts treated with dendritic cell or peptide vaccines; however, these findings are descriptive and hypothesis-generating given the predominance of single-arm studies, limited sample size, and potential confounding by baseline prognosis. Future prospective controlled trials are needed to determine whether specific immunotherapy approaches provide benefit in these glioma subgroups.

Introduction

High-grade gliomas (HGG), comprising World Health Organization (WHO) designated grade III and IV gliomas, are aggressive primary brain tumors originating in the central nervous system that are associated with significant morbidity and mortality despite standard multimodal treatment approaches [1]. However, prognosis varies by tumor subtype and classification as defined by the WHO. The most common and aggressive tumor, historically designated WHO grade IV glioblastoma (GBM), yields median overall survival rates of approximately 14–16 months with current standard of care [2], consisting of maximal safe surgical resection followed by chemoradiation with temozolomide, with some estimates as low as 9 months [3]. In contrast, historically designated WHO grade III anaplastic astrocytoma and anaplastic oligodendroglioma, have an improved prognosis. Although WHO grade III tumors are more rare, estimates of median survival with standard of care ranges from 15 to 24 months [4].

Immunotherapy has emerged as a novel alternative therapeutic approach across cancers [5]. Within the realm of HGGs, several immunotherapeutic strategies have been investigated, including dendritic cell vaccines, oncolytic virotherapy, and immune checkpoint inhibitors, primarily targeted to GBM [6]. However, despite the growing body of literature on immunotherapy for GBM, outcomes in other gliomas are understudied. This represents a significant knowledge gap, as the distinct molecular and immunological profiles of these tumor subsets may confer differential responses to immunotherapeutic interventions.

In addition to histological grade, the WHO classification of central nervous system tumors has evolved significantly, The 2016 WHO classification system integrated genetic markers such as 1p/19q co-deletions and presence of isocitrate dehydrogenase (IDH) mutation to classify grade II and III tumors [7]. The 2021 WHO classification further refined this framework by formally incorporating IDH1 or IDH2 mutation status as a definitive molecular marker for diffuse glioma classification and prognostication [8]. IDH-mutant (IDHmt) gliomas demonstrate significantly improved survival outcomes compared to IDH-wildtype (IDHwt) counterparts, with median overall survival extending to 2–5 years in some IDHmt cohorts, regardless of histological grade [9], [10]. This molecular stratification has fundamentally altered our understanding of glioma biology and clinical behavior, but their responses in immunotherapy trials has not been explored.

The present study aims to address this gap by summarizing reported survival outcomes among patients with historically designated grade III gliomas and IDH-mutant gliomas treated with immunotherapy. Given the heterogeneity of existing studies in the literature and lack of double-arm studies when examining these specific glioma subsets, we conducted a systematic review and random-effects *meta-analysis* of reported mortality, overall survival (OS), and progression-free survival (PFS) outcomes across clinical trials treating grade III and IDHmt glioma subtypes. Our secondary objective was to identify differences in survival outcomes between various immunotherapeutic agents across grade III and IDHmt glioma cohorts. Our aim was to describe the available clinical evidence for immunotherapy use in these understudied glioma cohorts, compare reported outcomes across treatment modalities where possible, and identify patterns that may inform future controlled trial design.

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Search strategy

The search methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines examining medical literature from PubMed/MEDLINE, SCOPUS, Embase, Google Scholar, and Science Direct databases up to June 2026 (see Fig. 1). This study was not registered in the International Prospective Register of Systematic Reviews registry. The searches combined immunotherapy-related terms, including immunotherapy, dendritic cell vaccine, tumor vaccine, CAR-T cell …

Electronic search yield and study characteristics

A total of 1,355 records were identified through database searching and manual review. After removal of 54 duplicates, 1,301 records underwent screening. Following application of the inclusion and exclusion criteria, 1,269 records were excluded, leaving 32 articles included in the final analysis. These included 21 articles involving 207 patients with historically designated grade III glioma and 11 articles involving 115 patients with IDH-mutant glioma (Fig. 1). Following assessment of …

Discussion

In recent years, the development of immune-mediated therapy for specific molecular targeting of solid CNS tumors has risen dramatically, showing promise in treatment of high-grade gliomas including glioblastoma [48]. Notably, historic grade III gliomas such as histological anaplastic astrocytoma have demonstrably better prognoses than glioblastoma, with estimated median OS at 3 years after diagnosis, and many patients surviving beyond 5–10 years [49], [50]. However, understanding the impact of …

Conclusions

The treatment of adult diffuse gliomas remains a persistent clinical challenge in the field of neuro-oncology. This meta-analysis provides the first evaluation of immunotherapy outcomes in historically designated grade III and IDHmt gliomas. This meta-analysis summarizes reported outcomes among patients with historically designated grade III and IDHmt gliomas treated with immunotherapy. Lower histological grade, IDHmt status, and newly diagnosed disease were associated with more favorable …

CRediT authorship contribution statement

Srivats Srinivasan: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mohammad Mirahmadi Eraghi:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Peace Odiase:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Methodology, Investigation, Formal …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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