

# Update on glioblastoma: Biology, clinical management and emerging therapeutic strategies (Review)

SASAN M. AHMED<sup>1,2</sup> and BERUN A. ABDALLA<sup>1,3</sup>

<sup>1</sup>Kscien Organization for Scientific Research (Middle East Office), Sulaymaniyah 46001, Iraq; <sup>2</sup>Green Apple Organization for Health Awareness, Sulaymaniyah 46001, Iraq; <sup>3</sup>Department of Scientific Affairs, Smart Health Tower, Sulaymaniyah 46001, Iraq

Received December 30, 2025; Accepted January 23, 2026

DOI: 10.3892/wasj.2026.439

**Abstract.** Glioblastoma, an isocitrate dehydrogenase (IDH)-wildtype central nervous system (CNS) World Health Organization grade 4 diffuse astrocytic tumor, remains the most aggressive primary malignancy of the adult CNS, with persistently poor outcomes despite advances in multimodal therapy. The present narrative review summarizes current knowledge on the glioblastoma epidemiology, molecular classification, prognostic biomarkers, standard treatment strategies, mechanisms of treatment resistance and emerging therapeutic approaches. The current standard of care consists of maximal safe surgical resection followed by radiotherapy to a total dose of 60 Gy with concurrent and adjuvant temozolomide. This approach results in a median overall survival of ~12-15 months, with <10% of patients surviving >5 years. Clinical outcomes are strongly influenced by molecular characteristics, particularly the IDH mutation status and O<sup>6</sup>-methylguanine-DNA methyltransferase promoter methylation. However, durable disease control remains uncommon due to multiple resistance mechanisms, including limited drug delivery across the blood-brain barrier, enhanced DNA repair capacity, the persistence of glioblastoma stem-like cells, profound immunosuppression within the tumor microenvironment, and extensive intratumoral heterogeneity with ongoing clonal evolution. Emerging therapeutic modalities, including tumor-treating fields, laser interstitial thermal therapy, dendritic cell vaccination, chimeric antigen receptor T-cell therapy and immune checkpoint inhibition, have demonstrated biological activity and modest clinical benefit in selected settings; however, they have not yet produced transformative improvements in survival. Overall, meaningful progress in the management of glioblastoma will likely depend on precision

medicine approaches that integrate molecular profiling, rational multimodal treatment combinations, and improved strategies for drug delivery and immune modulation.

## Contents

1. Introduction
2. Epidemiology and clinical presentation
3. Molecular classification and prognostic biomarkers
4. Standard of care treatment
5. Treatment outcomes
6. Glioblastoma stem cell enrichment
7. Tumor microenvironment and immunosuppression
8. Tumor heterogeneity and clonal evolution
9. Emerging therapeutic modalities
10. Management of recurrent glioblastoma
11. Conclusion and future directions

## 1. Introduction

Glioblastoma is the most common malignant primary central nervous system (CNS) tumor in adults, accounting for ~46.6% of all malignant primary tumors of the CNS. It is also the most lethal, with a median overall survival of ~12-15 months despite contemporary multimodal treatment, and <10% of patients surviving >5 years following diagnosis (1). The aggressive clinical course of glioblastoma is driven by rapid cellular proliferation, highly infiltrative growth and the early acquisition of therapeutic resistance (2). In addition, the limited permeability of the blood-brain barrier restricts the effective delivery of a number of systemic therapies, further constraining the efficacy of both local and systemic treatment approaches, and necessitating the continual refinement of therapeutic strategies (3).

The understanding of glioblastoma has evolved substantially over the past century. Early recognition of these tumors relied solely on histopathological examination, with Bailey and Cushing (4) providing the first comprehensive classification of gliomas in 1926. In subsequent decades, increasingly refined histological grading systems were developed, culminating in the World Health Organization (WHO) classification schemes introduced in 1979 and periodically updated thereafter. The therapeutic landscape remained limited until

---

*Correspondence to:* Dr Berun A. Abdalla, Department of Scientific Affairs, Smart Health Tower, Madam Mitterrand Street, HC8V+F66, Sulaymaniyah 46001, Iraq  
E-mail: berun.anwer95@gmail.com

*Key words:* temozolomide, tumor-treating fields, immunotherapy, molecular classification, prognostic biomarkers, treatment resistance

the late 20th century, when advances in surgical technique, radiation oncology and systemic therapy began to improve outcomes incrementally. The integration of molecular diagnostics in the 2000s, particularly the discovery of prognostic significance of isocitrate dehydrogenase (IDH) mutations and O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) promoter methylation, fundamentally transformed glioblastoma classification and risk stratification (4,5).

Glioblastoma has an annual incidence of ~3.2 cases per 100,000 person-years globally, with marked variations observed across geographic regions and age groups. The incidence of the disease increases markedly with an advancing age, peaking in the seventh decade of life, demonstrating a modest male predominance with a male-to-female ratio of ~1.6:1. Despite representing <2% of all primary brain tumors, glioblastoma accounts for the majority of malignant primary CNS neoplasms in adults and remains a leading cause of cancer-related mortality and morbidity in this population (1).

The modern standard of care for patients newly diagnosed glioblastoma was established by the landmark 2009 EORTC-NCIC trial (6). That study demonstrated that the addition of concurrent and adjuvant temozolomide to post-operative external beam radiotherapy significantly improved patient survival compared with radiotherapy alone. The standard treatment paradigm consists of maximal safe surgical resection followed by radiotherapy to a total dose of 60 Gy delivered in 30 fractions, with concomitant and subsequent temozolomide chemotherapy (6).

Over subsequent years, advances in molecular neuropathology have profoundly reshaped the understanding of glioblastoma pathobiology. These discoveries have prompted a shift from purely histological classification toward integrated diagnostic frameworks that incorporate molecular markers with established biological, prognostic, and predictive significance (7,8).

The 2021 WHO Classification of Tumors of the Central Nervous System formalized this integrated approach by defining glioblastoma exclusively as an IDH-wildtype diffuse astrocytic tumor meeting CNS WHO grade 4 criteria (7). By contrast, diffuse astrocytic tumors harboring IDH mutations are now classified separately as astrocytoma, IDH-mutant, CNS WHO grade 2-4, reflecting their distinct molecular pathogenesis and comparatively a more favorable prognosis (7,9). Within this framework, the IDH mutation status and MGMT promoter methylation provide powerful prognostic and predictive information and currently underpin contemporary risk stratification and therapeutic decision-making in clinical practice (8,9).

In parallel with advances in molecular classification, several investigational therapeutic strategies have emerged in recent years, including tumor-treating fields, laser interstitial thermal therapy, dendritic cell vaccination, chimeric antigen receptor T-cell therapies and immune checkpoint inhibitors (2,10-14). Despite a strong biological rationale and encouraging early clinical signals, these approaches have generally produced incremental rather than transformative improvements in overall survival (2).

The aim of the present narrative review was to summarize the currently available knowledge on the biology, clinical management and emerging therapeutic strategies of

glioblastoma, and to highlight key challenges and future directions in patient care.

## 2. Epidemiology and clinical presentation

**Epidemiology.** Population-based cancer registries indicate that glioblastoma has an incidence of ~3.2 cases per 100,000 person-years (1). The disease predominantly affects adults and older individuals. By contrast, glioblastoma is relatively uncommon in children and adolescents aged 0-19 years, accounting for only ~2.9% of all brain and other CNS tumors reported in this age group. The incidence increases steadily with an advancing age and peaks in older adults, with a median age at diagnosis of ~64 years in large epidemiological series. In the majority of cases, no predisposing hereditary cancer syndrome or identifiable genetic susceptibility is present (1). The etiology of glioblastoma remains largely unknown, with the majority of cases arising sporadically and without identifiable environmental or inherited predisposing factors. Aside from prior exposure to therapeutic cranial irradiation and rare cancer predisposition syndromes, no definitive causal factors have been established (1).

Under the 2021 WHO classification, glioblastoma is defined as an IDH-wildtype diffuse astrocytic tumor that fulfills CNS WHO grade 4 criteria (7). Diffuse astrocytic tumors harboring IDH mutations are classified separately as astrocytoma, IDH-mutant, CNS WHO grade 2-4, reflecting their distinct molecular biology and clinical behavior (7,9). Historically, glioblastomas were subdivided into so-called primary (*de novo*) tumors, which arise without a known precursor lesion, and secondary tumors, which develop through malignant progression from lower-grade diffuse astrocytomas (9). These historical designations describe two major biological pathways, characterized by rapidly presenting IDH-wildtype tumors in older adults and more slowly evolving IDH-mutant tumors in younger patients. However, these terms are no longer formal diagnostic entities within the current WHO framework, having been superseded by molecularly defined classifications (7,9).

**Clinical presentation.** The clinical presentation of glioblastoma is largely determined by tumor location, size, growth kinetics and the extent of associated peritumoral edema. Patients commonly present with a progressive headache, focal neurological deficits, such as hemiparesis, aphasia, or visual field disturbances, seizures and cognitive or personality changes resulting from tumor infiltration or mass effect (15). Lesions involving the frontal or temporal lobes frequently manifest with behavioral changes, executive dysfunction, or new-onset epilepsy, whereas tumors affecting the motor cortex or internal capsule more often present with focal motor weakness. In a minority of cases, patients may present acutely with stroke-like symptoms caused by tumor-associated hemorrhage or sudden worsening of cerebral edema leading to increased intracranial pressure (15).

Neuroimaging, most commonly magnetic resonance imaging, typically demonstrates a heterogeneously enhancing mass with central necrosis, surrounding vasogenic edema, and associated mass effect. Despite these characteristic features, imaging alone cannot reliably distinguish glioblastoma

from other high-grade gliomas or metastatic brain lesions. Consequently, a histopathological examination combined with the molecular analysis of tumor tissue obtained through stereotactic biopsy or surgical resection remains essential for a definitive diagnosis and classification (7,15).

### 3. Molecular classification and prognostic biomarkers

*Integrated molecular classification.* The 2021 WHO classification formalized an integrated diagnostic framework in which histopathological features are combined with key molecular alterations to define diffuse gliomas. Within this system, glioblastoma is defined as an IDH-wildtype diffuse astrocytic tumor that demonstrates at least one criterion of CNS WHO grade 4 disease, including microvascular proliferation, necrosis, telomerase reverse transcriptase (TERT) promoter mutation, epidermal growth factor receptor (EGFR) amplification, or the combined presence of whole-chromosome 7 gain and chromosome 10 loss (7). By contrast, diffuse astrocytic tumors harboring IDH mutations are classified separately as astrocytoma, IDH-mutant, CNS WHO grade 2-4, regardless of histological grade. These tumors are biologically distinct from glioblastoma and are associated with a substantially different clinical behavior and prognosis (7,9).

*IDH status.* Mutations in the IDH1 and IDH2 genes represent a fundamental molecular determinant in diffuse gliomas. IDH-wildtype tumors constitute the vast majority of glioblastomas and correspond to the canonical aggressive phenotype that typically presents in older adults with rapid clinical progression. By contrast, IDH-mutant diffuse astrocytomas more commonly arise in younger patients, often evolve over a period of several years from lower-grade precursor lesions, and are associated with a significantly prolonged overall survival (9).

At the molecular level, IDH mutations result in the accumulation of the oncometabolite 2-hydroxyglutarate, which drives widespread epigenetic reprogramming and contributes to the development of the glioma CpG island methylator phenotype. Across multiple clinical series, the presence of an IDH mutation has been consistently associated with an improved response to alkylating chemotherapy and a longer survival, independent of MGMT promoter methylation status and treatment modality (9).

*MGMT promoter methylation.* MGMT promoter methylation is the most clinically relevant predictive biomarker for response to temozolomide in IDH-wildtype glioblastoma. The MGMT gene encodes a DNA repair enzyme that removes alkyl adducts from the O<sup>6</sup> position of guanine, thereby directly reversing the cytotoxic DNA lesions induced by temozolomide. The hypermethylation of the MGMT promoter leads to the transcriptional silencing of the gene, reduced DNA repair capacity and an increased susceptibility of tumor cells to temozolomide-induced cell death (8).

The pivotal EORTC-NCIC trial demonstrated a marked survival advantage for patients with MGMT-methylated glioblastoma treated with combined chemoradiation, with a median overall survival of 23.4 months vs. 12.6 months in those with

unmethylated tumors (6). These findings established MGMT promoter methylation as both a potent prognostic marker and a critical determinant of therapeutic benefit from temozolomide in clinical practice (8).

*Glioma CpG island methylator phenotype (G-CIMP).* The G-CIMP describes a distinct epigenetic state characterized by widespread promoter hypermethylation and is strongly associated with IDH-mutant tumors. G-CIMP-positive gliomas are mainly observed in younger patient populations, demonstrate a lower proliferative activity, and are associated with significantly improved clinical outcomes compared with G-CIMP-negative tumors (9). The recognition of this phenotype further refines prognostic stratification within IDH-mutant astrocytomas and may have implications for responsiveness to epigenetic or molecularly targeted therapies (9).

*Additional prognostic factors.* In addition to molecular biomarkers, several clinical and treatment-related variables provide independent prognostic information in glioblastoma. A younger age at diagnosis and good functional performance status are consistently associated with longer survival across multiple studies (16,17). The extent of surgical resection is particularly influential, with volumetric analyses demonstrating that resection of at least 95 percent of contrast-enhancing tumor is associated with a significant survival advantage compared with subtotal resection or biopsy alone (16,17). Conversely, tumors involving deep or eloquent brain regions, such as the motor cortex, language areas, or basal ganglia, are often less amenable to aggressive resection and are associated with poorer outcomes (16,17).

Collectively, age, performance status, IDH mutation status, MGMT promoter methylation and the extent of resection constitute the core elements of contemporary prognostic models used to guide risk stratification and therapeutic decision-making in glioblastoma.

### 4. Standard of care treatment

*Surgical management.* Maximal safe surgical resection is the cornerstone of initial glioblastoma management when anatomically and clinically feasible (6,17). The primary surgical objective is to achieve the greatest possible cytoreduction of contrast-enhancing tumor, while preserving neurological function and maintaining quality of life. Advances in neurosurgical techniques, including neuronavigation, intraoperative neuromonitoring, awake language mapping, intraoperative ultrasound, intraoperative magnetic resonance imaging and 5-aminolevulinic acid-guided fluorescence surgery, have significantly improved the extent of resection, while minimizing operative morbidity (6,17).

Multiple studies have demonstrated that complete or near-complete resection of enhancing tumor, commonly defined as at least 95% volumetric reduction, is associated with significantly prolonged survival compared with subtotal resection or biopsy alone (6,15,17,18). In large clinical series, median overall survival increases from ~9-10 months following biopsy alone to 15-18 months following gross-total resection when combined with standard post-operative chemoradiation (17). Nevertheless, only ~50-70% of patients are candidates for

near-complete resection. Tumors located in deep or eloquent brain regions, poor baseline performance status, advanced age, or significant medical comorbidities frequently limit the feasibility of aggressive surgical intervention. In such cases, patients typically undergo limited debulking or stereotactic biopsy and experience substantially poorer clinical outcomes (6,17).

**Radiotherapy.** Post-operative external beam radiotherapy remains a critical component of standard glioblastoma treatment. The established regimen delivers a total dose of 60 Gy in daily fractions of 1.8-2.0 Gy over a 6-week period (6). Randomized clinical trials evaluating radiation dose escalation beyond 60 Gy have failed to demonstrate a survival benefit and have instead shown increased rates of late neurotoxicity, including radiation necrosis and cognitive impairment (6). Contemporary three-dimensional conformal and intensity-modulated radiotherapy techniques allow more precise target coverage, while reducing radiation exposure to surrounding normal brain tissue and critical structures (6).

For fit, non-elderly patients, conventional fractionation to 60 gray remains the standard approach (16). In elderly or medically frail patients, hypofractionated radiotherapy schedules, such as 40-50 Gy delivered in 15-20 fractions, have demonstrated comparable survival outcomes with improved tolerability and shorter overall treatment duration (15,19). The selection of fractionation strategy is generally guided by patient age, functional status, comorbidities, and individual treatment goals (15,19).

**Chemotherapy.** Temozolomide is the standard systemic therapy for patients newly diagnosed with glioblastoma (6,20). It is an oral alkylating agent with favorable CNS penetration that exerts cytotoxic effects primarily through methylation of the O<sup>6</sup> position of guanine and the N7 position of adenine (20). In the pivotal EORTC-NCIC trial, the addition of concurrent and adjuvant temozolomide to radiotherapy improved median overall survival from 12.1 to 14.6 months and increased the 2-year survival rate from 10 to 26% (6). These findings established the so-called Stupp protocol as the global standard of care for newly diagnosed glioblastoma (6).

Prior research evaluating alternative alkylating chemotherapy regimens, including the combination of procarbazine, lomustine and vincristine (PCV), has not demonstrated a clear survival benefit in patients newly diagnosed with glioblastoma (18). In a phase III randomized trial, Cairncross *et al* (18) reported that the addition of PCV chemotherapy failed to produce a meaningful improvement in clinical outcomes and was associated with greater toxicity compared with standard treatment, underscoring the limited role of this regimen in this disease setting. These results further reinforced the adoption of temozolomide-based chemoradiation as the preferred therapeutic approach.

During the concurrent chemoradiation phase, temozolomide is administered at a daily dose of mg/m<sup>2</sup> throughout the 6-week course of radiotherapy. Following a 4-week treatment break, adjuvant temozolomide is typically administered at 150-200 mg/m<sup>2</sup> on days 1-5 of each 28-day cycle for six to twelve cycles, depending on patient tolerance and institutional practice (6,20). The most common adverse effects include hematologic toxicity, particularly thrombocytopenia and

lymphopenia, as well as fatigue and nausea. Although dose reductions or early discontinuation are required in a substantial proportion of patients, cumulative temozolomide exposure appears to be associated with improved clinical outcomes, particularly in tumors with MGMT promoter methylation (20).

## 5. Treatment outcomes

In unselected patient populations treated according to the Stupp protocol, the median overall survival has been shown to be ~14-16 months, with 2-year survival rates of 26-30% and 5-year survival rates <10% (1,6,19). Clinical outcomes are strongly influenced by molecular and patient-specific prognostic factors. Patients with MGMT-methylated tumors frequently achieve median survival approaching 20-21 months with standard chemoradiation, whereas those with unmethylated MGMT typically experience median survival just >12 months despite identical treatment (8,16).

Diffuse astrocytic tumors harboring IDH mutations, now classified separately from glioblastoma, demonstrate a distinct clinical course and a substantially longer median survival, often >24-36 months in grade 4 disease, underscoring the prognostic importance of molecular classification in contemporary glioma management (9,18).

**Mechanisms of treatment resistance.** Glioblastoma is characterized by a high propensity for early recurrence and therapeutic failure, reflecting the convergence of multiple resistance mechanisms operating at different biological levels. These include limitations in drug delivery, enhanced DNA repair capacity, hierarchical cellular organization, an immunosuppressive tumor microenvironment and extensive intratumoral heterogeneity with dynamic clonal evolution under therapeutic pressure (21-27).

**Blood-brain barrier dysfunction.** The blood-brain barrier represents a major anatomic and functional obstacle to effective systemic therapy in glioblastoma. It is composed of specialized endothelial cells connected by tight junctions, along with a basement membrane, pericytes and astrocytic end-feet, together forming a highly selective interface between the systemic circulation and CNS parenchyma (3). This structure restricts the passage of most macromolecules and many small-molecule agents, such that an estimated 98% of systemically administered drugs exhibit limited penetration into the brain (3).

Although glioblastoma disrupts blood-brain barrier integrity in regions of contrast enhancement, barrier function is frequently preserved in infiltrative tumor margins. This spatial heterogeneity results in regions of subtherapeutic drug exposure within the tumor, often referred to as drug-penetration deserts, which contribute to treatment failure (3). In addition, efflux transporters such as P-glycoprotein and multidrug resistance-associated proteins are overexpressed in both brain endothelium and glioblastoma cells, actively exporting chemotherapeutic agents in an ATP-dependent manner and further reducing effective intratumoral drug concentrations (3).

Strategies under investigation to overcome blood-brain barrier-related resistance include osmotic or pharmacologic barrier disruption, nanoparticle-based drug delivery systems,

convection-enhanced delivery via intraparenchymal catheters, and the development of engineered biologics with improved CNS penetration (3,22).

**MGMT-mediated chemotherapy resistance.** Temozolomide exerts its primary cytotoxic effect through the formation of O<sup>6</sup>-methylguanine DNA adducts, which mispair with thymine during DNA replication and initiate mismatch repair-mediated cell death when unrepaired (20,23). MGMT directly counteracts this mechanism by removing methyl groups from the O<sup>6</sup> position of guanine, thereby restoring normal base pairing and preventing activation of the mismatch repair pathway (8,23). A high expression of MGMT, typically driven by an unmethylated MGMT promoter or transcriptional upregulation, therefore confers intrinsic resistance to temozolomide (8,23).

In addition to MGMT activity, defects in mismatch repair genes, such as MSH6 or MLH1 can paradoxically promote resistance by preventing recognition of O<sup>6</sup>-methylguanine-thymine mismatches. This allows tumor cells to evade lethal mismatch repair cycles and continue replicating despite ongoing DNA damage (23). Together, these mechanisms explain early treatment failure in a subset of patients and underscore why MGMT promoter methylation, although highly informative, remains an incomplete predictor of sensitivity to alkylating chemotherapy (8,23).

## 6. Glioblastoma stem cell enrichment

Glioblastoma exhibits a hierarchical cellular organization that includes a subpopulation of tumor-initiating cells commonly referred to as glioblastoma stem cells. These cells possess self-renewal capacity, multipotency and the ability to recapitulate the histological and molecular features of the parental tumor in experimental models (24). Glioblastoma stem cells are relatively quiescent, demonstrate efficient DNA damage repair, overexpress drug efflux transporters and rely on pro-survival signaling pathways, such as Notch, Hedgehog and Wnt/ $\beta$ -catenin, all of which contribute to resistance to both radiotherapy and chemotherapy (24).

Cytotoxic therapies preferentially eliminate more differentiated tumor cells, resulting in relative enrichment of the stem-like compartment within residual disease. Surviving glioblastoma stem cells can subsequently drive tumor recurrence, which is often characterized by increased aggressiveness and treatment resistance compared with the primary lesion (24). Therapeutic strategies targeting stem cell-specific pathways, promoting differentiation, or disrupting the supportive stem cell niche remain largely investigational; however, they represent a critical avenue for addressing recurrence and resistance (21,24).

## 7. Tumor microenvironment and immunosuppression

Glioblastoma develops within a profoundly immunosuppressive tumor microenvironment characterized by high densities of regulatory T cells, tumor-associated macrophages with an M2-like phenotype, myeloid-derived suppressor cells, and elevated levels of immunosuppressive cytokines, such as transforming growth factor  $\beta$ , interleukin 10 and vascular endothelial growth factor (25). The expression of immune checkpoint ligands, including programmed death ligand 1, on

both tumor and immune cells further promotes T-cell exhaustion and functional anergy (25).

In addition, glioblastomas generally exhibit a relatively low tumor mutational burden compared with other solid tumors, limiting neoantigen availability and further constraining effective antitumor immune responses (25). These features help explain the limited efficacy of programmed death 1 and programmed death ligand 1 inhibitors as monotherapy in glioblastoma, despite their success in other malignancies such as melanoma and lung cancer (14,25,26). Emerging evidence suggests that meaningful immune activation in glioblastoma will require combination strategies integrating checkpoint blockade with vaccines, cellular therapies, or agents targeting immunosuppressive myeloid and regulatory T-cell populations (21,25,26).

## 8. Tumor heterogeneity and clonal evolution

Single-cell genomic and transcriptomic analyses have revealed profound intratumoral heterogeneity in glioblastoma, with multiple genetically and transcriptionally distinct subclones coexisting within individual tumors. These subpopulations differ in driver mutations, proliferative capacity, metabolic programming and sensitivity to therapeutic agents (27). Under selective pressure from treatment, sensitive clones are eliminated, while resistant populations expand, driving clonal evolution toward increasingly aggressive and therapy-refractory disease states (27).

Beyond genetic diversity, glioblastoma cells exhibit remarkable transcriptional plasticity, with dynamic transitions between proneural, classical, and mesenchymal-like states in response to microenvironmental cues and therapeutic interventions. This adaptability further complicates durable disease control and makes it unlikely that single-agent therapies will be curative. These observations strongly support the rationale for rationally designed combination regimens that target multiple vulnerabilities simultaneously and adapt to tumor evolution over time (2,21,22).

## 9. Emerging therapeutic modalities

**Tumor-treating fields (TTFields).** TTFields are low-intensity, intermediate-frequency alternating electric fields in the range of 100-300 kilohertz, delivered non-invasively through transducer arrays applied to the scalp. These fields selectively disrupt mitosis in rapidly dividing tumor cells by interfering with mitotic spindle formation, chromosome segregation and cytokinesis, ultimately leading to mitotic catastrophe and apoptosis (10). Additional biological effects include the impairment of DNA damage repair, induction of autophagy, reduced cellular invasiveness and the potential modulation of blood-brain barrier permeability (10,28).

In the phase III EF-14 trial, the addition of tumor-treating fields to maintenance temozolomide following chemoradiation significantly prolonged median progression-free survival from 4.0-6.7 months and median overall survival from 16.0-20.9 months, corresponding to a hazard ratio of 0.63 (10). The principal adverse effect was low-grade scalp irritation at array application sites, while systemic toxicity was minimal (28). Real-world registry data from the PRiDE study

have confirmed the feasibility and safety of tumor-treating fields in broader clinical populations, with survival outcomes comparable to or slightly exceeding those observed in clinical trials (28). However, prolonged daily usage requirements, typically >18 h per day, as well as cosmetic and quality-of-life considerations, have limited adoption in some clinical settings (28).

*Laser interstitial thermal therapy (LITT).* LITT is a minimally invasive neurosurgical technique that employs stereotactically placed laser fibers to deliver focal thermal energy, resulting in the coagulative necrosis of tumor tissue under real-time magnetic resonance thermometry guidance (11). This approach is particularly attractive for recurrent glioblastoma located in deep or eloquent brain regions where open surgical resection carries substantial morbidity (11).

Clinical reports have suggested that LITT performed at the first recurrence is associated with a median overall survival of ~11-12 months from the time of treatment, compared with roughly 9-10 months in patients managed with biopsy and systemic therapy alone. The procedure is typically associated with relatively short hospital stays and acceptable complication rates (11). Although the available evidence is largely derived from retrospective analyses and single-arm series, LITT is increasingly incorporated into individualized salvage treatment strategies for carefully selected patients (11).

*Dendritic cell vaccination.* Dendritic cell vaccines are designed to enhance antitumor immunity by priming or amplifying tumor-specific T-cell responses through antigen presentation in an immunostimulatory context (12,21). Autologous dendritic cells are generated *ex vivo* from peripheral blood monocytes, loaded with tumor lysate or defined antigens, matured, and subsequently administered via intradermal, subcutaneous, or intranodal routes (12,21). Among these platforms, DCVax-L, an autologous tumor lysate-loaded dendritic cell vaccine, has been the most extensively studied in glioblastoma (12,29).

In a large phase III trial and subsequent pooled analyses, the addition of DCVax-L to standard therapy was associated with encouraging survival outcomes in patients both newly diagnosed with and recurrent glioblastoma when compared with external control cohorts, including the presence of a subset of long-term survivors (12,29). A recent meta-analysis of dendritic cell vaccine studies reported a significant survival benefit in patients with glioblastoma treated with dendritic cell vaccines in addition to standard therapy. The pooled analysis demonstrated an overall survival hazard ratio of approximately 0.71, indicating a meaningful reduction in mortality compared with standard therapy alone (30). Treatment was generally well tolerated, with predominantly low-grade, transient flu-like symptoms. Nevertheless, variability in trial design, logistical complexity of vaccine production, prolonged manufacturing timelines, and cost have limited widespread implementation outside specialized centers (12,21,29).

*Chimeric antigen receptor (CAR) T-cell therapy.* CAR T-cell therapy involves the genetic modification of autologous T-cells to express synthetic receptors that recognize tumor-associated

antigens and trigger T-cell activation upon antigen binding (13). In glioblastoma, targets under active investigation include interleukin-13 receptor  $\alpha 2$ , EGFR variant III, human epidermal growth factor receptor 2 and GD2 (13). Early-phase clinical trials of interleukin-13 receptor  $\alpha 2$ -directed CAR T-cells delivered intratumorally or intraventricularly have demonstrated objective radiographic responses, including partial and complete responses, in heavily pretreated patients with recurrent glioblastoma (13). However, these responses have generally been transient, with disease progression often occurring within months (13).

Barriers to durable efficacy include antigen heterogeneity and antigen loss, limited persistence of CAR T-cells within the CNS, profound local immunosuppression and logistical challenges related to manufacturing timelines in the setting of rapidly progressive disease (13,25,31). Current research efforts are focused on the development of multi-antigen CAR constructs, armored CAR T-cells with enhanced resistance to exhaustion, combination strategies incorporating checkpoint inhibition or myeloid-targeted therapies, and optimization of delivery routes and dosing schedules (13,21,31).

*Checkpoint immunotherapy.* Immune checkpoint inhibitors targeting the programmed death 1 and programmed death ligand 1 pathway have revolutionized the treatment of several systemic malignancies, but clinical outcomes in glioblastoma have been disappointing (14,26,31). In the randomized CheckMate 143 trial, nivolumab failed to improve overall survival compared with bevacizumab in patients with recurrent glioblastoma, despite an acceptable safety profile (14,26). Similarly, phase II studies evaluating pembrolizumab or nivolumab, either alone or in combination with bevacizumab, have demonstrated limited efficacy in unselected patient populations (26,31).

Several factors likely contribute to these results, including low tumor mutational burden, the limited infiltration of effector T-cells, dominant myeloid-mediated immunosuppression and the regulatory effects of the blood-brain barrier (25,31). Consequently, current strategies emphasize rational combination approaches that integrate checkpoint blockade with vaccines, cellular therapies, oncolytic viruses, or agents targeting regulatory T-cells and tumor-associated macrophages, as well as biomarker-driven patient selection (21,25,31).

*Anti-angiogenic therapy and reirradiation.* Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor A, received accelerated approval for recurrent glioblastoma based on high radiographic response rates and improvements in progression-free survival (32). However, subsequent randomized research has consistently failed to demonstrate a corresponding improvement in overall survival in either recurrent or newly diagnosed disease settings (32,33). As a result, bevacizumab is best regarded as a palliative therapy that can reduce peritumoral edema, improve or stabilize neurological symptoms and facilitate corticosteroid tapering, without fundamentally altering the natural history of the disease (32,33).

Reirradiation, typically delivered using hypofractionated schedules and occasionally combined with bevacizumab, represents a treatment option for selected patients with

localized recurrence and preserved performance status (34). The NRG/RTG 1205 trial demonstrated an improved progression-free survival with the combination of reirradiation and bevacizumab compared with bevacizumab alone, although no significant overall survival benefit was observed (34). These findings reinforce the role of anti-angiogenic therapy and reirradiation as disease-modifying rather than curative interventions in the recurrent setting.

## 10. Management of recurrent glioblastoma

Recurrent glioblastoma remains a major therapeutic challenge, with a median survival of ~6 months from the time of first progression reported in the majority of clinical series (35). Recurrence most commonly occurs within or immediately adjacent to the original radiation field, reflecting predominant local treatment failure rather than the development of distant intracranial disease (35). Management in the recurrent setting should therefore be highly individualized and guided by multiple factors, including the interval since initial therapy, patient age and functional performance status, tumor size and anatomical location, prior treatments received, and patient preferences and goals of care (35).

Available therapeutic options include repeat surgical resection for surgically accessible lesions, re-irradiation with or without concurrent systemic therapy, bevacizumab-based regimens, alkylating chemotherapy such as lomustine or combination PCV, tumor-treating fields, laser interstitial thermal therapy, dendritic cell vaccination, participation in clinical trials evaluating novel agents or combination strategies, and best supportive care (11,12,32,34,35). In medically fit patients, multimodal approaches combining local therapies with systemic treatment are frequently employed in an effort to maximize disease control (35).

Despite these interventions, outcomes remain poor, and no salvage strategy has consistently demonstrated an ability to extend median survival beyond approximately 12-15 months following recurrence. This persistent limitation underscores the urgent need for more effective systemic, molecularly targeted, and immune-based therapies capable of overcoming treatment resistance and achieving durable disease control in the recurrent setting (35).

## 11. Conclusion and future directions

The future of glioblastoma treatment will likely emphasize precision medicine approaches integrating comprehensive molecular profiling with individualized multimodal therapy. Expanded molecular profiling beyond current IDH and MGMT assessment, including tumor protein p53 mutations, EGFR alterations, B-Raf proto-oncogene, serine/threonine kinase (BRAF) mutations and neurofibromin 1 loss, may identify tumor subtypes responsive to specific targeted therapies. IDH-mutant glioblastomas may preferentially benefit from IDH inhibitors, while BRAF V600E-mutant tumors may respond to BRAF inhibitors and EGFRvIII-expressing tumors to targeted EGFRvIII therapy.

Combination immunotherapy strategies represent a rational approach to overcome the immunosuppressive glioblastoma microenvironment, combining checkpoint inhibitors

with dendritic cell vaccination, CAR T-cell therapy and agents targeting regulatory T-cell biology or transforming growth factor- $\beta$  signaling. Next-generation drugs designed with enhanced blood-brain barrier penetration, nanoparticle-based drug delivery systems, and local delivery approaches such as convection-enhanced delivery and sustained-release implants offer promise for overcome the critical drug delivery challenge.

Advanced imaging biomarkers, including advanced magnetic resonance imaging techniques, positron emission tomography imaging and radiomics-based approaches may increasingly enable patient selection, early response prediction, and treatment adaptation during therapy. These precision approaches, though still largely experimental, represent the emerging treatment paradigm for the management of glioblastoma.

In conclusion, glioblastoma remains a highly aggressive malignancy with limited long-term survival despite substantial advances in multimodal treatment and molecular stratification. The persistence of complex and overlapping resistance mechanisms continues to undermine durable therapeutic benefit, underscoring the limitations of uniform treatment approaches. Consequently, future progress will depend on integrated, precision-based strategies that combine molecularly guided therapy, immune modulation, and innovative drug delivery systems.

### Acknowledgements

Not applicable.

### Funding

No funding was received.

### Availability of data and materials

Not applicable.

### Authors' contributions

SMA was a major contributor to the conception of the study, as well as to the literature search for related studies and the critical revision of the manuscript. BAA was involved in the literature review, study design and writing the manuscript, assisted with data acquisition and interpretation. Both authors have read and approved the final manuscript. Data authentication is not applicable.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

## References

- Ostrom QT, Gittleman H, Xu J, Kromer C, Wolinsky Y, Kruchko C and Barnholtz-Sloan JS: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the united states in 2009-2013. *Neuro Oncol* 18 (suppl 5): v1-v75, 2016.
- Oronsky B, Reid TR, Oronsky A, Sandhu N and Knox SJ: A review of newly diagnosed glioblastoma. *Front Oncol* 10: 574012, 2021.
- Abbott NJ, Patabendige AA, Dolman DE, Yusof SR and Begley DJ: Structure and function of the blood-brain barrier. *Neurobiol Dis* 37: 13-25, 2010.
- Bailey P and Cushing H: A classification of the tumours of the glioma group on a histogenetic basis, with a correlated study of prognosis. *Medium 8vo*. Pp. 175, with 108 illustrations. 1926. Volume 14. Issue 55. J. B. Lippincott Company. 21s. net, British Journal of Surgery, Philadelphia, London, and Montreal, pp554-555 1927.
- Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P and Ellison DW: The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A summary. *Acta Neuropathol* 131: 803-820, 2016.
- Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, *et al*: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma: a randomised phase III study: 5-year analysis of the EORTC/NCIC trial. *Lancet Oncol* 10: 459-466, 2009.
- Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, *et al*: The 2021 WHO classification of tumors of the central nervous system: A summary. *Neuro Oncol* 23: 1231-1251, 2021.
- Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, *et al*: MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 352: 997-1003, 2005.
- Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, Gilbert MR and Yang C: IDH mutation in glioma: Molecular mechanisms and potential therapeutic targets. *Br J Cancer* 122: 1580-1589, 2020.
- Stupp R, Taillandier L, Kanner AA, Kesari S, Steinberg DM, Toms SA, Taylor LP, Lieberman F, Silvani A, Fink KL, *et al*: Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: A Randomized Clinical Trial. *JAMA* 314: 2535-2543, 2015.
- Munoz-Casabella A, Alvi MA, Rahman M, Burns TC and Brown DA: Laser interstitial thermal therapy for recurrent glioblastoma: Pooled analyses of available literature. *World Neurosurg* 153: 91-97.e1, 2021.
- Liau LM, Ashkan K, Brem S, Campian JL, Trusheim JE, Iwamoto FM, Tran DD, Anstas G, Cobbs CS, Heth JA, *et al*: Association of autologous tumor lysate-loaded dendritic cell vaccination with extension of survival among patients with newly diagnosed and recurrent glioblastoma: A phase 3 prospective externally controlled cohort trial. *JAMA Oncol* 9: 112-121, 2023.
- Brown CE, Alizadeh D, Starr R, Weng L, Wagner JR, Naranjo A, Ostberg JR, Blanchard MS, Kilpatrick J, Simpson J, *et al*: Regression of glioblastoma after chimeric antigen receptor T-cell therapy. *N Engl J Med* 375: 2561-2569, 2016.
- Manz C, Chivers C, Liu M, Regli SB, Channgolkar S, Evans CN, Draugelis M, Braun J, Navathe AS, Kumar P, *et al*: Prospective validation of a machine learning algorithm to predict short-term mortality among outpatients with cancer. *J Clin Oncol* 38: 15\_suppl, 2009.
- Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS and Khasraw M: Management of glioblastoma: State of the art and future directions. *CA Cancer J Clin* 70: 299-312, 2020.
- Iwamoto FM, Cooper AR, Reiner AS, Nayak L and Abrey LE: Glioblastoma in the elderly: The memorial sloan-kettering cancer center experience (1997-2007). *Cancer* 115: 3758-3766, 2009.
- Sanai N, Polley MY, McDermott MW, Parsa AT and Berger MS: An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg* 115: 3-8, 2011.
- Cairncross G, Wang M, Jenkins RB, *et al*: Benefit of procarbazine, lomustine, and vincristine in glioblastoma. *J Clin Oncol* 32: 294-301, 2014.
- Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, Kantor G, Guillo JM, Jadaud E, Colin P, Bondiau PY, *et al*: Radiotherapy for glioblastoma in the elderly. *N Engl J Med* 356: 1527-1535, 2007.
- Grossman SA and Batare JF: Current management of glioblastoma multiforme. *Semin Oncol* 31: 635-644, 2004.
- Weller M, Roth P, Preusser M, Wick W, Reardon DA, Platten M and Sampson JH: Vaccine-based immunotherapeutic approaches to gliomas and beyond. *Nat Rev Neurol* 13: 363-374, 2017.
- Weller M, Wick W, Aldape K, Brada M, Berger M, Pfister SM, Nishikawa R, Rosenthal M, Wen PY, Stupp R and Reifenberger G: Glioblastoma. *Nat Rev Dis Primers* 1: 15017, 2015.
- Karsy M, Arslan E and Moy F: Current progress on understanding microRNAs in glioblastoma multiforme. *Genes Cancer* 3: 3-15, 2012.
- Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD and Dirks PB: Identification of human brain tumour initiating cells. *Nature* 432: 396-401, 2004.
- Woroniecka K, Chongsathidkiet P, Rhodin K, Kemeny H, Dechant C, Farber SH, Elsamadicy AA, Cui X, Koyama S, Jackson C, *et al*: T-cell exhaustion signatures vary with tumor type and are severe in glioblastoma. *Clin Cancer Res* 24: 4175-4186, 2018.
- Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, Baehring J, Ahluwalia MS, Roth P, Bähr O, *et al*: Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 Randomized clinical trial. *JAMA Oncol* 6: 1003-1010, 2020.
- Müller S, Kohanbash G, Liu SJ, Alvarado B, Carrera D, Bhaduri A, Watchmaker PB, Yagnik G, Di Lullo E, Malatesta M, *et al*: Single-cell profiling of human gliomas reveals macrophage ontogeny as a basis for regional differences in macrophage activation in the tumor microenvironment. *Genome Biol* 18: 234, 2017.
- Mrugala MM, Engelhard HH, Dinh Tran D, Kew Y, Cavaliere R, Villano JL, Annemiele Bota D, Rudnick J, Love Sumrall A, Zhu JJ and Butowski N: Clinical experience with NovoTTF-100A™ system for glioblastoma: The Patient Registry Dataset (PRIDe). *Semin Oncol* 41 (Suppl 6): S4-S13, 2014.
- Liau LM, Ashkan K, Tran DD, Campian JL, Trusheim JE, Cobbs CS, Heth JA, Salacz M, Taylor S, D'Andre SD, *et al*: First results on survival from phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. *J Transl Med* 16: 142, 2018.
- Wong CE, Chang Y, Chen PW, Huang YT, Chang YC, Chiang CH, Wang LC, Lee PH, Huang CC, Hsu HJ and Lee JS: Dendritic cell vaccine for glioblastoma: An updated meta-analysis and trial sequential analysis. *J Neurooncol* 170: 253-263, 2024.
- Sampson JH, Maus MV and April CB: Immunotherapy for brain tumors. *J Clin Oncol* 35: 2450-2456, 2017.
- Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, *et al*: Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol*. 2009;27: 4733-4740, 2009.
- Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, *et al*: Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 370: 709-722, 2014.
- Tsien CI, Pugh SL, Dicker AP, Raizer JJ, Matuszak MM, Lallana EC, Huang J, Algan O, Deb N, Portelance L, *et al*: NRG Oncology/RTOG1205: A randomized phase II trial of concurrent bevacizumab and reirradiation versus bevacizumab alone as treatment for recurrent glioblastoma. *J Clin Oncol* 41: 1285-1295, 2023.
- Chen W, Wang Y, Zhao B, Liu P, Liu L, Wang Y and Ma W: Optimal therapies for recurrent glioblastoma: A bayesian network meta-analysis. *Front Oncol* 11: 641878, 2021.

