Review

Discovery Medicine 2025; 37(200): 1721–1744
https://doi.org/10.24976/Discov.Med.202537200.150

Glioblastoma Multiforme: Navigating Treatment, Recent Breakthroughs and Therapies

Allison B. Reiss[1,2,*], Shelly Gulkarov[2], Ariel Z. De Leon[1], Ankita Srivastava[2], Aaron Pinkhasov[1], Joshua De Leon[1], Sara Haddock[3], Dimitris G. Placantonakis[3,4,5]

[1]Department of Medicine, NYU Grossman Long Island School of Medicine, Mineola, NY 11501, USA
[2]Department of Foundations of Medicine, NYU Grossman Long Island School of Medicine, Mineola, NY 11501, USA
[3]Department of Neurosurgery, NYU Grossman School of Medicine, New York, NY 10016, USA
[4]Department of Cell Biology, NYU Grossman School of Medicine, New York, NY 10016, USA
[5]Perlmutter Cancer Center, NYU Grossman School of Medicine, New York, NY 10016, USA
*Correspondence: Allison.Reiss@nyulangone.org (Allison B. Reiss)
Submitted: 8 May 2025 Revised: 8 July 2025 Accepted: 5 August 2025 Published: 20 September 2025

Glioblastoma multiforme (GBM) is a highly aggressive and invasive type of primary brain tumor. Despite maximal safe surgical resection followed by concurrent adjuvant chemotherapy and radiotherapy, the clinical prognosis is grim, with only marginal prolongation of survival and poor quality of life. Median survival time is 15 months. This review will discuss the pathogenesis of GBM, diagnostic challenges, clinical evaluation, imaging, genomics and current therapeutic options. The intrinsic immunosuppressive properties of GBM and additional adverse changes in immune surveillance and the systemic immune environment brought about by chemoradiotherapy will be addressed. GBM stem cell properties and their role in local recurrence and preclusion of cure will be covered. We will discuss the limited penetration of the blood-brain barrier by therapeutics as a major obstacle in treatment. Advances in novel therapeutic strategies using personalized approaches, cell-based therapies, tumor vaccines and targeted drug delivery will be considered.

Keywords: glioblastoma; blood-brain barrier; tumor microenvironment; temozolomide; nanoparticles; radiotherapy

Introduction

Glioblastoma multiforme (GBM) is the most prevalent malignant primary tumor of the brain and is characterized by its invasiveness and lethality despite treatment with a combination of surgical resection, radiotherapy, and chemotherapy. Incidence rises with age and has thus increased with the growing older population, even in the face of tremendous efforts to design new therapies [1,2]. The breakthroughs needed to substantially prolong the survival of persons with GBM likely require an understanding of the molecular mechanisms responsible for tumor progression, but that understanding remains elusive.

This narrative review aims to summarize the latest information on GBM diagnosis, etiology, underlying mechanisms and therapeutic advances—with a special focus on strategies to address current treatment challenges.

An Overview of GBM

Epidemiology

GBM is the most common and aggressive primary central nervous system (CNS) malignancy, with a median survival of 15 months with treatment and a 5-year survival of under 7% [3,4]. Its average incidence rate is 3.26/100,000 population and the median age for diagnosis is 64 years [5]. The location of GBM is most concentrated in the frontal, temporal, and parietal lobes [6]. With the recent improvement in diagnostic techniques, its incidence ranges from most common to least common in the frontal, temporal, parietal, occipital, and other structures of the brain, respectively.

Age is also an important factor, and many studies show that it occurs mostly in people over the age of 40 years [7,8]. To that end, it has been observed that the incidence of GBM increases with age, peaking at 75–84 years and decreasing thereafter [9]. Other factors, such as socioeconomic status, have been shown to play a role in GBM incidence and the standard of care [10,11]. Gorenflo *et al.* [12] conducted a literature review on papers that analyze socioeconomic status and GBM, and with a sample size of greater than 1530 patients, found a positive correlation between area socioeconomic status level and GBM incidence or prognosis. This could ideally be used to devise interventions with improved outcomes and prevention strategies.

Etiology

In the vast majority of GBM cases, tumors are sporadic and no risk factors are identified. Rare but estab-

lished risk factors include exposure to radiation and certain genetic syndromes. Ionizing radiation is commonly used for diagnostic and treatment purposes, as patients who have been exposed to high doses of radiation earlier in life have a higher risk for brain tumors in general [13,14]. There is also a positive association between ionizing radiation and risk for glioma at younger compared to older age at time of exposure.

At least three genetic syndromes are associated with a risk for developing GBM: Li-Fraumeni syndrome, neurofibromatosis type 1 (NF1), and Turcot syndrome. Li Fraumeni syndrome is a hereditary cancer predisposition syndrome caused by germline mutations in *TP53*, a gene that encodes the 393 amino acid P53 tumor suppressor protein [15]. Mutations or deletions in the *TP53* gene are one of the most common mutations in cancer and occur in over 30% of glioblastomas [16–18]. Various studies have found an association between germline mutations in TP53 and CNS tumors [19,20]. Reed *et al.* [21] used comparative transcriptomics to identify genes that are uniquely overexpressed in a Li-Fraumeni syndrome GBM patient relative to other cancer patients, including 200 GBMs. They found that signal transducer and activator of transcription 1 (STAT1) and signal transducer and activator of transcription 2 (STAT2) were significantly overexpressed in the Li-Fraumeni syndrome patient, hence identifying an actionable therapeutic target and further supporting the association between the syndrome and glioblastoma [21].

Although very rare, high-grade gliomas similar to GBM are seen in patients with NF1, a multisystem genetic disorder with autosomal dominant inheritance that predisposes individuals to specific CNS benign and malignant tumors [22,23]. Neurofibromin is a tumor suppressor protein that is the product of the *NF1* gene, which belongs to the guanosine triphosphatase (GTPase) activating protein (GAP) family, which inactivates the rat sarcoma (RAS) signaling pathway by promoting hydrolysis of guanosine triphosphate (GTP) to guanosine diphosphate (GDP) [24]. Patients born with a germline mutation of NF1 with the somatic inactivation of the second NF1 allele have a loss of neurofibromin expression and function. This loss of neurofibromin expression in Schwann cells and astrocytes is associated with hyperactivation of RAS, driving tumor growth and the appearance of cutaneous neurofibromas. In early childhood, individuals with NF1 may be subject to gliomas affecting the optic pathway, while adults with NF1 are prone to higher-grade gliomas. GBM is rare, but when it occurs in persons with NF1, it is found at younger ages than sporadic GBM [25,26].

Turcot syndrome is another rare hereditary disorder associated with colorectal polyposis with primary neuroepithelial tumors of the CNS, such as GBM or medulloblastoma [27,28]. One case report revealed an 11-year-old boy with a synchronous clinical presentation of both GBM and colonic adenocarcinoma [29]. The synchronous management of CNS tumors and colonic adenocarcinoma makes management more difficult and shortens the survival rate. Hence, the presence of GBM in Turcot syndrome may suggest a lower survival rate in contrast with other CNS tumors.

Grading, Classification and Prognosis

Classification and Grading

Traditional diagnosis of and grading of gliomas is largely based on their histopathological features, with GBM designated as the highest-grade (Grade 4) category of glioma. Gliomas can be classified as diffuse or circumscribed [30,31]. Circumscribed (Grade 1) gliomas have well-defined margins and are considered benign and surgically curable [32]. Most glial neoplasms in adult patients are diffuse gliomas, which are characterized by infiltrative growth within the CNS parenchyma. Tumor cells invade either individually or as a group of cells and form a network throughout the neuropil. Diffuse gliomas can be separated into three malignancy grades by histology: World Health Organization (WHO) Grades 2, 3, and 4. Diffuse gliomas can also be histologically subtyped as astrocytomas or oligodendrogliomas, although histologic classification has recently taken a back seat to molecular characterization. Astrocytoma Grade 4 is essentially synonymous with GBM and is the most common subtype [33].

In 2021, the WHO classification of CNS tumors underwent significant changes, incorporating molecular features for the classification of gliomas, glioneuronal tumors, and neuronal tumors. One key change adopted by the 2021 WHO classification system is the recognition that the mutational status of isocitrate dehydrogenase 1 or 2 (*IDH1* or *IDH2*) separates gliomas into distinct disease entities, with a diagnosis of GBM requiring wild-type IDH status [30,34,35].

In addition to IDH-wild type status, three other molecular features characterize the diagnosis of GBM: chromosome 7 gain and chromosome 10 loss, telomerase reverse transcriptase promoter (p*TERT*) mutation, and epidermal growth factor receptor (*EGFR*) amplification [36,37]. The presence of one or more of these genetic alterations supersedes histological features that would otherwise suggest a lower-grade tumor [34] (Fig. 1).

Prognosis

The overall prognosis for GBM is poor, with a 5-year survival rate of only 7.2%. The median survival after diagnosis is only 15 months [38]. There have been over 1200 GBM clinical trials in the last 2 decades; however, the vast majority failed to produce a clinically meaningful survival benefit. Other factors can be considered when determining prognosis. One study analyzed the mRNA gene expression for 525 patients with GBM from the Cancer Genome Atlas (TCGA) database and found 33 genes whose expressions showed significant independent associations with overall

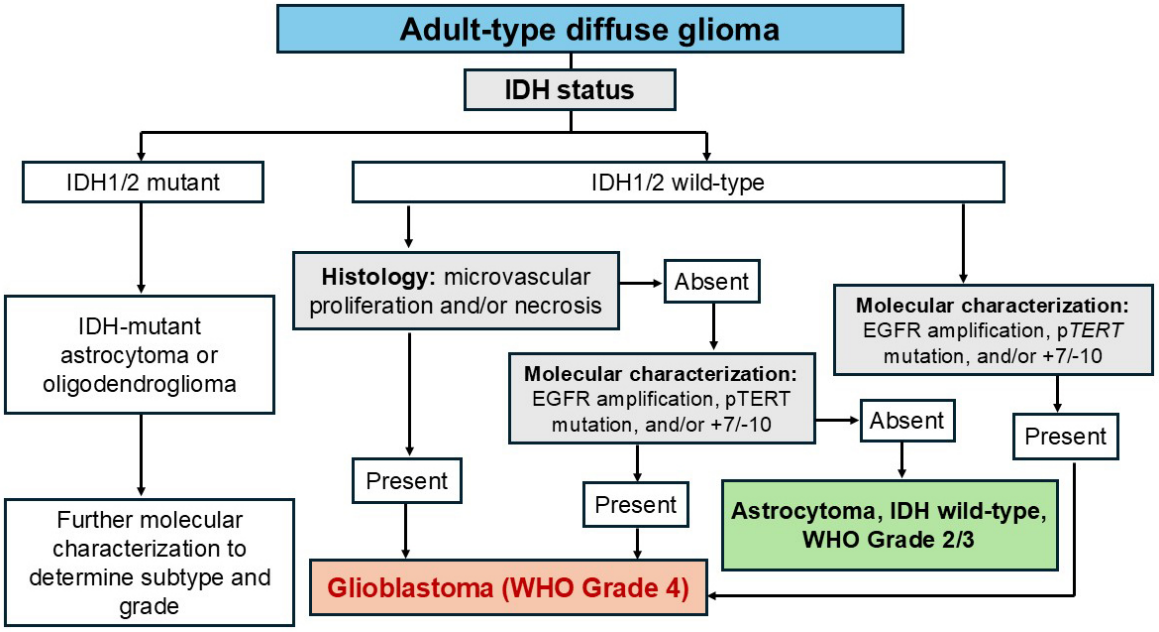

Fig. 1. Flow chart illustrating the integration of histological and molecular features for the diagnosis of GBM. GBM, glioblastoma multiforme; IDH, isocitrate dehydrogenase; EGFR, epidermal growth factor receptor; p*TERT*, telomerase reverse transcriptase promoter; WHO, World Health Organization. The figure was created using Microsoft PowerPoint (Version 2024, Microsoft Corporation, Redmond, WA, USA).

survival [39]. Future studies could be conducted to further understand the mechanisms of GBM and possible treatment methods through gene expression or repression.

Pathogenesis of GBM

Genetics and Epigenetics

GBM has been associated with three main genetic events: (i) receptor tyrosine kinase (RTK) mutational activation and amplification, (ii) inactivation of tumor suppressors, such as phosphatase and tensin homolog (PTEN), tumor protein p53 (TP53), neurofibromin 1 (NF1) and retinoblastoma protein (RB1), and (iii) phosphatidylinositol 3-kinase (PI3K) pathway activation [40–46]. Pathogenesis is not strictly reliant on these factors, however. Alteration and upregulation of multiple other signaling pathways have been associated with the mechanistic development of GBM. Among these are loss of cyclin-dependent kinase inhibitor 2A (CDKN2A), and activation of several oncogenic pathways: Wnt, transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), nuclear factor (NF)-κB, AKT, and mammalian target of rapamycin (mTOR) [47–50].

Molecular Pathogenesis

IDH

IDH enzymes catalyze the conversion of isocitrate to α-ketoglutarate. The cytosolic IDH enzyme plays a pivotal role in generating α-ketoglutarate as a cofactor for cytosolic dioxygenases, while IDH2 and IDH3 are essential components of the Krebs cycle in mitochondria. IDH mutations are found frequently in lower-grade gliomas (Grades 2–3). Tumors with a mutated *IDH1* or *IDH2* gene tend to have a better prognosis than GBM [51,52]. IDH-mutant Grade 4 astrocytomas, previously designated as IDH mutant GBM, have been reclassified as WHO Grade 4 IDH-mutant astrocytoma [34,53].

TERT and EGFR Mechanisms in GBM

TERT is the catalytic component of the telomerase enzyme, which adds hexamer repeats to telomeres, and it is upregulated in multiple types of human cancers, including GBM [54]. Maintaining telomere length is a hallmark of oncogenesis and is required for cellular immortality and prevention of cellular replicative senescence [55,56]. In GBM, stereotypical *TERT* promoter mutations predominate as the mechanism of transcriptional upregulation of telomerase and are seen in about 80% of cases [57,58].

Some studies have found that *TERT* promoter mutations are associated with worse prognosis and overall survival, while others show no survival effect of TERT mutations [59,60]. In 20% of GBM, telomeres are elongated through a distinct mechanism termed alternate lengthening of telomeres (ALT), which occurs independently of *TERT* promoter mutations [61,62].

EGFR, a transmembrane receptor tyrosine kinase of the erythroblastic oncogene B (ERBB) family, is involved in cell proliferation and differentiation. *EGFR* amplifica-

tion in the form of extrachromosomal DNA known as double minutes is often found in GBM [63,64]. In addition, by virtue of its localization to chromosome 7, EGFR is frequently overexpressed in tumors with a gain of chromosome 7. Upon binding to ligands, which include epidermal growth factor (EGF), EGFR forms homodimers or heterodimers with other ERBB family members, which leads to autophosphorylation of its C-terminal tail [65]. This serves as a docking site for SRC homology 2 domain-containing signaling proteins, including phosphoinositide 3-kinase and signal transducer and activator of STAT proteins. In GBM, EGFR signaling may occur aberrantly, independent of ligand binding, and can incite pathophysiological processes leading to unconstrained cell growth. EGFR variant III (EGFRvIII) is the most common EGFR mutant found in GBM and lacks amino acids 6-273 (exons 2-7). EGFRvIII is constitutively active and forms molecular clusters on the cell membrane that can be important for its pro-tumorigenic function [66,67]. EGFRvIII promotes cell proliferation, angiogenesis, and invasion. EGFR may therefore be a valuable treatment target [68]. Since *EGFR* and *TERT* alterations carry biological significance in GBM, these molecular parameters have also been utilized for molecular grading of gliomas independently of histologic features [69].

Reports on the prognostic role of EGFRvIII are conflicting and not definitive [70,71]. A meta-omics analysis from Hoogstrate *et al.* [72] combining four large datasets into one large GBM transcriptome dataset of 741 participants found that within patients with EGFR-amplified tumors (those with high copy number of the *EGFR* gene), there was no significant difference in patients with EGFRvIII positive and negative tumors, as well as no association of EGFRvIII and patient survival. Missense mutations within the ectodomain of EGFR are associated with shorter survival [73]. These prognostic associations and the ability to detect these mutations in plasma samples provide important directions for future therapies targeting either EGFR or *TERT* or both [74].

Microenvironment and Niches

The myriad genetic mutations and epigenetic factors that incite tumor development correspond with other key factors that contribute to GBM pathogenesis, including tumor microenvironment, metabolism, the immune system, and GBM's niches [75–77]. The concepts of tumor microenvironment and the GBM niche are deeply intertwined [78]. The tumor microenvironment refers to all non-neoplastic cells within a tumor that may directly influence the tumor's growth [79,80]. In the glioblastoma microenvironment, this includes microglia/macrophages, monocytes, dendritic cells, neutrophils, myeloid-derived suppressor cells, lymphocytes, neurons, astrocytes, oligodendrocytes, endothelial cells and pericytes [81,82]. GBM tumors interact extensively with the surrounding brain tissue. A series of high-profile publications over the last several years have shown that GBM cells form electrically active networks and exhibit complex signaling dynamics with nearby brain cells and with each other [83–87].

Metastasis of GBM outside of the CNS is exceedingly rare, with some estimates placing the incidence of GBM metastasis as low as 0.4–0.5% [88,89]. This observation suggests that GBM is more dependent on its primary tissue microenvironment than other malignancies. GBM is highly unusual in this respect; metastatic dissemination is almost universally observed in aggressive cancers and is the leading cause of cancer-related mortality. Circulating tumor cells have been isolated from the blood of GBM patients, demonstrating the ability of these cancer cells to cross the blood-brain barrier and access extracranial sites [90,91]. GBM's apparent inability to establish distant metastases despite access to the circulation remains unexplained.

The elements of the microenvironment are found in variable proportions in GBM niches, with the distinguishing feature among niches considered to be their anatomic location and the predominant means of pathogenesis utilizing these tumor microenvironment elements. Three niches have been characterized in GBM: the perivascular, hypoxic, and invasive [92–94] (Fig. 2). The perivascular tumor niche supports rapid angiogenesis and endothelial cell recruitment to create an environment that promotes GBM survival, growth and spread into healthy brain parenchyma [95,96]. Interaction between the endothelium and GBM stem cells is achieved via nitric oxide, cyclic guanosine monophosphate (cGMP), and induction of Notch signaling [97–100]. Notch proteins are expressed on the membrane of GBM stem cells, while the ligands delta-like ligand 4 (DLL4) and Jagged 1 (JAG1) that interact with Notch-1 and Notch-2 are expressed on the membranes of endothelial cells, thus promoting the production of VEGF and angiogenesis [101–103]. Nitric oxide has multiple effects on GBM, but many studies indicate that nitric oxide synthase inhibition can reduce endothelial cell proliferation and migration and decrease tumor invasiveness [104,105].

The hypoxic niche refers to pseudopalisading areas with low oxygen and a necrotic core that are ideally suited to foster immunosuppression [106–108]. Hypoxic conditions stabilize hypoxia inducible factor (HIF)1α and upregulate HIF2α, transcription factors that activate genes that bring about adaptation to low oxygen conditions and promote the growth of cancer stem cells [82,109,110]. The invasive niche is similar to the perivascular niche in its relation to surrounding vasculature, but differs in location (being situated adjacent to normal brain parenchyma) and its utilization of the surrounding vasculature [111]. Invasive niches have a relatively low density of tumor cells and are able to commandeer existing, adjacent physiologic vasculature [112]. In this niche, glioma cells displace perivascular astrocytes significantly, inducing astrocytes to express several factors, including fibroblast growth factor and TGF-β,

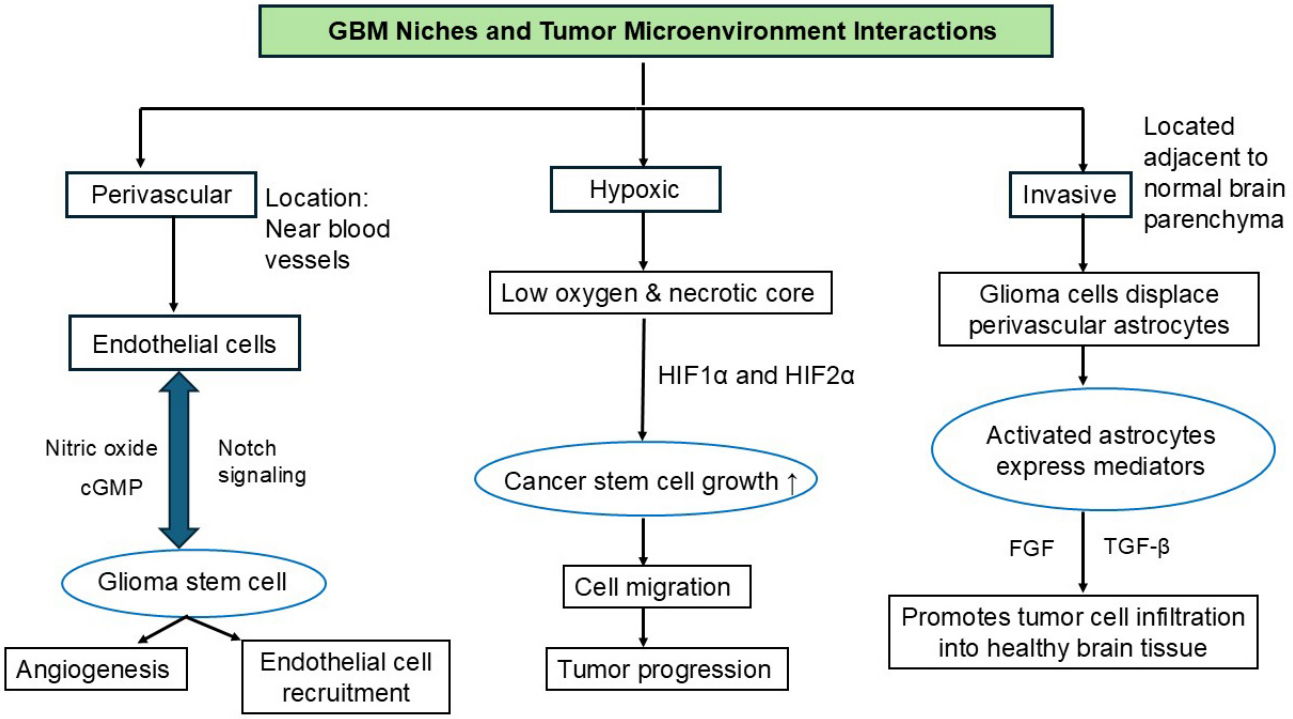

Fig. 2. Key features of GBM niches. The 3 niches are perivascular, hypoxic, and invasive. The perivascular niche creates an environment that promotes GBM growth and immune evasion. Endothelial cells interact with glioma stem cells via Notch signaling, nitric oxide, and cyclic guanosine monophosphate (cGMP). These interactions support angiogenesis and endothelial cell recruitment. In the hypoxic niche, hypoxic conditions stabilize hypoxia inducible factors (HIF), leading to adaptation to low oxygen conditions, enhanced cancer stem cell growth, and tumor progression. Finally, the invasive niche, located adjacent to normal brain parenchyma, consists of glioma cells displacing perivascular astrocytes, thereby activating astrocytes to express fibroblast growth factor (FGF) and transforming growth factor (TGF)-β, thus fostering tumor infiltration. ↑ indicates increase. The figure was created using Microsoft PowerPoint (Version 2024, Microsoft Corporation, Redmond, WA, USA).

implicated in tumor cell infiltration [113,114]. Relevant to the invasive niche is the phenomenon of perineuronal satellitosis, where GBM cells interact with neurons to form one of the secondary structures of Scherer.

The Immune System and Metabolism

Two other factors inciting tumor development, mentioned previously, are the immune system and metabolism. GBM evade and suppress the host immune system through a variety of mechanisms [115]. For one, these tumor cells reduce the expression of major histocompatibility complex class II (MHC II), cluster of differentiation (CD)40, and CD80, factors which would otherwise assist the immune system in targeting tumor cells [116–120]. Higher levels of the CD40 glycoprotein and its ligand are associated with better prognosis [121]. Moreover, glioma-associated cancer-initiating cells have been shown to express factors that induce T-cell apoptosis, such as the programmed death-ligand 1 (PD-L1) and Galectin-3 [122–125].

Metabolically, glioblastoma stem-like cells have been shown to favor glycolysis over oxidative phosphorylation, referred to as the Warburg effect [126,127]. While glycolysis is more predominant in hypoxic conditions, it gives way to the pentose phosphate pathway in normoxic states within actively proliferating cancer cells, which ensures production of biomolecules necessary for DNA replication. The principal means of metabolism switches whether the tumor cells are invading/migrating or proliferating [128,129]. More specifically, pentose phosphate pathway enzyme expression is increased in GBM cells when compared to normal brain tissue, particularly in highly proliferative tumor regions, whereas glycolysis enzymes are markedly elevated in GBM cells in severely hypoxic tumor regions [128,130]. Hypoxic conditions also promote the migration of tumor cells to evade hypoxic cell damage. In such conditions, GBM stem cells upregulate the expression of glucose transporters for enhanced glucose uptake in order to outcompete surrounding non-neoplastic cells [131].

Immunosuppressive cells are participants in the disarming of immune defenses against GBM [132,133]. There are several key immunosuppressive cells that contribute to GBM proliferation (Table 1, Ref. [107,134–139]). Tumor-associated microglia/macrophages are known to differentiate towards the M2 phenotype, and through multiple mech-

Table 1. Mechanisms of action of key immunosuppressive cells within the GBM microenvironment.

Cell type	Known immunosuppressive features	References
Tumor-associated microglia /macrophages	Differentiate toward the M2 phenotype Release anti-inflammatory cytokines Incite angiogenesis Nourish tumor stem cells Enhance tumor invasiveness through augmented epithelial-mesenchymal transformation. Activate immune checkpoints	[107,134,135]
Myeloid-derived suppressor cells	Promote T cell inactivation and inhibit T proliferation	[136,137]
Regulatory T-cells	Suppress T-cell antigen–specific anti-tumor responses and cytotoxic functions. Foster tolerance by secreting cytokines such as TGF-β and IL-10 Cytotoxicity and degranulation of natural killer cells are impeded by regulatory T cells and hypoxia	[138,139]

anisms such as releasing anti-inflammatory cytokines and inciting angiogenesis, enhance tumor growth and progression [134,135]. Myeloid-derived suppressor cells further suppress anti-tumor immune activation by inhibiting T-cell activation and proliferation [136]. Regulatory T-cells participate in suppression of antigen-specific anti-tumor responses, secrete immunosuppressive cytokines, and impair natural killer cell function [138,139].

Strategies for Clinical and Radiological Evaluation

Initial Detection and Evaluation

Radiographic evaluation plays a pivotal role in the diagnosis and treatment of GBM. At first presentation, patients usually undergo a computed tomography (CT) scan, which characteristically reveals a low-attenuating tumor with poorly defined irregular margins and a substantial mass effect [140]. A standard CT is not specific or sensitive for evaluating GBM [141]. Radiological evaluation is largely informed by magnetic resonance imaging (MRI) [142,143]. T2-weighted sequence, fluid attenuated inversion recovery (FLAIR), and gadolinium-enhanced T1-weighted MRI are routinely used for diagnosis, surgical planning, and evaluation of treatment response in patients with GBM [144]. Some features that are particularly noted include tumor volume, peritumoral edema, microvasculature, necrosis, degree of enhancement, and the presence of cysts [145].

Tumor Characterization and Monitoring

Radiological evaluation using diffusion-weighted imaging (DWI) applies an estimate of the random diffusional (Brownian) motion of water molecules in biological tissues to enable the calculation and mapping of the apparent diffusion coefficient (ADC) of various regions of the mass *in vivo*. ADC is inversely proportional to tumor density and extent of cell proliferation and is therefore helpful in estimating the tumor growth potential and clinical prognosis of glioma patients [146,147]. In a study from Lawrence and colleagues [148] with 75 subjects (mean age 53 years $\pm$ 12) presenting with IDH wild-type GBM, 32 were treated with dose-escalated radiotherapy on a 1.5 Tesla MRI-linear accelerator, and 28 patients had additional DWI sequences. They used frequent DWI longitudinally to yield volumetric measures and found that low-ADC tumor volumes correlated with improved overall survival [148]. Another study conducted by Wu *et al.* [149] investigated the clinical value of DWI in the grading of glioma and its application in clinical surgery by assessing ADC values for low and high-grade gliomas. They found a difference in ADC values of normal white matter between the two groups, although this difference was not statistically significant [149]. Nonetheless, DWI has a promising prognostic value in preoperative differential diagnosis and pathological classification of gliomas [150].

Positron emission tomography (PET) scans can provide additional information about GBM metabolism and recurrence beyond that yielded from MRI [151]. Radiolabeled glucose ([^{18}F] FDG) is the most common probe utilized in PET imaging [152]. Additional probes have been designed, and this has expanded the value of PET scans in clinical oncology [153]. Amino acid-based PET imaging tracer agents can act as adjunct tools to increase accuracy in detecting and monitoring GBM [154]. Among the most common of these amino acid tracers are [^{11}C]methionine, [^{18}F]fluoro-ethyl-L-tyrosine, and [^{18}F]fluorodopa. As previously mentioned, radiolabeled glucose is typically the gold standard radiotracer; however, the brain has a naturally high uptake of [^{18}F]FDG, so GBM lesions near gray matter can be difficult to interpret [155]. [^{11}C]Methionine and other amino acid tracers can better delineate tumor from background in comparison to [^{18}F]FDG and add prognostic and diagnostic information beyond the MRI [156,157]. [^{18}F]Fluorodopa is a dopamine analogue that is taken up by L-amino acid transporter 1, an amino acid transporter ex-

pressed at high levels in gliomas [158–160]. [^{18}F]Fluoroethyl-L-tyrosine is another amino acid-based alternative to [^{18}F]FDG that can provide information about tumor volume, detect recurrence and hone in upon metabolically active areas of the tumor [161,162]. [^{18}F]Fluoromisonidazole ([^{18}F]FMISO) is a hypoxia-sensing tracer that signals the hypoxic microenvironment found around GBM. Hypoxia is a marker of poor prognosis that incites radioresistance, invasiveness and microvascular proliferation [163].

Immuno-PET is another approach that uses several cell differentiation markers, such as CD146, to indicate tumor aggressiveness or CD11b to indicate tumor-associated myeloid cells (TAMCs) as effective targets for treatment guidance [164]. CD146 is a cell adhesion molecule and a member of the immunoglobulin superfamily. Higher levels of this glycoprotein within the GBM tissue detected non-invasively with immune-PET are considered an indicator of poorer prognosis and tumor aggressiveness [165,166]. TAMCs comprise as much as 40% of the GBM tumor mass and contribute to immunosuppression [167]. The integrin CD11b is found in abundance on the surface of TAMCs and microglia, and leveraging anti-CD11b tracers to monitor TAMCs could be valuable in determining treatment efficacy. Additional PET biomarkers specifically for patients with GBM include integrin receptor family, fibroblast activation protein, somatostatin receptors, and chemokine receptor-4 [168].

Tumor Vasculature

Assessment of tumor vasculature and blood flow is an important aspect of GBM evaluation. T2*-based dynamic susceptibility contrast (DSC) MRI is often employed to look at blood volume and flow within GBM but requires gadolinium or other contrast agents [169]. Arterial spin labelling is an MRI-based technique for measuring cerebral blood flow without the need for intravenous contrast [170]. It can be useful in tumor grading and in differentiating between GBM and primary CNS lymphoma [171,172].

GBM vessel walls may exhibit fragmentation [173]. In a retrospective study, Yadav *et al*. [174] were able to distinguish IDH wild-type GBM from IDH mutant high-grade astrocytoma with preoperative susceptibility-weighted MRI, which was applied to detect fragmented vessels. Fragmented thrombosed microvasculature was found in more than 90% of the patients with IDH wild type and was absent in all of the IDH mutant imaging.

Overall, there are several methods of radiological evaluation employed along with genetic and molecular profiling to create a personalized treatment plan for patients with GBM and allow clinicians to make accurate diagnostic evaluations [175,176].

Therapeutic Approaches to GBM

The standard treatment of GBM uses a three-pronged approach consisting of surgical resection with subsequent concurrently administered radiation and chemotherapy with temozolomide [177,178]. The subsections below will discuss each of these dimensions of therapy and investigational approaches currently in development.

Chemotherapy

Currently Available Treatment-Temozolomide

The current standard chemotherapy drug treatment of GBM is the oral alkylating agent temozolomide [179]. Temozolomide is the only drug approved for first-line treatment of GBM [180]. Its efficacy has been highlighted in various studies, with improved survival [181,182]. The methylation status of the O6-methylguanine-DNA methyltransferase (*MGMT*) promoter is an important predictive biomarker for the response to temozolomide. The tumor of about 60% of GBM patients shows no methylation of the promoter, which predicts a poor response to temozolomide, as opposed to the remaining 40% of patients, whose tumors show hypermethylation of the promoter [183].

The timing within the 24-hour day/night cycle of temozolomide administration has emerged as a possible factor in its efficacy [180,184]. A chronotherapy study from Damato *et al*. [185] found that administering temozolomide in the morning, before 10 AM, was associated with longer overall survival compared to treatment in the evening, after 8 PM. This was a retrospective study with 166 eligible GBM patients who were newly diagnosed and had undergone both surgery and chemoradiation. This difference can be explained by circadian medicine, which maximizes treatment efficacy and minimizes toxicity by timing the delivery of medications in accordance with the circadian rhythms of the patient [186]. Along these lines, evidence suggests that the circadian clock in tumor cells is linked to DNA damage response mechanisms, which involve DNA damage checkpoints, nucleotide excision repair mechanisms, as well as survival pathways [187].

Chemotherapies in Development in Animal and Cell-Based Models

Nanoparticle Delivery. Another obstacle to efficient drug delivery is the blood-brain barrier, which consists of multiple layers surrounding brain vessels and prevents the passage of drugs into the brain [188]. To mitigate this issue, there is a need to enhance the delivery of drugs to the brain and improve the penetration of drugs into the brain [189]. Nanocarrier-based therapy can bring about drug penetration and delivery into the brain. This technology has several advantages that can be leveraged against GBM, such as drug encapsulation and solubilization, increased cellular uptake via endocytosis, targeted delivery, and controlled release [190]. The small carrier particles can

be composed of organic or inorganic materials and can cross the blood-brain barrier. They may be engineered in the form of nanopolymers, micelles, or liposomes [191]. They offer greater bioavailability and lengthened drug half-life [192]. Murine models have shown that nanoparticles can deliver temozolomide to the brain via an intranasal route [193]. When encapsulated in a chitosan-based nanoparticle, the half-life of temozolomide in phosphate-buffered saline (PBS) was enhanced to 13.4 hours compared to 1.8 hours for the free drug and, when given to mice intravenously, these temozolomide-carrying chitosan particles penetrated the blood-brain barrier [194].

Penetrating the Brain-Tumor Barrier. Identifying molecular signatures of the GBM vasculature has been utilized to target the brain-tumor barrier [195]. For instance, Jimenez-Macias *et al*. [196] used publicly available single-cell RNA-seq data to perform a transcriptomic analysis to identify endothelial-related genes that were enriched in perivascular regions of GBM and found that many of the enriched transcripts were involved in angiogenesis and recruitment of blood vessels. They then treated endothelial monolayers and endothelial cells grown within blood-brain barrier 3D spheroids with 6′-bromoindirubin-3′-acetoxime (BIA), an anti-invasive and anti-angiogenic compound, and found that BIA downregulated brain-tumor barrier signature genes, causing endothelial barrier disruption in these *in vitro* models. They then used a synthetic nanoparticle to deliver BIA into a murine GBM model and showed an *in vivo* increase in blood-tumor barrier permeability. Zdioruk *et al*. [197] also formulated a nanoparticle-encapsulated form of BIA for intravenous injection and showed that this treatment changed the tumor microenvironment in ways that would foster anti-tumor responses. The BIA treatment led to improved survival and an increase in the proportion of CD8+T lymphocytes and CD103+ dendritic cells.

Thus, nanocarrier-based therapy could be a useful therapeutic for optimizing blood-brain barrier permeability. Although we have not found human trials as of this writing, research into developing different types of particles is ongoing [198,199].

Immunotherapy and Combination Therapy. Another difficulty in chemotherapy administration is the heterogeneity of GBM, since this is a mechanism that contributes to temozolomide resistance [200]. Other factors that contribute to temozolomide resistance include the DNA repair system mechanisms, and other mechanisms like autophagy [201–203]. Therefore, temozolomide-dosing schedule modulation and combination therapy are prominent areas of study. Immunotherapy may also be incorporated into GBM treatment. The anti-VEGF monoclonal antibody bevacizumab has been FDA-approved since 2017 to treat recurrent GBM, where it extends progression-free survival and overall survival [204,205].

Combination therapy is a growing area of study and may confer synergistic inhibition of GBM. Combining temozolomide or bevacizumab with another drug, such as the oral antineoplastic alkyl-phospholipid perifosine, may amplify their efficacy. Perifosine is an AKT pathway inhibitor that prevents its translocation to the plasma membrane and subsequent phosphorylation [206]. It is not effective as a monotherapy for GBM [207,208]. Zhao *et al*. [209] studied the effects of temozolomide and perifosine together in cultured GBM cell lines and a mouse model. They found that the combination of temozolomide and perifosine diminished expression of the BRCA1 tumor suppressor gene, hampered DNA repair mechanisms, elicited caspase-dependent apoptosis, and decreased GBM cell viability and proliferation [209–211]. Ramezani and colleagues [212] looked at perifosine and bevacizumab in a heterotopic mouse GBM model and found that perifosine enhanced apoptosis induction by bevacizumab.

Another study looked at combining temozolomide and cryptotanshinone, a diterpenoid quinone compound, in cell culture using LN229 and U87-MG human GBM cell lines [213]. In these cell types, they found that the combination had cytotoxic and anti-proliferative effects. An obstacle to its use is the low solubility and poor penetration of cryptotanshinone into tumors [214].

Surgical Resection

Techniques for Improving Precision

The poor prognosis and relatively high incidence of GBM have brought much effort to develop new therapies, but despite this focus, the gold standard treatment remains surgical resection followed by radiation therapy combined with temozolomide chemotherapy. This has been the case since the introduction of temozolomide in 2005 [215,216]. However, technical advances have allowed improved surgical outcomes that align with the concept of safe maximal tumor resection [217]. Surgery is the starting point of GBM treatment, where the greater the extent of resection, the better the survival [218–220]. One particular study analyzed the impact of the extent of resection, residual tumor volume, and gross total resection in glioblastoma subgroups in relation to their neurological and functional outcomes. The study by Gerritsen *et al*. [221] found that more extensive resection and lower residual tumor volume were significantly associated with improved overall survival and progression-free survival across all subgroups, with residual tumor volume the stronger prognostic factor. These findings can help aid surgical decision-making with regard to individual GBM patients.

Intraoperative MRI

There are various surgical innovations used in GBM treatment, summarized in Table 2 (Ref. [222–231]). One of these, intraoperative MRI, defines the location of anatomical structures and gives real-time information on tumor

boundaries that improves the accuracy of resection. This is an important prognostic factor for patient outcomes. Madani *et al*. [232] compared the frequency of further resection prompted by intraoperative MRI across different tumor subtypes from a surgeon's perspective and found that intraoperative MRI appeared most useful in cases of high-grade and low-grade gliomas. This could be attributed to the challenge of differentiating glioma margins from normal brain tissue. A retrospective study from Mirzayeva *et al*. [233] found that intraoperative MRI-guided resection makes it easier for surgeons to assess the extent of resection of high-grade or low-grade gliomas intraoperatively. Finally, fusing preoperative MRI with intraoperative MRI data can be used to develop a prototype elastic image fusion algorithm that can compensate for surgery-related brain shift [222,223].

Fluorescence-Guided Surgery

Fluorescence-guided surgery uses fluorophores such as 5-aminolevulinic acid (5-ALA) to enhance visualization of enhancing and non-enhancing malignant tumors and increase the extent of resection while decreasing residual tumor volume [234]. Intraoperative functional ultrasound can detect changes in brain tissue perfusion [235,236]. Fluorescein is another fluorescent marker that has the capacity to accumulate in cerebral areas as a result of damage to the blood-brain barrier. This allows fluorescein to be concentrated at tumor sites, making the tumor more visible [224,237].

Intraoperative Mapping and Intraoperative Neuromonitoring

Intraoperative mapping is a method of direct cortical stimulation that induces a neuronal excitation that can be used to map in real-time language and motor function both cortically and subcortically [225,238]. Another imaging tool is functional ultrasound, which provides spatiotemporal resolution and allows for changes in blood dynamics that reflect changes in metabolic activity [226,239]. Continuous dynamic mapping is another tool that maps the corticospinal tract by sending a short train of pulses [227,240]. Awake mapping is used during GBM resections to prevent potential neurological deficits, and it has been associated with increased extent of resection and decreased neurological deficits [228].

Intraoperative neuromonitoring includes a variety of different modalities in which different neuropathways are monitored throughout the neurosurgical procedure. Examples of these modalities include electroencephalogram (EEG), sensory evoked potentials, electromyography, motor evoked potentials, direct cortical stimulation, and brainstem auditory evoked responses [229,241]. The EEG records the average extracellular field potentials of the spontaneous activity of cortical neurons near the recording electrodes. Sensory evoked potentials monitor sensory pathway integrity by recording points cranial and caudal to the surgical field. Electromyography monitors the spontaneous activity in muscles by placing 2 electrodes that are approximately 1 cm apart into the body of the muscle and continuously monitoring [242,243]. Motor evoked potentials monitor the efferent motor pathways from the motor cortex and fibers in the internal capsule to the muscle. Direct cortical stimulation involves direct contact with the cortex when a charge is transferred, thus identifying eloquent areas to be avoided in surgery and minimizing neurologic deficits [244]. Brainstem auditory evoked responses monitor the auditory pathway from the eighth nerve to the auditory radiations [245,246].

Raman Spectroscopy

Raman spectroscopy technology is an intraoperative real-time decision support system for neurosurgical guidance in brain tumors that does not require a contrast agent [247,248]. Leblond *et al*. [249] used a machine learning model incorporating Raman spectroscopy to characterize live tissue during neurosurgery to distinguish tumor from non-tumor spectra. The model was trained on data from a multicenter clinical study and their analysis attained a diagnostic accuracy of 91% for GBM. Statistical analyses demonstrated that the inclusion of Raman spectroscopy improved detectability, setting the stage for a potentially new predictive model.

Virtual reality technology using an algorithm for intraoperative MRI-based navigation during GBM surgery has shown promise in finding residual tumor and improving progression-free survival [230,231].

Overall, these innovations, as well as the others mentioned in Table 2, have helped with the management of GBM and optimizing the extent of resection.

Radiotherapy and Stereotactic Radiosurgery

A therapeutic approach utilized to maximize survival and prognosis is conventional radiotherapy, which is typically begun after surgery and is considered a part of the standard of care for GBM [250]. Significant advances have been made to optimize external beam radiotherapy, but there is still some controversy regarding its use and safety [251,252]. Age is a factor that greatly influences prognosis, and GBM management in elderly patients can be complex [253]. While younger patients are typically treated with 60 Gy in 30 fractions, alternate dosing regimens are often considered in the elderly, because the aging brain may be more susceptible to the toxic effects of radiation. Elderly patients between 65–70 years of age with excellent functionality are good candidates for surgery and radiotherapy with concomitant and adjuvant temozolomide.

Hypo-Fractionated Radiotherapy

Elderly patients with good functionality above the age of 70 or with frailty are generally considered for the

Table 2. Surgical innovations used in GBM treatment.

Surgical techniques	Description	References
Intraoperative MRI	Better visualization and resection of the tumor for greater efficiency	[222,223]
5-ALA	Fluorescent tracer that identifies gadolinium-enhancing tumor	[224]
Intraoperative mapping	Cortical stimulation to induce neuronal excitation and map both motor and language function to maximize the extent of resection and spare function	[225]
Functional ultrasound	Using Doppler ultrasound images to detect changes in brain perfusion, enhancing spatiotemporal resolution	[226]
Continuous dynamic mapping	Maps the corticospinal tract using a monopolar suction probe, applying a modified Taniguchi technique with a short train of impulses	[227]
Awake mapping	Decreases neurological deficits and increases the extent of resection	[228]
Intraoperative neurophysiological monitoring	A set of techniques that reduces the risk of neurological injury: electroencephalogram, sensory evoked potentials, electromyography, motor evoked potentials, direct cortical stimulation, and brainstem auditory evoked responses	[229]
Virtual intraoperative technology	Overlays 3-dimensional anatomy of the brain over the surgical field to improve the accuracy of resection	[230,231]

5-ALA, 5-aminolevulinic acid; MRI, magnetic resonance imaging.

same treatment as younger persons, except with a shortened course of radiotherapy, referred to as hypofractionation [254,255]. Hypofractionation entails giving a larger daily dose (>1.8 Gy per fraction) within a shorter overall treatment timespan [256]. A recent retrospective study from Korea found that hypofractionated radiotherapy in persons aged 65 and over with GBM yielded comparable overall survival with lower cost when compared to long-course radiotherapy [257].

Hypofractionated radiotherapy has also been explored in the pre-operative setting for newly diagnosed and recurrent disease. This is a research area that is rapidly evolving. Some advantages of pre-operative hypofractionated radiotherapy are the ability for more distinct target delineation and a possible amplified anti-tumor immune response [258].

Stereotactic Radiosurgery

Stereotactic radiosurgery, using either a hypofractionated approach with dose escalation or a single dose, can deliver ablative radiation to the tumor while minimizing the dose received by adjacent normal structures [259]. Its benefit in select GBM patients is controversial because GBM is known to be an infiltrative disease, and skeptics argue that this local therapy does not improve overall survival [260,261]. However, it does seem to confer significant benefit in specific GBM patient populations. One retrospective observational multi-institutional study looked at the efficacy and safety of stereotactic radiosurgery for GBM patients with consideration of molecular tumor profiles. A total of ninety-six patients underwent stereotactic radiosurgery (median dose 15 Gy) at 147 tumor sites. Most (85%) of the patients were treated at recurrence, and stereotactic radiosurgery was used for 12% of patients. Researchers concluded that post-stereotactic radiosurgery survival was similar as a function of IDH mutation and *MGMT* promoter methylation status. They also found that stereotactic radiosurgery prescription dose >15 Gy and treatment target volume less than 5 cm^3 were predictors of overall survival in GBM patients, independent of age and IDH status [262]. Stereotactic radiosurgery can be applied to treat smaller, focal recurrent tumors after prior treatment with surgery, radiotherapy, and temozolomide [263]. Morris *et al*. [264] observed that stereotactic radiosurgery in combination with bevacizumab, an anti-VEGF monoclonal antibody, can be safely used to treat focal GBM recurrence.

Two clinical trials are evaluating pre-operative hypofractionated radiotherapy in GBM patients. The NeoGlioma Trial is a phase I trial that is studying the safety, feasibility, and maximum tolerated dosage of pre-operative radiosurgery in patients with proven high-grade glioma [265]. The patients undergo MRI-guided stereotactic biopsy and then either standard of care surgery or radiosurgery in 1 fraction within 14 days. After 14 more days, patients who have received radiosurgery undergo surgery. Within another 4–6 weeks, all patients will receive standard of care radiation therapy over 30 fractions and temozolomide daily with or without tumor-treating fields. The study is expected to enroll 25 subjects and to continue until September 2025, with a 3-year follow-up planned. Another clinical study looked at pre-operative hypofractionated radiotherapy in patients with a new radiological diagnosis of GBM that received a single fraction of preoperative radiotherapy ranging from 6 to 14 Gy, followed by standard of care surgery and postoperative chemoradiotherapy [266]. Part of the tumor was excluded from the radiation field, and this non-irradiated portion, known as the cold spot, was reserved for pathology and molecular profiling. These are

ongoing studies that are still recruiting, and these results can prove to be useful in understanding the benefits of preoperative hypofractionation radiotherapy. Preclinical studies in mice have been encouraging [267].

Combination Chemotherapy and Radiotherapy

Combination therapy of temozolomide and radiotherapy (40 Gy in 15 fractions) demonstrated better outcomes than radiotherapy alone, if tolerated [268]. The addition of tumor-treating fields, alternating low-intensity electric fields via transducer arrays, combined with temozolomide, also improved overall survival [269]. The tumor treating fields device consists of four transducer arrays, a field generator, and a power source. The patient's head must be shaved, and the field generator delivers these alternating electric fields through the transducer arrays across the brain and to the tumor site [270]. This type of anti-mitotic therapy also exerts its effects by promoting autophagy, augmenting cell permeability and strengthening the anti-tumor immune response [271,272]. Overall, radiotherapy is a crucial part of the current standard of care for patients with GBM, and there are multiple considerations that are individualized to the patient. The field is evolving to incorporate finer techniques to make resection and radiotherapy more precise [273].

A recent study looked at ways to improve the efficacy of radiotherapy by performing both single-cell RNA sequencing on tumors from patients with GBM and complementary *in vivo* murine experiments [274]. Their goal was to identify mechanisms of immunosuppression. They found that GBM responsiveness to radiotherapy was associated with expression of pyroptosis-related genes in humans. By promoting apoptosis, the stimulator of interferon genes (STING) pathway activation may be the mediating factor in conferring radiation responsiveness. They demonstrated this effect using a STING agonist in a murine GBM model. Golgi phosphoprotein 3-like (GOLPH3L) could interact with STING and inhibit its activity by facilitating its transport from the Golgi to the endoplasmic reticulum. This action of GOLPH3L on STING led to radiation resistance and, in GBM patients, lower GOLPH3L expression was associated with longer survival with radiotherapy. In a small retrospective case-controlled human study, they administered the GOLPH3L inhibitor vitamin B5 calcium (VB5) and showed a delay in tumor recurrence [274]. Therefore, they posit that inhibiting GOLPH3L could be applied to improve the efficacy of radiotherapy.

Another recent study seeks to improve the poor GBM prognosis by adding an antisecretory factor to the current standard therapy of surgical tumor removal, radiotherapy, and chemotherapy [275]. Antisecretory factor is an endogenous protein that may potentiate the antineoplastic effect of temozolomide and also alleviate edema surrounding the tumor [276]. In a double-blind randomized multicenter phase 2 clinical trial being conducted in Sweden (NCT05669820), the effect of adding Salovum, an egg yolk product containing high levels of antisecretory factor, to temozolomide therapy is being assessed in 300 patients with newly diagnosed GBM. The trial is still in progress and recruitment is estimated to be complete during 2026, with primary endpoints defined as survival at 6 and 12 months after diagnosis.

Viruses and Immunotherapy

Oncolytic viruses, either genetically engineered or naturally occurring, can infect GBM tumor cells and cause them to undergo lysis, thus releasing debris and tumor antigens that incite an immune response, transforming an immunologically "cold" tumor microenvironment to a "hot" environment [277]. In addition to attracting dendritic cells, natural killer cells, and cytotoxic T lymphocytes, oncolytic immunotherapy can lower the immunosuppressive barrier by reducing regulatory T cells. In a clinical trial, Ling *et al*. [278] found that GBM patients seropositive for herpes simplex virus type 1 given an oncolytic herpes virus by intralesional injection had an increase in survival to 14.2 months (95% CI = 9.5–15.7 months) compared to the expected survival of 6–9 months.

Chimeric antigen receptor (CAR)-T cell therapy can alter patient-derived T cells so that they become capable of recognizing antigens present on GBM tumor cells [279]. Although very effective for hematologic malignancies, success in solid tumors has been elusive. Use of CAR-T therapy for GBM is being explored in animal models and early human trials [280,281]. Choi *et al*. [282] applied CAR-T targeting EGFRvIII in 3 patients and documented strong, but transient anti-tumor responses, with tumors progressing in 2 of the 3 patients in this very early first-in-human study. Bagley *et al*. [283] published interim data from their human trial targeting EGFR and interleukin-13 receptor α2 in 6 patients with recurrent multifocal GBM and found early signs of efficacy.

Translational Challenges

The biological properties of GBM pose significant challenges to therapy. Infiltration of normal brain by tumor cells precludes surgical cure, while stem-like cells within possess a number of properties that allow them to resist conventional chemoradiotherapy [284]. Furthermore, the immunologically cold tumor microenvironment has rendered immune therapies, such as immune checkpoint inhibition, which have been successful in other solid tumors, ineffective [115]. Finally, the blood-brain and blood-tumor barriers limit the availability of both small molecules, biologics and cell therapies within tumors and in the tumor-infiltrated brain [188]. It is, therefore, incontestable that a deeper understanding of tumor biology is warranted in order to design improved therapies.

The current neuro-oncology landscape has benefited from extensive basic science investigation of tumor cells and their interactions with the microenvironment. This has led to the development of experimental therapies, which are tested in mouse models of GBM, the vast majority of the time. Indeed, the mouse has been utilized extensively as the host for xenografting human GBM cells, with the caveat that such mice need to be immunodeficient to prevent graft rejection, thereby preventing the study of the immune component of the tumor microenvironment. Immunocompetent mouse models of GBM that enable the study of the microenvironment are available, but their caveats include the differences between mouse and human immune systems and the fact that the biology is performed on mouse rather than human tumor cells. A collective deficiency of mouse models is that several candidate therapies demonstrate efficacy in preclinical mouse models but then fail in clinical trials [285].

To mitigate the inadequacy of mouse models, some groups have turned to the use of brain organoids as the host of patient-derived GBM grafts. This technology allows the study of interactions between tumor cells and human neural tissues and eliminates the possibility of heterophilic interactions between human proteins on tumor cells and mouse proteins in the host, possibly altering tumor biology [286]. This promising platform may improve in the future by virtue of synthetic organoid designs incorporating vasculature and immunity into cerebral organoids [287].

As an alternative to mouse models and human cerebral organoids, there has been sporadic use of canine and primate models. The major limitation of this approach is the high cost and, as a result, limited throughput [288].

The most prevalent current translational pipeline consists of preclinical testing in mouse models followed by Phase I clinical trials for the most promising candidate therapies. This has been a reasonable approach for translating the most efficacious and safe new treatments, as assessed in mouse models, to the clinic for initial testing on patients. Future improvements may consist of more rigorous selection of candidate therapies for clinical testing, clinical trials targeting newly diagnosed rather than recurrent tumors, and window of opportunity trials that assess tumor pharmacokinetic and pharmacodynamic properties of therapeutic agents in conjunction with surgical resection.

Intersection of GBM With Alzheimer's Disease

GBM and Alzheimer's disease (AD) both affect brain tissue, show an increase in prevalence with age, and carry a poor prognosis. They can be seen as opposites because GBM involves uncontrolled nerve cell growth while AD reflects neurodegeneration and nerve cell death [289,290]. Dementia rarely co-occurs with GBM and some studies point to a possible inverse correlation between them [291]. Techniques such as network analysis, single-cell RNA sequencing and machine learning have uncovered dysregulated pathways in common that may be leveraged to find treatments for each [292,293]. Recently, interest has focused on the mitochondrial dysfunction characteristic of both AD and GBM as a key therapeutic target. In particular, mitochondrial pathways that control energy metabolism may be important in the progression of both diseases, with poor energy generation in AD leading to apoptosis and cell death, while robust mitochondria can fuel invasiveness in GBM [294–296]. Microglia involvement and neuroinflammatory cascades are also prominent in both [297,298]. Interestingly, a pathologic evaluation of postmortem brain tissue in over 200 persons with GBM by Greutter *et al.* [299] found neuropathologic changes consistent with AD in tumor-adjacent cerebral cortex in 106 out of 205 (52%) patients. The authors speculate that this might be attributable to accelerated brain aging brought on by GBM treatment. Manipulating identical mitochondrial and immune pathways in opposite directions may be viable ways of treating AD and GBM, respectively, so that a breakthrough in one may lead to insights into the other [300]. Further, innovative techniques for blood-brain barrier-penetrating targeted delivery of treatment may be applied to both GBM and AD [301].

Conclusion

GBM is a highly aggressive primary brain tumor that carries a poor prognosis despite the gold standard treatment regimen of surgical resection, radiotherapy, and chemotherapy. Our understanding of the molecular mechanisms and pathogenesis allows for the characterization of tumors and the prediction of progression and natural history, but this has not led to any major increases in survival. The need for further research on treatments and breakthroughs to prolong the lifespan and improve the quality of life of individuals with GBM is crucial and highlighted throughout this review. Advances in surgical approaches, more accurate radiological techniques and the creation of personalized treatment plans that include tumor vaccines and targeted drug delivery are all indications of progress, but ultimately, residual tumor prevails. As new cutting-edge methodologies are developed, there is hope for a pathway to eliminate all tumor cells so that recurrence is prevented.

Availability of Data and Materials

Not applicable.

Author Contributions

ABR, SG, JD and DGP conceived the review. ABR and AS supervised. ABR, SG, SH, AZD and AS performed the literature research. AP contributed to visualizing and preparing the figures. ABR, SG, AZD and DGP were in-

volved in drafting the manuscript. ABR, DGP, SH, JD, AS and AP revised the manuscript and added critically important intellectual content. Visualization was conducted by SH and DGP. All authors have given final approval for the version to be published. All authors have participated sufficiently in the work to take public responsibility for its content and agreed to be accountable for all aspects of this work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors would like to thank Edmonds Bafford, Dolores McCormack, Anita Greiner and The Buescher family. We thank Dr. Amy Glass for her assistance with references.

Funding

This work was supported by The Alzheimer's Foundation of America Award AWD00004772 and The Herb and Evelyn Abrams Family Amyloid Research Fund.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Ladomersky E, Scholtens DM, Kocherginsky M, Hibler EA, Bartom ET, Otto-Meyer S, *et al*. The Coincidence Between Increasing Age, Immunosuppression, and the Incidence of Patients With Glioblastoma. Frontiers in Pharmacology. 2019; 10: 200. https://doi.org/10.3389/fphar.2019.00200.

[2] Kim M, Ladomersky E, Mozny A, Kocherginsky M, O'Shea K, Reinstein ZZ, *et al*. Glioblastoma as an age-related neurological disorder in adults. Neuro-oncology Advances. 2021; 3: vdab125. https://doi.org/10.1093/noajnl/vdab125.

[3] Fyllingen EH, Bø LE, Reinertsen I, Jakola AS, Sagberg LM, Berntsen EM, *et al*. Survival of glioblastoma in relation to tumor location: a statistical tumor atlas of a population-based cohort. Acta Neurochirurgica. 2021; 163: 1895–1905. https://doi.org/10.1007/s00701-021-04802-6.

[4] Wee CW, Lee JH, Lee HI, Kim J, Chang JH, Kang SG, *et al*. To Use or Not to Use: Temozolomide in Elderly Patients with IDH Wild-Type MGMT Promoter Unmethylated Glioblastoma Treated with Radiotherapy. Cancer Research and Treatment. 2025; 57: 693–700. https://doi.org/10.4143/crt.2024.945.

[5] Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, *et al*. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015-2019. Neuro-oncology. 2022; 24: v1–v95. https://doi.org/10.1093/neuonc/noac202.

[6] Cini NT, Pennisi M, Genc S, Spandidos DA, Falzone L, Mitsias PD, *et al*. Glioma lateralization: Focus on the anatomical localization and the distribution of molecular alterations (Review). Oncology Reports. 2024; 52: 139. https://doi.org/10.3892/or.2024.8798.

[7] Dunn GP, Rinne ML, Wykosky J, Genovese G, Quayle SN, Dunn IF, *et al*. Emerging insights into the molecular and cellular basis of glioblastoma. Genes & Development. 2012; 26: 756–784. https://doi.org/10.1101/gad.187922.112.

[8] Colopi A, Fuda S, Santi S, Onorato A, Cesarini V, Salvati M, *et al*. Impact of age and gender on glioblastoma onset, progression, and management. Mechanisms of Ageing and Development. 2023; 211: 111801. https://doi.org/10.1016/j.mad.2023.111801.

[9] Grochans S, Cybulska AM, Simińska D, Korbecki J, Kojder K, Chlubek D, *et al*. Epidemiology of Glioblastoma Multiforme-Literature Review. Cancers. 2022; 14: 2412. https://doi.org/10.3390/cancers14102412.

[10] Stubbs NM, Garner JA, Akinwunmi-Williams T, Jani J, Ngo S, Ma T, *et al*. Financial Toxicity in High-Grade Glioma Resection: A Retrospective Analysis. World Neurosurgery. 2025; 194: 123477. https://doi.org/10.1016/j.wneu.2024.11.060.

[11] Tini P, Rubino G, Pastina P, Chibbaro S, Cerase A, Marampon F, *et al*. Challenges and Opportunities in Accessing Surgery for Glioblastoma in Low-Middle Income Countries: A Narrative Review. Cancers. 2024; 16: 2870. https://doi.org/10.3390/cancers16162870.

[12] Gorenflo MP, Shen A, Murphy ES, Cullen J, Yu JS. Area-level socioeconomic status is positively correlated with glioblastoma incidence and prognosis in the United States. Frontiers in Oncology. 2023; 13: 1110473. https://doi.org/10.3389/fonc.2023.1110473.

[13] Vienne-Jumeau A, Tafani C, Ricard D. Environmental risk factors of primary brain tumors: A review. Revue Neurologique. 2019; 175: 664–678. https://doi.org/10.1016/j.neurol.2019.08.004.

[14] Hirata T, Umekawa M, Shinya Y, Hasegawa H, Katano A, Shinozaki-Ushiku A, *et al*. Radiation-induced malignancies after stereotactic radiosurgery for brain arteriovenous malformations: a large single-center retrospective study and systematic review. Neurosurgical Review. 2024; 47: 870. https://doi.org/10.1007/s10143-024-03093-6.

[15] Mitchell M, Restrepo-Orozco A, Verhey LH, Vitaz T. Long-term survival in a patient with Li-Fraumeni syndrome-associated giant cell glioblastoma treated with nivolumab: illustrative case. Journal of Neurosurgery. Case Lessons. 2024; 8: CASE24539. https://doi.org/10.3171/CASE24539.

[16] Wang LB, Karpova A, Gritsenko MA, Kyle JE, Cao S, Li Y, *et al*. Proteogenomic and metabolomic characterization of human glioblastoma. Cancer Cell. 2021; 39: 509–528.e20. https://doi.org/10.1016/j.ccell.2021.01.006.

[17] de Andrade KC, Strande NT, Kim J, Haley JS, Hatton JN, Frone MN, *et al*. Genome-first approach of the prevalence and cancer phenotypes of pathogenic or likely pathogenic germline TP53 variants. HGG Advances. 2024; 5: 100242. https://doi.org/10.1016/j.xhgg.2023.100242.

[18] Zhang Y, Dube C, Gibert M, Jr, Cruickshanks N, Wang B, Coughlan M, *et al*. The p53 Pathway in Glioblastoma. Cancers. 2018; 10: 297. https://doi.org/10.3390/cancers10090297.

[19] Orr BA, Clay MR, Pinto EM, Kesserwan C. An update on the central nervous system manifestations of Li-Fraumeni syndrome. Acta Neuropathologica. 2020; 139: 669–687. https://doi.org/10.1007/s00401-019-02055-3.

[20] Wang C, Chen J, Wang Y, Luo N, Han T, Yin X, *et al*. Genetic and clinical characteristics of genetic tumor syndromes in the central nervous system cancers: Implications for clinical practice. iScience. 2024; 27: 111073. https://doi.org/10.1016/j.isci.2024.111073.

[21] Reed MR, Lyle AG, De Loose A, Maddukuri L, Learned K, Beale HC, *et al*. A Functional Precision Medicine Pipeline Com-

bines Comparative Transcriptomics and Tumor Organoid Modeling to Identify Bespoke Treatment Strategies for Glioblastoma. Cells. 2021; 10: 3400. https://doi.org/10.3390/cells10123400.

[22] Derakhshan N, Azadeh N, Saffarian A, Taghipour M, Eghbal K, Dehghanian A. Cerebellar glioblastoma multiforme in an adult patient with neurofibromatosis type 1: an extremely rare report with review of literature. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2019; 55: 85. https://doi.org/10.1186/s41983-019-0135-2.

[23] Ayasa LA, Rahhal S, Najjar AK, Suboh BN, Aliwaiai M, Daqour AM, *et al*. Glioblastoma multiforme in a patient with neurofibromatosis type 1: a case report and review of literature. Journal of Surgical Case Reports. 2024; 2024: rjae517. https://doi.org/10.1093/jscr/rjae517.

[24] Chang M, Sherief M, Ioannou M, Chinnasamy V, Chen L, Frost M, *et al*. NF1 expression profiling in IDH-wildtype glioblastoma: genomic associations and survival outcomes. Acta Neuropathologica Communications. 2024; 12: 172. https://doi.org/10.1186/s40478-024-01875-z.

[25] Costa ADA, Gutmann DH. Brain tumors in Neurofibromatosis type 1. Neuro-oncology Advances. 2019; 1: vdz040. https://doi.org/10.1093/noajnl/vdz040.

[26] Basindwah S, Alkhalidi H, Abdelwarith A, Elwatidy S. Ten-year survival in glioblastoma patient with neurofibromatosis type 1: illustrative case. Journal of Neurosurgery. Case Lessons. 2022; 3: CASE21630. https://doi.org/10.3171/CASE21630.

[27] Lebrun C, Olschwang S, Jeannin S, Vandenbos F, Sobol H, Frenay M. Turcot syndrome confirmed with molecular analysis. European Journal of Neurology. 2007; 14: 470–472. https://doi.org/10.1111/j.1468-1331.2006.01669.x.

[28] Malbari F, Lindsay H. Genetics of Common Pediatric Brain Tumors. Pediatric Neurology. 2020; 104: 3–12. https://doi.org/10.1016/j.pediatrneurol.2019.08.004.

[29] Dipro S, Al-Otaibi F, Alzahrani A, Ulhaq A, Al Shail E. Turcot syndrome: a synchronous clinical presentation of glioblastoma multiforme and adenocarcinoma of the colon. Case Reports in Oncological Medicine. 2012; 2012: 720273. https://doi.org/10.1155/2012/720273.

[30] Wetzel EA, Nohman AI, Hsieh AL, Reuss D, Unterberg AW, Eyüpoglu IY, *et al*. A multi-center, clinical analysis of IDH-mutant gliomas, WHO Grade 4: implications for prognosis and clinical trial design. Journal of Neuro-oncology. 2025; 171: 373–381. https://doi.org/10.1007/s11060-024-04852-7.

[31] Rudà R, Capper D, Waldman AD, Pallud J, Minniti G, Kaley TJ, *et al*. EANO - EURACAN - SNO Guidelines on circumscribed astrocytic gliomas, glioneuronal, and neuronal tumors. Neuro-oncology. 2022; 24: 2015–2034. https://doi.org/10.1093/neuonc/noac188.

[32] Chen J, Dahiya SM. Update on Circumscribed Gliomas and Glioneuronal Tumors. Surgical Pathology Clinics. 2020; 13: 249–266. https://doi.org/10.1016/j.path.2020.02.004.

[33] Lan Z, Li X, Zhang X. Glioblastoma: An Update in Pathology, Molecular Mechanisms and Biomarkers. International Journal of Molecular Sciences. 2024; 25: 3040. https://doi.org/10.3390/ijms25053040.

[34] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, *et al*. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-oncology. 2021; 23: 1231–1251. https://doi.org/10.1093/neuonc/noab106.

[35] Stoyanov GS, Lyutfi E, Georgieva R, Georgiev R, Dzhenkov DL, Petkova L, *et al*. Reclassification of Glioblastoma Multiforme According to the 2021 World Health Organization Classification of Central Nervous System Tumors: A Single Institution Report and Practical Significance. Cureus. 2022; 14: e21822. https://doi.org/10.7759/cureus.21822.

[36] van Opijnen MP, Tesileanu CMS, Dirven L, van der Meer PB, Wijnenga MMJ, Vincent AJPE, *et al*. IDH1/2 wildtype gliomas grade 2 and 3 with molecular glioblastoma-like profile have a distinct course of epilepsy compared to IDH1/2 wildtype glioblastomas. Neuro-oncology. 2023; 25: 701–709. https://doi.org/10.1093/neuonc/noac197.

[37] Olympios N, Gilard V, Marguet F, Clatot F, Di Fiore F, Fontanilles M. *TERT* Promoter Alterations in Glioblastoma: A Systematic Review. Cancers. 2021; 13: 1147. https://doi.org/10.3390/cancers13051147.

[38] Mahmoud AB, Ajina R, Aref S, Darwish M, Alsayb M, Taher M, *et al*. Advances in immunotherapy for glioblastoma multiforme. Frontiers in Immunology. 2022; 13: 944452. https://doi.org/10.3389/fimmu.2022.944452.

[39] Yoon HG, Cheong JH, Ryu JI, Won YD, Min KW, Han MH. The genes significantly associated with an improved prognosis and long-term survival of glioblastoma. PloS One. 2023; 18: e0295061. https://doi.org/10.1371/journal.pone.0295061.

[40] Fathi Kazerooni A, Akbari H, Hu X, Bommineni V, Grigoriadis D, Toorens E, *et al*. The radiogenomic and spatiogenomic landscapes of glioblastoma and their relationship to oncogenic drivers. Communications Medicine. 2025; 5: 55. https://doi.org/10.1038/s43856-025-00767-0.

[41] Khedri A, Guo S, Ramar V, Hudson B, Liu M. FOSL1's Oncogene Roles in Glioma/Glioma Stem Cells and Tumorigenesis: A Comprehensive Review. International Journal of Molecular Sciences. 2024; 25: 5362. https://doi.org/10.3390/ijms25105362.

[42] Ahanger AB, Aalam SW, Masoodi TA, Shah A, Khan MA, Bhat AA, *et al*. Radiogenomics and machine learning predict oncogenic signaling pathways in glioblastoma. Journal of Translational Medicine. 2025; 23: 121. https://doi.org/10.1186/s12967-025-06101-5.

[43] Alshammari QA, Alshammari SO, Alshammari A, Alfarhan M, Baali FH. Unraveling the mechanisms of glioblastoma's resistance: investigating the influence of tumor suppressor p53 and non-coding RNAs. Naunyn-Schmiedeberg's Archives of Pharmacology. 2025; 398: 2569–2585. https://doi.org/10.1007/s00210-024-03564-z.

[44] Murugan AK, Kannan S, Alzahrani AS. Immune checkpoint expression and therapeutic implications in IDH1-mutant and wild-type glioblastomas. Current Problems in Cancer. 2025; 55: 101182. https://doi.org/10.1016/j.currproblcancer.2025.101182.

[45] Sun P, Liu F, Huo K, Wang J, Cheng Y, Shang S, *et al*. Adiponectin facilitates the cell cycle, inhibits cell apoptosis and induces temozolomide resistance in glioblastoma via the Akt/mTOR pathway. Oncology Letters. 2025; 29: 127. https://doi.org/10.3892/ol.2025.14875.

[46] Ahir BK, Engelhard HH, Lakka SS. Tumor Development and Angiogenesis in Adult Brain Tumor: Glioblastoma. Molecular Neurobiology. 2020; 57: 2461–2478. https://doi.org/10.1007/s12035-020-01892-8.

[47] Xue Z, Zhang X, Mao B, Mu G, Zhang Y, Liu J, *et al*. Dual role of WNT10A in promoting the malignancy of glioblastoma and remodeling the tumor microenvironment. Neuro-oncology. 2025; noaf075. https://doi.org/10.1093/neuonc/noaf075.

[48] Thanh HD, Lee S, Nguyen TT, Huu TN, Ahn EJ, Cho SH, *et al*. Temozolomide promotes matrix metalloproteinase 9 expression through p38 MAPK and JNK pathways in glioblastoma cells. Scientific Reports. 2024; 14: 14341. https://doi.org/10.1038/s41598-024-65398-2.

[49] Burghardt I, Ventura E, Weiss T, Schroeder JJ, Seystahl K, Zielasek C, *et al*. Endoglin and TGF-β signaling in glioblastoma. Cell and Tissue Research. 2021; 384: 613–624. https://doi.org/10.1007/s00441-020-03323-5.

[50] Begagić E, Bečulić H, Džidić-Krivić A, Kadić Vukas S, Hadžić S, Mekić-Abazović A, *et al*. Understanding the Significance of

Hypoxia-Inducible Factors (HIFs) in Glioblastoma: A Systematic Review. Cancers. 2024; 16: 2089. https://doi.org/10.3390/cancers16112089.

[51] Yin N, Xie T, Zhang H, Chen J, Yu J, Liu F. IDH1-R132H mutation radiosensitizes U87MG glioma cells via epigenetic down-regulation of TIGAR. Oncology Letters. 2020; 19: 1322–1330. https://doi.org/10.3892/ol.2019.11148.

[52] Fares J, Wan Y, Mair R, Price SJ. Molecular diversity in isocitrate dehydrogenase-wild-type glioblastoma. Brain Communications. 2024; 6: fcae108. https://doi.org/10.1093/braincomms/fcae108.

[53] Lee SH, Kim TG, Ryu KH, Kim SH, Kim YZ. *CDKN2A* Homozygous Deletion Is a Stronger Predictor of Outcome than *IDH1/2*-Mutation in CNS WHO Grade 4 Gliomas. Biomedicines. 2024; 12: 2256. https://doi.org/10.3390/biomedicines12102256.

[54] Giunco S, Padovan M, Angelini C, Cavallin F, Cerretti G, Morello M, *et al*. Prognostic role and interaction of TERT promoter status, telomere length and MGMT promoter methylation in newly diagnosed IDH wild-type glioblastoma patients. ESMO Open. 2023; 8: 101570. https://doi.org/10.1016/j.esmoop.2023.101570.

[55] Terzi NK, Yilmaz I, Oz AB. The Place and Prognostic Value of TERT Promoter Mutation in Molecular Classification in Grade II-III Glial Tumors and Primary Glioblastomas. Turk Patoloji Dergisi. 2022; 38: 90–98. https://doi.org/10.5146/tjpath.2021.01555.

[56] Shay JW, Wright WE. Telomeres and telomerase: three decades of progress. Nature Reviews. Genetics. 2019; 20: 299–309. https://doi.org/10.1038/s41576-019-0099-1.

[57] Kim S, Chowdhury T, Yu HJ, Kahng JY, Lee CE, Choi SA, *et al*. The telomere maintenance mechanism spectrum and its dynamics in gliomas. Genome Medicine. 2022; 14: 88. https://doi.org/10.1186/s13073-022-01095-x.

[58] Kikuchi Z, Shibahara I, Yamaki T, Yoshioka E, Shofuda T, Ohe R, *et al*. *TERT* promoter mutation associated with multifocal phenotype and poor prognosis in patients with *IDH* wild-type glioblastoma. Neuro-oncology Advances. 2020; 2: vdaa114. https://doi.org/10.1093/noajnl/vdaa114.

[59] Wijnenga MMJ, Dubbink HJ, French PJ, Synhaeve NE, Dinjens WNM, Atmodimedjo PN, *et al*. Molecular and clinical heterogeneity of adult diffuse low-grade IDH wild-type gliomas: assessment of TERT promoter mutation and chromosome 7 and 10 copy number status allows superior prognostic stratification. Acta Neuropathologica. 2017; 134: 957–959. https://doi.org/10.1007/s00401-017-1781-z.

[60] Dundar B, Alsawas M, Masaadeh A, Conway K, Snow AN, Sompallae RR, *et al*. Molecular characterization and survival analysis of a cohort of glioblastoma, IDH-wildtype. Pathology, Research and Practice. 2024; 257: 155272. https://doi.org/10.1016/j.prp.2024.155272.

[61] Ohba S, Kuwahara K, Yamada S, Abe M, Hirose Y. Correlation between IDH, ATRX, and TERT promoter mutations in glioma. Brain Tumor Pathology. 2020; 37: 33–40. https://doi.org/10.1007/s10014-020-00360-4.

[62] Rosso I, Jones-Weinert C, Rossiello F, Cabrini M, Brambillasca S, Munoz-Sagredo L, *et al*. Alternative lengthening of telomeres (ALT) cells viability is dependent on C-rich telomeric RNAs. Nature Communications. 2023; 14: 7086. https://doi.org/10.1038/s41467-023-42831-0.

[63] Hölzl D, Hutarew G, Zellinger B, Alinger-Scharinger B, Schlicker HU, Schwartz C, *et al*. *EGFR* Amplification Is a Phenomenon of *IDH* Wildtype and *TERT* Mutated High-Grade Glioma: An Integrated Analysis Using Fluorescence In Situ Hybridization and DNA Methylome Profiling. Biomedicines. 2022; 10: 794. https://doi.org/10.3390/biomedicines10040794.

[64] Rodriguez SMB, Kamel A, Ciubotaru GV, Onose G, Sevastre AS, Sfredel V, *et al*. An Overview of EGFR Mechanisms and Their Implications in Targeted Therapies for Glioblastoma. International Journal of Molecular Sciences. 2023; 24: 11110. https://doi.org/10.3390/ijms241311110.

[65] Pan PC, Magge RS. Mechanisms of EGFR Resistance in Glioblastoma. International Journal of Molecular Sciences. 2020; 21: 8471. https://doi.org/10.3390/ijms21228471.

[66] An Z, Aksoy O, Zheng T, Fan QW, Weiss WA. Epidermal growth factor receptor and EGFRvIII in glioblastoma: signaling pathways and targeted therapies. Oncogene. 2018; 37: 1561–1575. https://doi.org/10.1038/s41388-017-0045-7.

[67] Boyd PS, Struve N, Bach M, Eberle JP, Gote M, Schock F, *et al*. Clustered localization of EGFRvIII in glioblastoma cells as detected by high precision localization microscopy. Nanoscale. 2016; 8: 20037–20047. https://doi.org/10.1039/c6nr05880a.

[68] Keller S, Schmidt MHH. EGFR and EGFRvIII Promote Angiogenesis and Cell Invasion in Glioblastoma: Combination Therapies for an Effective Treatment. International Journal of Molecular Sciences. 2017; 18: 1295. https://doi.org/10.3390/ijms18061295.

[69] Li J, Liang R, Song C, Xiang Y, Liu Y. Prognostic significance of epidermal growth factor receptor expression in glioma patients. OncoTargets and Therapy. 2018; 11: 731–742. https://doi.org/10.2147/OTT.S155160.

[70] Álvarez-Vázquez A, San-Segundo L, Cerveró-García P, Flores-Hernández R, Ollauri-Ibáñez C, Segura-Collar B, *et al*. EGFR amplification and EGFRvIII predict and participate in TAT-Cx43266-283 antitumor response in preclinical glioblastoma models. Neuro-oncology. 2024; 26: 1230–1246. https://doi.org/10.1093/neuonc/noae060.

[71] Felsberg J, Hentschel B, Kaulich K, Gramatzki D, Zacher A, Malzkorn B, *et al*. Epidermal Growth Factor Receptor Variant III (EGFRvIII) Positivity in *EGFR*-Amplified Glioblastomas: Prognostic Role and Comparison between Primary and Recurrent Tumors. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2017; 23: 6846–6855. https://doi.org/10.1158/1078-0432.CCR-17-0890.

[72] Hoogstrate Y, Ghisai SA, de Wit M, de Heer I, Draaisma K, van Riet J, *et al*. The EGFRvIII transcriptome in glioblastoma: A meta-omics analysis. Neuro-oncology. 2022; 24: 429–441. https://doi.org/10.1093/neuonc/noab231.

[73] Ezzati S, Salib S, Balasubramaniam M, Aboud O. Epidermal Growth Factor Receptor Inhibitors in Glioblastoma: Current Status and Future Possibilities. International Journal of Molecular Sciences. 2024; 25: 2316. https://doi.org/10.3390/ijms25042316.

[74] Jones JJ, Nguyen H, Wong SQ, Whittle J, Iaria J, Stylli S, *et al*. Plasma ctDNA liquid biopsy of IDH1, TERTp, and EGFRvIII mutations in glioma. Neuro-oncology Advances. 2024; 6: vdae027. https://doi.org/10.1093/noajnl/vdae027.

[75] Biserova K, Jakovlevs A, Uljanovs R, Strumfa I. Cancer Stem Cells: Significance in Origin, Pathogenesis and Treatment of Glioblastoma. Cells. 2021; 10: 621. https://doi.org/10.3390/cells10030621.

[76] Boyd NH, Tran AN, Bernstock JD, Etminan T, Jones AB, Gillespie GY, *et al*. Glioma stem cells and their roles within the hypoxic tumor microenvironment. Theranostics. 2021; 11: 665–683. https://doi.org/10.7150/thno.41692.

[77] De Silva MI, Stringer BW, Bardy C. Neuronal and tumourigenic boundaries of glioblastoma plasticity. Trends in Cancer. 2023; 9: 223–236. https://doi.org/10.1016/j.trecan.2022.10.010.

[78] Bikfalvi A, da Costa CA, Avril T, Barnier JV, Bauchet L, Brisson L, *et al*. Challenges in glioblastoma research: focus on the tumor microenvironment. Trends in Cancer. 2023; 9: 9–27. https://doi.org/10.1016/j.trecan.2022.09.005.

[79] Schiffer D, Annovazzi L, Casalone C, Corona C, Mellai M. Glioblastoma: Microenvironment and Niche Concept. Cancers. 2018; 11: 5. https://doi.org/10.3390/cancers11010005.

[80] Fei X, Wu J, Tian H, Jiang D, Chen H, Yan K, *et al*. Glioma stem cells remodel immunotolerant microenvironment in GBM and are associated with therapeutic advancements. Cancer Biomarkers: Section a of Disease Markers. 2024; 41: 1–24. https://doi.org/10.3233/CBM-230486.

[81] Hermelo I, Virtanen T, Salonen I, Nätkin R, Keitaanniemi S, Tiihonen AM, *et al*. Unsupervised clustering reveals noncanonical myeloid cell subsets in the brain tumor microenvironment. Cancer Immunology, Immunotherapy: CII. 2025; 74: 63. https://doi.org/10.1007/s00262-024-03920-1.

[82] Onubogu U, Gatenbee CD, Prabhakaran S, Wolfe KL, Oakes B, Salatino R, *et al*. Spatial analysis of recurrent glioblastoma reveals perivascular niche organization. JCI Insight. 2024; 9: e179853. https://doi.org/10.1172/jci.insight.179853.

[83] Hausmann D, Hoffmann DC, Venkataramani V, Jung E, Horschitz S, Tetzlaff SK, *et al*. Autonomous rhythmic activity in glioma networks drives brain tumour growth. Nature. 2023; 613: 179–186. https://doi.org/10.1038/s41586-022-05520-4.

[84] Venkataramani V, Yang Y, Schubert MC, Reyhan E, Tetzlaff SK, Wißmann N, *et al*. Glioblastoma hijacks neuronal mechanisms for brain invasion. Cell. 2022; 185: 2899–2917.e31. https://doi.org/10.1016/j.cell.2022.06.054.

[85] Venkatesh HS, Morishita W, Geraghty AC, Silverbush D, Gillespie SM, Arzt M, *et al*. Electrical and synaptic integration of glioma into neural circuits. Nature. 2019; 573: 539–545. https://doi.org/10.1038/s41586-019-1563-y.

[86] Venkataramani V, Tanev DI, Strahle C, Studier-Fischer A, Fankhauser L, Kessler T, *et al*. Glutamatergic synaptic input to glioma cells drives brain tumour progression. Nature. 2019; 573: 532–538. https://doi.org/10.1038/s41586-019-1564-x.

[87] Venkatesh HS, Johung TB, Caretti V, Noll A, Tang Y, Nagaraja S, *et al*. Neuronal Activity Promotes Glioma Growth through Neuroligin-3 Secretion. Cell. 2015; 161: 803–816. https://doi.org/10.1016/j.cell.2015.04.012.

[88] Noch EK, Sait SF, Farooq S, Trippett TM, Miller AM. A case series of extraneural metastatic glioblastoma at Memorial Sloan Kettering Cancer Center. Neuro-oncology Practice. 2021; 8: 325–336. https://doi.org/10.1093/nop/npaa083.

[89] Pasquier B, Pasquier D, N'Golet A, Panh MH, Couderc P. Extraneural metastases of astrocytomas and glioblastomas: clinicopathological study of two cases and review of literature. Cancer. 1980; 45: 112–125. https://doi.org/10.1002/1097-0142(19800101)45:1<112::aid-cncr2820450121>3.0.co;2-9.

[90] Sullivan JP, Nahed BV, Madden MW, Oliveira SM, Springer S, Bhere D, *et al*. Brain tumor cells in circulation are enriched for mesenchymal gene expression. Cancer Discovery. 2014; 4: 1299–1309. https://doi.org/10.1158/2159-8290.CD-14-0471.

[91] Müller C, Holtschmidt J, Auer M, Heitzer E, Lamszus K, Schulte A, *et al*. Hematogenous dissemination of glioblastoma multiforme. Science Translational Medicine. 2014; 6: 247ra101. https://doi.org/10.1126/scitranslmed.3009095.

[92] Hambardzumyan D, Bergers G. Glioblastoma: Defining Tumor Niches. Trends in Cancer. 2015; 1: 252–265. https://doi.org/10.1016/j.trecan.2015.10.009.

[93] Srivastava R, Dodda M, Zou H, Li X, Hu B. Tumor Niches: Perspectives for Targeted Therapies in Glioblastoma. Antioxidants & Redox Signaling. 2023; 39: 904–922. https://doi.org/10.1089/ars.2022.0187.

[94] Uribe D, Niechi I, Rackov G, Erices JI, San Martín R, Quezada C. Adapt to Persist: Glioblastoma Microenvironment and Epigenetic Regulation on Cell Plasticity. Biology. 2022; 11: 313. https://doi.org/10.3390/biology11020313.

[95] Jung E, Osswald M, Ratliff M, Dogan H, Xie R, Weil S, *et al*. Tumor cell plasticity, heterogeneity, and resistance in crucial microenvironmental niches in glioma. Nature Communications. 2021; 12: 1014. https://doi.org/10.1038/s41467-021-21117-3.

[96] Ghochani Y, Muthukrishnan SD, Sohrabi A, Kawaguchi R, Condro MC, Bastola S, *et al*. A molecular interactome of the glioblastoma perivascular niche reveals integrin binding sialoprotein as a mediator of tumor cell migration. Cell Reports. 2022; 41: 111511. https://doi.org/10.1016/j.celrep.2022.111511.

[97] Kristoffersen K, Villingshøj M, Poulsen HS, Stockhausen MT. Level of Notch activation determines the effect on growth and stem cell-like features in glioblastoma multiforme neurosphere cultures. Cancer Biology & Therapy. 2013; 14: 625–637. https://doi.org/10.4161/cbt.24595.

[98] Kots AY, Bian K. Regulation and Pharmacology of the Cyclic GMP and Nitric Oxide Pathway in Embryonic and Adult Stem Cells. Cells. 2024; 13: 2008. https://doi.org/10.3390/cells13232008.

[99] Charles N, Ozawa T, Squatrito M, Bleau AM, Brennan CW, Hambardzumyan D, *et al*. Perivascular nitric oxide activates notch signaling and promotes stem-like character in PDGF-induced glioma cells. Cell Stem Cell. 2010; 6: 141–152. https://doi.org/10.1016/j.stem.2010.01.001.

[100] Aderetti DA, Hira VVV, Molenaar RJ, van Noorden CJF. The hypoxic peri-arteriolar glioma stem cell niche, an integrated concept of five types of niches in human glioblastoma. Biochimica et Biophysica Acta. Reviews on Cancer. 2018; 1869: 346–354. https://doi.org/10.1016/j.bbcan.2018.04.008.

[101] Staberg M, Michaelsen SR, Olsen LS, Nedergaard MK, Villingshøj M, Stockhausen MT, *et al*. Combined EGFR- and notch inhibition display additive inhibitory effect on glioblastoma cell viability and glioblastoma-induced endothelial cell sprouting in vitro. Cancer Cell International. 2016; 16: 34. https://doi.org/10.1186/s12935-016-0309-2.

[102] Deng Y, Yuan Z, Jin X, Wang Z, Gong R, Ren S, *et al*. Synapsin III promotes neuronal-like transdifferentiation of glioblastoma stem cells by disrupting JAG1-Notch1 interaction. Neuro-oncology. 2025; noaf056. https://doi.org/10.1093/neuonc/noaf056. (online ahead of print)

[103] Bazzoni R, Bentivegna A. Role of Notch Signaling Pathway in Glioblastoma Pathogenesis. Cancers. 2019; 11: 292. https://doi.org/10.3390/cancers11030292.

[104] Mazurek M, Rola R. The implications of nitric oxide metabolism in the treatment of glial tumors. Neurochemistry International. 2021; 150: 105172. https://doi.org/10.1016/j.neuint.2021.105172.

[105] Ho IAW, Shim WSN. Contribution of the Microenvironmental Niche to Glioblastoma Heterogeneity. BioMed Research International. 2017; 2017: 9634172. https://doi.org/10.1155/2017/9634172.

[106] Rashidi A, Billingham LK, Zolp A, Chia TY, Silvers C, Katz JL, *et al*. Myeloid cell-derived creatine in the hypoxic niche promotes glioblastoma growth. Cell Metabolism. 2024; 36: 62–77.e8. https://doi.org/10.1016/j.cmet.2023.11.013.

[107] Sattiraju A, Kang S, Giotti B, Chen Z, Marallano VJ, Brusco C, *et al*. Hypoxic niches attract and sequester tumor-associated macrophages and cytotoxic T cells and reprogram them for immunosuppression. Immunity. 2023; 56: 1825–1843.e6. https://doi.org/10.1016/j.immuni.2023.06.017.

[108] Feldman L. Hypoxia within the glioblastoma tumor microenvironment: a master saboteur of novel treatments. Frontiers in Immunology. 2024; 15: 1384249. https://doi.org/10.3389/fimmu.2024.1384249.

[109] Marallano VJ, Ughetta ME, Tejero R, Nanda S, Ramalingam R, Stalbow L, *et al*. Hypoxia drives shared and distinct tran-

scriptomic changes in two invasive glioma stem cell lines. Scientific Reports. 2024; 14: 7246. https://doi.org/10.1038/s41598-024-56102-5.

[110] Shi T, Zhu J, Zhang X, Mao X. The Role of Hypoxia and Cancer Stem Cells in Development of Glioblastoma. Cancers. 2023; 15: 2613. https://doi.org/10.3390/cancers15092613.

[111] Diksin M, Smith SJ, Rahman R. The Molecular and Phenotypic Basis of the Glioma Invasive Perivascular Niche. International Journal of Molecular Sciences. 2017; 18: 2342. https://doi.org/10.3390/ijms18112342.

[112] Ren Y, Huang Z, Zhou L, Xiao P, Song J, He P, *et al*. Spatial transcriptomics reveals niche-specific enrichment and vulnerabilities of radial glial stem-like cells in malignant gliomas. Nature Communications. 2023; 14: 1028. https://doi.org/10.1038/s41467-023-36707-6.

[113] Zhang H, Zhou Y, Cui B, Liu Z, Shen H. Novel insights into astrocyte-mediated signaling of proliferation, invasion and tumor immune microenvironment in glioblastoma. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2020; 126: 110086. https://doi.org/10.1016/j.biopha.2020.110086.

[114] Catalano M, Limatola C, Trettel F. Non-neoplastic astrocytes: key players for brain tumor progression. Frontiers in Cellular Neuroscience. 2024; 17: 1352130. https://doi.org/10.3389/fncel.2023.1352130.

[115] Yu C, Hsieh K, Cherry DR, Nehlsen AD, Resende Salgado L, Lazarev S, *et al*. Immune Escape in Glioblastoma: Mechanisms of Action and Implications for Immune Checkpoint Inhibitors and CAR T-Cell Therapy. Biology. 2023; 12: 1528. https://doi.org/10.3390/biology12121528.

[116] Wei J, Barr J, Kong LY, Wang Y, Wu A, Sharma AK, *et al*. Glioblastoma cancer-initiating cells inhibit T-cell proliferation and effector responses by the signal transducers and activators of transcription 3 pathway. Molecular Cancer Therapeutics. 2010; 9: 67–78. https://doi.org/10.1158/1535-7163.MCT-09-0734.

[117] Ispirjan M, Marx S, Freund E, Fleck SK, Baldauf J, Roessler K, *et al*. Markers of tumor-associated macrophages and microglia exhibit high intratumoral heterogeneity in human glioblastoma tissue. Oncoimmunology. 2024; 13: 2425124. https://doi.org/10.1080/2162402X.2024.2425124.

[118] Werner JM, Kuhl S, Ulrich K, Krischek B, Stavrinou P, Goldbrunner R, *et al*. Expression of CD40 Correlates Negatively with Overall and Progression-Free Survival of Low- and High-Grade Gliomas. World Neurosurgery. 2019; 130: e17–e25. https://doi.org/10.1016/j.wneu.2019.05.112.

[119] Ahmed MH, Hernández-Verdin I, Bielle F, Verreault M, Lerond J, Alentorn A, *et al*. Expression and Prognostic Value of CD80 and CD86 in the Tumor Microenvironment of Newly Diagnosed Glioblastoma. The Canadian Journal of Neurological Sciences. Le Journal Canadien des Sciences Neurologiques. 2023; 50: 234–242. https://doi.org/10.1017/cjn.2022.5.

[120] Kilian M, Sheinin R, Tan CL, Friedrich M, Krämer C, Kaminitz A, *et al*. MHC class II-restricted antigen presentation is required to prevent dysfunction of cytotoxic T cells by blood-borne myeloids in brain tumors. Cancer Cell. 2023; 41: 235–251.e9. https://doi.org/10.1016/j.ccell.2022.12.007.

[121] Chonan M, Saito R, Shoji T, Shibahara I, Kanamori M, Sonoda Y, *et al*. CD40/CD40L expression correlates with the survival of patients with glioblastomas and an augmentation in CD40 signaling enhances the efficacy of vaccinations against glioma models. Neuro-oncology. 2015; 17: 1453–1462. https://doi.org/10.1093/neuonc/nov090.

[122] Qi Y, Huang X, Ji C, Wang C, Yao Y. The co-inhibitory immune checkpoint proteins B7-H1(PD-L1) and B7-H4 in high grade glioma: From bench to bedside. Translational Oncology. 2024; 39: 101793. https://doi.org/10.1016/j.tranon.2023.101793.

[123] Du W, Chen D, Wei K, Yu D, Gan Z, Xu G, *et al*. MiR-10b-5p Impairs TET2-Mediated Inhibition of PD-L1 Transcription Thus Promoting Immune Evasion and Tumor Progression in Glioblastoma. The Tohoku Journal of Experimental Medicine. 2023; 260: 205–214. https://doi.org/10.1620/tjem.2023.J028.

[124] Wang F, Yue J, Zhang M, Sun M, Luo X, Zhang H, *et al*. NPRL2 promotes TRIM16-mediated ubiquitination degradation of Galectin-3 to prevent CD8^{+}T lymphocyte cuproptosis in glioma. Cellular and Molecular Life Sciences: CMLS. 2024; 81: 424. https://doi.org/10.1007/s00018-024-05454-2.

[125] Rivera-Ramos A, Cruz-Hernández L, Talaverón R, Sánchez-Montero MT, García-Revilla J, Mulero-Acevedo M, *et al*. Galectin-3 depletion tames pro-tumoural microglia and restrains cancer cells growth. Cancer Letters. 2024; 591: 216879. https://doi.org/10.1016/j.canlet.2024.216879.

[126] Koppenol WH, Bounds PL, Dang CV. Otto Warburg's contributions to current concepts of cancer metabolism. Nature Reviews. Cancer. 2011; 11: 325–337. https://doi.org/10.1038/nrc3038.

[127] Tamas C, Tamas F, Kovecsi A, Cehan A, Balasa A. Metabolic Contrasts: Fatty Acid Oxidation and Ketone Bodies in Healthy Brains vs. Glioblastoma Multiforme. International Journal of Molecular Sciences. 2024; 25: 5482. https://doi.org/10.3390/ijms25105482.

[128] Kathagen A, Schulte A, Balcke G, Phillips HS, Martens T, Matschke J, *et al*. Hypoxia and oxygenation induce a metabolic switch between pentose phosphate pathway and glycolysis in glioma stem-like cells. Acta Neuropathologica. 2013; 126: 763–780. https://doi.org/10.1007/s00401-013-1173-y.

[129] Liu X, Liu X, Dong W, Wang P, Liu L, Liu L, *et al*. KHDRBS1 regulates the pentose phosphate pathway and malignancy of GBM through SNORD51-mediated polyadenylation of ZBED6 pre-mRNA. Cell Death & Disease. 2024; 15: 802. https://doi.org/10.1038/s41419-024-07163-x.

[130] Franceschi S, Lessi F, Morelli M, Menicagli M, Pasqualetti F, Aretini P, *et al*. Correction: Franceschi et al. Sedoheptulose Kinase SHPK Expression in Glioblastoma: Emerging Role of the Nonoxidative Pentose Phosphate Pathway in Tumor Proliferation. *Int. J. Mol. Sci.* 2022, *23*, 5978. International Journal of Molecular Sciences. 2025; 26: 1044. https://doi.org/10.3390/ijms26031044.

[131] Flavahan WA, Wu Q, Hitomi M, Rahim N, Kim Y, Sloan AE, *et al*. Brain tumor initiating cells adapt to restricted nutrition through preferential glucose uptake. Nature Neuroscience. 2013; 16: 1373–1382. https://doi.org/10.1038/nn.3510.

[132] Mi Y, Guo N, Luan J, Cheng J, Hu Z, Jiang P, *et al*. The Emerging Role of Myeloid-Derived Suppressor Cells in the Glioma Immune Suppressive Microenvironment. Frontiers in Immunology. 2020; 11: 737. https://doi.org/10.3389/fimmu.2020.00737.

[133] He X, Guo Y, Yu C, Zhang H, Wang S. Epithelial-mesenchymal transition is the main way in which glioma-associated microglia/macrophages promote glioma progression. Frontiers in Immunology. 2023; 14: 1097880. https://doi.org/10.3389/fimmu.2023.1097880.

[134] Zhang Q, Wang J, Yao X, Wu S, Tian W, Gan C, *et al*. Programmed Cell Death 10 Mediated CXCL2-CXCR2 Signaling in Regulating Tumor-Associated Microglia/Macrophages Recruitment in Glioblastoma. Frontiers in Immunology. 2021; 12: 637053. https://doi.org/10.3389/fimmu.2021.637053.

[135] Fermi V, Warta R, Wöllner A, Lotsch C, Jassowicz L, Rapp C, *et al*. Effective Reprogramming of Patient-Derived M2-Polarized Glioblastoma-Associated Microglia/Macrophages by Treatment with GW2580. Clinical Cancer Research: an Official Journal of the American Association for Cancer Research. 2023; 29: 4685–4697. https://doi.org/10.1158/1078-0432.CCR-23-0576.

[136] Jackson C, Cherry C, Bom S, Dykema AG, Wang R, Thompson E, *et al*. Distinct myeloid-derived suppressor cell populations in human glioblastoma. Science (New York, N.Y.). 2025; 387: eabm5214. https://doi.org/10.1126/science.abm5214.

[137] Alban TJ, Bayik D, Otvos B, Rabljenovic A, Leng L, Jia-Shiun L, *et al*. Glioblastoma Myeloid-Derived Suppressor Cell Subsets Express Differential Macrophage Migration Inhibitory Factor Receptor Profiles That Can Be Targeted to Reduce Immune Suppression. Frontiers in Immunology. 2020; 11: 1191. https://doi.org/10.3389/fimmu.2020.01191.

[138] Kollis PM, Ebert LM, Toubia J, Bastow CR, Ormsby RJ, Poonnoose SI, *et al*. Characterising Distinct Migratory Profiles of Infiltrating T-Cell Subsets in Human Glioblastoma. Frontiers in Immunology. 2022; 13: 850226. https://doi.org/10.3389/fimmu.2022.850226.

[139] van Hooren L, Handgraaf SM, Kloosterman DJ, Karimi E, van Mil LWHG, Gassama AA, *et al*. CD103$^+$ regulatory T cells underlie resistance to radio-immunotherapy and impair CD8$^+$ T cell activation in glioblastoma. Nature Cancer. 2023; 4: 665–681. https://doi.org/10.1038/s43018-023-00547-6.

[140] Currie S, Fatania K, Frood R, Whitehead R, Start J, Lee MT, *et al*. Imaging Spectrum of the Developing Glioblastoma: A Cross-Sectional Observation Study. Current Oncology (Toronto, Ont.). 2023; 30: 6682–6698. https://doi.org/10.3390/curroncol30070490.

[141] Hooper GW, Ansari S, Johnson JM, Ginat DT. Advances in the Radiological Evaluation of and Theranostics for Glioblastoma. Cancers. 2023; 15: 4162. https://doi.org/10.3390/cancers15164162.

[142] Ellingson BM, Bendszus M, Boxerman J, Barboriak D, Erickson BJ, Smits M, *et al*. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro-oncology. 2015; 17: 1188–1198. https://doi.org/10.1093/neuonc/nov095.

[143] De Sutter S, Wuts J, Geens W, Vanbinst AM, Duerinck J, Vandemeulebroucke J. Modality redundancy for MRI-based glioblastoma segmentation. International Journal of Computer Assisted Radiology and Surgery. 2024; 19: 2101–2109. https://doi.org/10.1007/s11548-024-03238-4.

[144] Hosseini SA, Servaes S, Hall B, Bhaduri S, Rajan A, Rosa-Neto P, *et al*. Quantitative Physiologic MRI Combined with Feature Engineering for Developing Machine Learning-Based Prediction Models to Distinguish Glioblastomas from Single Brain Metastases. Diagnostics (Basel, Switzerland). 2024; 15: 38. https://doi.org/10.3390/diagnostics15010038.

[145] Bernstock JD, Gary SE, Klinger N, Valdes PA, Ibn Essayed W, Olsen HE, *et al*. Standard clinical approaches and emerging modalities for glioblastoma imaging. Neuro-oncology Advances. 2022; 4: vdac080. https://doi.org/10.1093/noajnl/vdac080.

[146] Gihr G, Horvath-Rizea D, Hekeler E, Ganslandt O, Henkes H, Hoffmann KT, *et al*. Diffusion weighted imaging in high-grade gliomas: A histogram-based analysis of apparent diffusion coefficient profile. PloS One. 2021; 16: e0249878. https://doi.org/10.1371/journal.pone.0249878.

[147] Cozzi FM, Mayrand RC, Wan Y, Price SJ. Predicting glioblastoma progression using MR diffusion tensor imaging: A systematic review. Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging. 2025; 35: e13251. https://doi.org/10.1111/jon.13251.

[148] Lawrence LSP, Chan RW, Chen H, Stewart J, Ruschin M, Theriault A, *et al*. Diffusion-weighted imaging on an MRI-linear accelerator to identify adversely prognostic tumour regions in glioblastoma during chemoradiation. Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology. 2023; 188: 109873. https://doi.org/10.1016/j.radonc.2023.109873.

[149] Wu J, Su R, Qiu D, Cheng X, Li L, Huang C, *et al*. Analysis of DWI in the classification of glioma pathology and its therapeutic application in clinical surgery: a case-control study. Translational Cancer Research. 2022; 11: 805–812. https://doi.org/10.21037/tcr-22-114.

[150] Rabe M, Dietrich O, Forbrig R, Niyazi M, Belka C, Corradini S, *et al*. Repeatability quantification of brain diffusion-weighted imaging for future clinical implementation at a low-field MR-linac. Radiation Oncology (London, England). 2024; 19: 31. https://doi.org/10.1186/s13014-024-02424-7.

[151] Treglia G, Muoio B, Trevisi G, Mattoli MV, Albano D, Bertagna F, *et al*. Diagnostic Performance and Prognostic Value of PET/CT with Different Tracers for Brain Tumors: A Systematic Review of Published Meta-Analyses. International Journal of Molecular Sciences. 2019; 20: 4669. https://doi.org/10.3390/ijms20194669.

[152] Toyonaga T, Yamaguchi S, Hirata K, Kobayashi K, Manabe O, Watanabe S, *et al*. Hypoxic glucose metabolism in glioblastoma as a potential prognostic factor. European Journal of Nuclear Medicine and Molecular Imaging. 2017; 44: 611–619. https://doi.org/10.1007/s00259-016-3541-z.

[153] Trotter J, Pantel AR, Teo BKK, Escorcia FE, Li T, Pryma DA, *et al*. Positron Emission Tomography (PET)/Computed Tomography (CT) Imaging in Radiation Therapy Treatment Planning: A Review of PET Imaging Tracers and Methods to Incorporate PET/CT. Advances in Radiation Oncology. 2023; 8: 101212. https://doi.org/10.1016/j.adro.2023.101212.

[154] Galldiks N, Lohmann P, Fink GR, Langen KJ. Amino Acid PET in Neurooncology. Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine. 2023; 64: 693–700. https://doi.org/10.2967/jnumed.122.264859.

[155] Drake LR, Hillmer AT, Cai Z. Approaches to PET Imaging of Glioblastoma. Molecules (Basel, Switzerland). 2020; 25: 568. https://doi.org/10.3390/molecules25030568.

[156] Chen Q, Wang K, Ren X, Zhao X, Chen Q, Fan D, *et al*. Individualized discrimination of tumor progression from treatment-related changes in different types of adult-type diffuse gliomas using [^{11}C]methionine PET. Journal of Neuro-oncology. 2023; 165: 547–559. https://doi.org/10.1007/s11060-023-04529-7.

[157] Müller KJ, Forbrig R, Reis J, Wiegand L, Barci E, Kunte SC, *et al*. Measurable disease as baseline criterion for response assessment in glioblastoma: A comparison of PET -based (PET RANO 1.0) and MRI-based (RANO) assessments. Neuro-oncology. 2025; 27: 77–88. https://doi.org/10.1093/neuonc/noae208.

[158] Papin-Michault C, Bonnetaud C, Dufour M, Almairac F, Coutts M, Patouraux S, *et al*. Study of LAT1 Expression in Brain Metastases: Towards a Better Understanding of the Results of Positron Emission Tomography Using Amino Acid Tracers. PloS One. 2016; 11: e0157139. https://doi.org/10.1371/journal.pone.0157139.

[159] Vora S, Pafundi D, Voss M, Buras M, Ashman J, Bendok B, *et al*. Short-course hypofractionated proton beam therapy, incorporating ^{18}F-DOPA PET and contrast-enhanced MRI targeting, for patients aged 65 years and older with newly diagnosed glioblastoma: a single-arm phase 2 trial. The Lancet. Oncology. 2024; 25: 1625–1634. https://doi.org/10.1016/S1470-2045(24)00585-0.

[160] Garelli G, Rovera G, Levis M, Lesca A, Pellerino A, Bruno F, *et al*. [18F]DOPA PET for lesion definition and contouring using different thresholds in patients with gliomas. The Quarterly Journal of Nuclear Medicine and Molecular Imaging: Official Publication of the Italian Association of Nuclear Medicine (AIMN) [and] the International Association of Radiopharmacology (IAR), [and] Section of the Society Of.... 2024; 68: 200–206. https://doi.org/10.23736/S1824-4785.24.03587-8.

[161] Santo G, Laudicella R, Linguanti F, Nappi AG, Abenavoli E, Vergura V, *et al*. The Utility of Conventional Amino Acid PET Radiotracers in the Evaluation of Glioma Recurrence also in Comparison with MRI. Diagnostics (Basel, Switzerland). 2022; 12: 844. https://doi.org/10.3390/diagnostics12040844.

[162] Ort J, Hamou HA, Kernbach JM, Hakvoort K, Blume C, Lohmann P, *et al*. ^{18}F-FET-PET-guided gross total resection improves overall survival in patients with WHO grade III/IV glioma: moving towards a multimodal imaging-guided resection. Journal of Neuro-oncology. 2021; 155: 71–80. https://doi.org/10.1007/s11060-021-03844-1.

[163] Bekaert L, Valable S, Lechapt-Zalcman E, Ponte K, Collet S, Constans JM, *et al*. [18F]-FMISO PET study of hypoxia in gliomas before surgery: correlation with molecular markers of hypoxia and angiogenesis. European Journal of Nuclear Medicine and Molecular Imaging. 2017; 44: 1383–1392. https://doi.org/10.1007/s00259-017-3677-5.

[164] Nigam S, McCarl L, Kumar R, Edinger RS, Kurland BF, Anderson CJ, *et al*. Preclinical ImmunoPET Imaging of Glioblastoma-Infiltrating Myeloid Cells Using Zirconium-89 Labeled Anti-CD11b Antibody. Molecular Imaging and Biology. 2020; 22: 685–694. https://doi.org/10.1007/s11307-019-01427-1.

[165] Liang Y, Voshart D, Paridaen JTML, Oosterhof N, Liang D, Thiruvalluvan A, *et al*. CD146 increases stemness and aggressiveness in glioblastoma and activates YAP signaling. Cellular and Molecular Life Sciences: CMLS. 2022; 79: 398. https://doi.org/10.1007/s00018-022-04420-0.

[166] de Lucas ÁG, Lamminmäki U, López-Picón FR. ImmunoPET Directed to the Brain: A New Tool for Preclinical and Clinical Neuroscience. Biomolecules. 2023; 13: 164. https://doi.org/10.3390/biom13010164.

[167] De Feo MS, Granese GM, Conte M, Palumbo B, Panareo S, Frantellizzi V, *et al*. Immuno-pet for Glioma Imaging: An update. Applied Sciences. 2024; 14: 1391. https://doi.org/10.3390/app14041391.

[168] Dadgar H, Jokar N, Nemati R, Larvie M, Assadi M. PET tracers in glioblastoma: Toward neurotheranostics as an individualized medicine approach. Frontiers in Nuclear Medicine. 2023; 3: 1103262. https://doi.org/10.3389/fnume.2023.1103262.

[169] Boxerman JL, Quarles CC, Hu LS, Erickson BJ, Gerstner ER, Smits M, *et al*. Consensus recommendations for a dynamic susceptibility contrast MRI protocol for use in high-grade gliomas. Neuro-oncology. 2020; 22: 1262–1275. https://doi.org/10.1093/neuonc/noaa141.

[170] Prysiazhniuk Y, Server A, Leske H, Bech-Aase Ø, Helseth E, Eijgelaar RS, *et al*. Diffuse glioma molecular profiling with arterial spin labeling and dynamic susceptibility contrast perfusion MRI: A comparative study. Neuro-oncology Advances. 2024; 6: vdae113. https://doi.org/10.1093/noajnl/vdae113.

[171] Alsaedi A, Doniselli F, Jäger HR, Panovska-Griffiths J, Rojas-Garcia A, Golay X, *et al*. The value of arterial spin labelling in adults glioma grading: systematic review and meta-analysis. Oncotarget. 2019; 10: 1589–1601. https://doi.org/10.18632/oncotarget.26674.

[172] You SH, Yun TJ, Choi HJ, Yoo RE, Kang KM, Choi SH, *et al*. Differentiation between primary CNS lymphoma and glioblastoma: qualitative and quantitative analysis using arterial spin labeling MR imaging. European Radiology. 2018; 28: 3801–3810. https://doi.org/10.1007/s00330-018-5359-5.

[173] Yang X, He D, Li Y, Li C, Wang X, Zhu X, *et al*. Deep learning-based vessel extraction in 3D confocal microscope images of cleared human glioma tissues. Biomedical Optics Express. 2024; 15: 2498–2516. https://doi.org/10.1364/BOE.516541.

[174] Yadav VK, Sharma S, Maurya S, Singh RK, Saini J, Jain P, *et al*. Presence of Fragmented Intratumoral Thrombosed Microvasculature in the Necrotic and Peri-Necrotic Regions on SWI Differentiates IDH Wild-Type Glioblastoma From IDH Mutant Grade 4 Astrocytoma. Journal of Magnetic Resonance Imaging: JMRI. 2025; 62: 258–270. https://doi.org/10.1002/jmri.29695.

[175] Alnahhas I. Molecular Testing in Gliomas: What is Necessary in Routine Clinical Practice? Current Oncology Reports. 2024; 26: 1277–1282. https://doi.org/10.1007/s11912-024-01602-w.

[176] Śledzińska-Bebyn P, Furtak J, Bebyn M, Bartoszewska-Kubiak A, Serafin Z. Investigating glioma genetics through perfusion MRI: rCBV and rCBF as predictive biomarkers. Magnetic Resonance Imaging. 2025; 117: 110318. https://doi.org/10.1016/j.mri.2024.110318.

[177] Wen PY, Weller M, Lee EQ, Alexander BM, Barnholtz-Sloan JS, Barthel FP, *et al*. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro-oncology. 2020; 22: 1073–1113. https://doi.org/10.1093/neuonc/noaa106.

[178] Lee JH, Wee CW. Treatment of Adult Gliomas: A Current Update. Brain & NeuroRehabilitation. 2022; 15: e24. https://doi.org/10.12786/bn.2022.15.e24.

[179] Inggas MAM, Patel U, Wijaya JH, Otinashvili N, Menon VR, Iyer AK, *et al*. The role of temozolomide as adjuvant therapy in glioblastoma management: a systematic review and meta-analysis. BMC Cancer. 2025; 25: 399. https://doi.org/10.1186/s12885-025-13757-1.

[180] Jia JL, Alshamsan B, Ng TL. Temozolomide Chronotherapy in Glioma: A Systematic Review. Current Oncology (Toronto, Ont.). 2023; 30: 1893–1902. https://doi.org/10.3390/curroncol30020147.

[181] SongTao Q, Lei Y, Si G, YanQing D, HuiXia H, XueLin Z, *et al*. IDH mutations predict longer survival and response to temozolomide in secondary glioblastoma. Cancer Science. 2012; 103: 269–273. https://doi.org/10.1111/j.1349-7006.2011.02134.x.

[182] Huang B, Yu Z, Liang R. Effect of long-term adjuvant temozolomide chemotherapy on primary glioblastoma patient survival. BMC Neurology. 2021; 21: 424. https://doi.org/10.1186/s12883-021-02461-9.

[183] Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, *et al*. MGMT gene silencing and benefit from temozolomide in glioblastoma. The New England Journal of Medicine. 2005; 352: 997–1003. https://doi.org/10.1056/NEJMoa043331.

[184] Lee SH, Hofstede RP, Noriega de la Colina A, Gunton JH, Bernstock JD, Traverso G. Implantable systems for neurological chronotherapy. Advanced Drug Delivery Reviews. 2025; 221: 115574. https://doi.org/10.1016/j.addr.2025.115574.

[185] Damato AR, Luo J, Katumba RGN, Talcott GR, Rubin JB, Herzog ED, *et al*. Temozolomide chronotherapy in patients with glioblastoma: a retrospective single-institute study. Neuro-oncology Advances. 2021; 3: vdab041. https://doi.org/10.1093/noajnl/vdab041.

[186] Damato AR, Katumba RGN, Luo J, Atluri H, Talcott GR, Govindan A, *et al*. A randomized feasibility study evaluating temozolomide circadian medicine in patients with glioma. Neuro-oncology Practice. 2022; 9: 193–200. https://doi.org/10.1093/nop/npac003.

[187] Roth P. Treatment of gliomas with temozolomide: Rather at sunrise or sunset? Neuro-oncology Practice. 2022; 9: 161–162. https://doi.org/10.1093/nop/npac024.

[188] Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood-brain barrier: structure, regulation, and drug delivery. Signal Transduction and Targeted Therapy. 2023; 8: 217. https://doi.org/10.1038/s41392-023-01481-w.

[189] Ahmed MH, Canney M, Carpentier A, Idbaih A. Overcom-

ing the blood brain barrier in glioblastoma: Status and future perspective. Revue Neurologique. 2023; 179: 430–436. https://doi.org/10.1016/j.neurol.2023.03.013.

[190] Zhao M, van Straten D, Broekman MLD, Préat V, Schiffelers RM. Nanocarrier-based drug combination therapy for glioblastoma. Theranostics. 2020; 10: 1355–1372. https://doi.org/10.7150/thno.38147.

[191] Afzal O, Altamimi ASA, Nadeem MS, Alzarea SI, Almalki WH, Tariq A, *et al*. Nanoparticles in Drug Delivery: From History to Therapeutic Applications. Nanomaterials (Basel, Switzerland). 2022; 12: 4494. https://doi.org/10.3390/nano12244494.

[192] Tan Q, Zhao S, Xu T, Wang Q, Lan M, Yan L, *et al*. Getting drugs to the brain: advances and prospects of organic nanoparticle delivery systems for assisting drugs to cross the blood-brain barrier. Journal of Materials Chemistry. B. 2022; 10: 9314–9333. https://doi.org/10.1039/d2tb01440h.

[193] Wang S, Yu Y, Wang A, Duan X, Sun Y, Wang L, *et al*. Temozolomide hexadecyl ester targeted plga nanoparticles for drug-resistant glioblastoma therapy via intranasal administration. Frontiers in Pharmacology. 2022; 13: 965789. https://doi.org/10.3389/fphar.2022.965789.

[194] Fang C, Wang K, Stephen ZR, Mu Q, Kievit FM, Chiu DT, *et al*. Temozolomide nanoparticles for targeted glioblastoma therapy. ACS Applied Materials & Interfaces. 2015; 7: 6674–6682. https://doi.org/10.1021/am5092165.

[195] Xie Y, Yang F, He L, Huang H, Chao M, Cao H, *et al*. Single-cell dissection of the human blood-brain barrier and glioma blood-tumor barrier. Neuron. 2024; 112: 3089–3105.e7. https://doi.org/10.1016/j.neuron.2024.07.026.

[196] Jimenez-Macias JL, Vaughn-Beaucaire P, Bharati A, Xu Z, Forrest M, Hong J, *et al*. Modulation of blood-tumor barrier transcriptional programs improves intratumoral drug delivery and potentiates chemotherapy in GBM. Science Advances. 2025; 11: eadr1481. https://doi.org/10.1126/sciadv.adr1481.

[197] Zdioruk M, Jimenez-Macias JL, Nowicki MO, Manz KE, Pennell KD, Koch MS, *et al*. PPRX-1701, a nanoparticle formulation of 6'-bromoindirubin acetoxime, improves delivery and shows efficacy in preclinical GBM models. Cell Reports. Medicine. 2023; 4: 101019. https://doi.org/10.1016/j.xcrm.2023.101019.

[198] Chithra P, Bhatia D, Solanki R. Advanced nanomicelles for targeted glioblastoma multiforme therapy. Biomaterials Advances. 2025; 170: 214221. https://doi.org/10.1016/j.bioadv.2025.214221.

[199] Rana R, Devi SN, Bhardwaj AK, Yashavarddhan MH, Bohra D, Ganguly NK. Exosomes as nature's nano carriers: Promising drug delivery tools and targeted therapy for glioma. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2025; 182: 117754. https://doi.org/10.1016/j.biopha.2024.117754.

[200] Becker AP, Sells BE, Haque SJ, Chakravarti A. Tumor Heterogeneity in Glioblastomas: From Light Microscopy to Molecular Pathology. Cancers. 2021; 13: 761. https://doi.org/10.3390/cancers13040761.

[201] Jiapaer S, Furuta T, Tanaka S, Kitabayashi T, Nakada M. Potential Strategies Overcoming the Temozolomide Resistance for Glioblastoma. Neurologia Medico-chirurgica. 2018; 58: 405–421. https://doi.org/10.2176/nmc.ra.2018-0141.

[202] Haynes T, Gilbert MR, Breen K, Yang C. Pathways to hypermutation in high-grade gliomas: Mechanisms, syndromes, and opportunities for immunotherapy. Neuro-oncology Advances. 2024; 6: vdae105. https://doi.org/10.1093/noajnl/vdae105.

[203] Palizkaran Yazdi M, Barjasteh A, Moghbeli M. MicroRNAs as the pivotal regulators of Temozolomide resistance in glioblastoma. Molecular Brain. 2024; 17: 42. https://doi.org/10.1186/s13041-024-01113-6.

[204] Ghiaseddin A, Peters KB. Use of bevacizumab in recurrent glioblastoma. CNS Oncology. 2015; 4: 157–169. https://doi.org/10.2217/cns.15.8.

[205] Zhang AB, Mozaffari K, Aguirre B, Li V, Kubba R, Desai NC, *et al*. Exploring the Past, Present, and Future of Anti-Angiogenic Therapy in Glioblastoma. Cancers. 2023; 15: 830. https://doi.org/10.3390/cancers15030830.

[206] Fensterle J, Aicher B, Seipelt I, Teifel M, Engel J. Current view on the mechanism of action of perifosine in cancer. Anti-cancer Agents in Medicinal Chemistry. 2014; 14: 629–635. https://doi.org/10.2174/1871520614666140309225912.

[207] Kaley TJ, Panageas KS, Mellinghoff IK, Nolan C, Gavrilovic IT, DeAngelis LM, *et al*. Phase II trial of an AKT inhibitor (perifosine) for recurrent glioblastoma. Journal of Neuro-oncology. 2019; 144: 403–407. https://doi.org/10.1007/s11060-019-03243-7.

[208] Kaley TJ, Panageas KS, Pentsova EI, Mellinghoff IK, Nolan C, Gavrilovic I, *et al*. Phase I clinical trial of temsirolimus and perifosine for recurrent glioblastoma. Annals of Clinical and Translational Neurology. 2020; 7: 429–436. https://doi.org/10.1002/acn3.51009.

[209] Zhao W, Zhou L, Zhao W, Yang H, Lu Z, Zhang L, *et al*. The combination of temozolomide and perifosine synergistically inhibit glioblastoma by impeding DNA repair and inducing apoptosis. Cell Death Discovery. 2024; 10: 315. https://doi.org/10.1038/s41420-024-02085-1.

[210] Miramova A, Gartner A, Ivanov D. How to sensitize glioblastomas to temozolomide chemotherapy: a gap-centered view. Frontiers in Cell and Developmental Biology. 2024; 12: 1436563. https://doi.org/10.3389/fcell.2024.1436563.

[211] Melhem JM, Tahir A, Calabrese E, Granovskaya I, Atenafu EG, Sahgal A, *et al*. Dose-dependent efficacy of bevacizumab in recurrent glioblastoma. Journal of Neuro-oncology. 2023; 161: 633–641. https://doi.org/10.1007/s11060-023-04248-z.

[212] Ramezani S, Vousooghi N, Ramezani Kapourchali F, Joghataei MT. Perifosine enhances bevacizumab-induced apoptosis and therapeutic efficacy by targeting PI3K/AKT pathway in a glioblastoma heterotopic model. Apoptosis: an International Journal on Programmed Cell Death. 2017; 22: 1025–1034. https://doi.org/10.1007/s10495-017-1382-2.

[213] Zhu S, Guo J, Yu L, Liu J, Chen J, Xin J, *et al*. Synergistic effect of cryptotanshinone and temozolomide treatment against human glioblastoma cells. Scientific Reports. 2023; 13: 21835. https://doi.org/10.1038/s41598-023-48777-z.

[214] Garcia-Oliveira P, Otero P, Pereira AG, Chamorro F, Carpena M, Echave J, *et al*. Status and Challenges of Plant-Anticancer Compounds in Cancer Treatment. Pharmaceuticals (Basel, Switzerland). 2021; 14: 157. https://doi.org/10.3390/ph14020157.

[215] Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, *et al*. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. The New England Journal of Medicine. 2005; 352: 987–996. https://doi.org/10.1056/NEJMoa043330.

[216] Ma R, Taphoorn MJB, Plaha P. Advances in the management of glioblastoma. Journal of Neurology, Neurosurgery, and Psychiatry. 2021; 92: 1103–1111. https://doi.org/10.1136/jnnp-2020-325334.

[217] Morello A, Rizzo F, Gatto A, Panico F, Bianconi A, Chiari G, *et al*. Safety and Efficacy in the Transcortical and Transsylvian Approach in Insular High-Grade Gliomas: A Comparative Series of 58 Patients. Current Oncology (Toronto, Ont.). 2025; 32: 98. https://doi.org/10.3390/curroncol32020098.

[218] Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, *et al*. Association of the Extent of Resection With Survival in Glioblastoma: A Systematic Review and Meta-

analysis. JAMA Oncology. 2016; 2: 1460–1469. https://doi.org/10.1001/jamaoncol.2016.1373.

[219] Revilla-Pacheco F, Rodríguez-Salgado P, Barrera-Ramírez M, Morales-Ruiz MP, Loyo-Varela M, Rubalcava-Ortega J, *et al*. Extent of resection and survival in patients with glioblastoma multiforme: Systematic review and meta-analysis. Medicine. 2021; 100: e26432. https://doi.org/10.1097/MD.0000000000026432.

[220] Young JS, Al-Adli NN, Muster R, Chandra A, Morshed RA, Pereira MP, *et al*. Does waiting for surgery matter? How time from diagnostic MRI to resection affects outcomes in newly diagnosed glioblastoma. Journal of Neurosurgery. 2023; 140: 80–93. https://doi.org/10.3171/2023.5.JNS23388.

[221] Gerritsen JKW, Zwarthoed RH, Kilgallon JL, Nawabi NL, Versyck G, Jessurun CAC, *et al*. Impact of maximal extent of resection on postoperative deficits, patient functioning, and survival within clinically important glioblastoma subgroups. Neuro-oncology. 2023; 25: 958–972. https://doi.org/10.1093/neuonc/noac255.

[222] Negwer C, Hiepe P, Meyer B, Krieg SM. Elastic Fusion Enables Fusion of Intraoperative Magnetic Resonance Imaging Data with Preoperative Neuronavigation Data. World Neurosurgery. 2020; 142: e223–e228. https://doi.org/10.1016/j.wneu.2020.06.166.

[223] Patel V, Chavda V. Intraoperative glioblastoma surgery-current challenges and clinical trials: An update. Cancer Pathogenesis and Therapy. 2023; 2: 256–267. https://doi.org/10.1016/j.cpt.2023.11.006.

[224] Neira JA, Ung TH, Sims JS, Malone HR, Chow DS, Samanamud JL, *et al*. Aggressive resection at the infiltrative margins of glioblastoma facilitated by intraoperative fluorescein guidance. Journal of Neurosurgery. 2017; 127: 111–122. https://doi.org/10.3171/2016.7.JNS16232.

[225] Osorio JA, Aghi MK. Optimizing glioblastoma resection: intraoperative mapping and beyond. CNS Oncology. 2014; 3: 359–366. https://doi.org/10.2217/cns.14.36.

[226] Dixon L, Lim A, Grech-Sollars M, Nandi D, Camp S. Intraoperative ultrasound in brain tumor surgery: A review and implementation guide. Neurosurgical Review. 2022; 45: 2503–2515. https://doi.org/10.1007/s10143-022-01778-4.

[227] Mughal AA, Holthe ØØ, Olsen K, Nævra M, Løvland G, Vatnehol S, *et al*. JS05.6.A continuous dynamic mapping of language function and cognitive control and spatial correlation to white matter tracts using intraoperative MRI tractography. Neuro-Oncology. 2023; 25: ii9–ii10. https://doi.org/10.1093/neuonc/noad137.025.

[228] Gerritsen JKW, Zwarthoed RH, Kilgallon JL, Nawabi NL, Jessurun CAC, Versyck G, *et al*. Effect of awake craniotomy in glioblastoma in eloquent areas (GLIOMAP): a propensity score-matched analysis of an international, multicentre, cohort study. The Lancet. Oncology. 2022; 23: 802–817. https://doi.org/10.1016/S1470-2045(22)00213-3.

[229] Wong AK, Shils JL, Sani SB, Byrne RW. Intraoperative Neuromonitoring. Neurologic Clinics. 2022; 40: 375–389. https://doi.org/10.1016/j.ncl.2021.11.010.

[230] Grasso E, Certo F, Ganau M, Bonomo G, Fiumanò G, Buscema G, *et al*. Role of Virtual iMRI in Glioblastoma Surgery: Advantages, Limitations, and Correlation with iCT and Brain Shift. Brain Sciences. 2024; 15: 35. https://doi.org/10.3390/brainsci15010035.

[231] Haemmerli J, Khatchatourov S, Chaboudez E, Roth L, Sandralegar A, Janssen I, *et al*. Surgical and clinical impacts of mixed reality-guided glioblastoma resection versus standard neuronavigation: improving tumor surgery. Frontiers in Oncology. 2025; 15: 1551937. https://doi.org/10.3389/fonc.2025.1551937.

[232] Madani D, Fonseka RD, Kim SJ, Tang P, Muralidharan K, Chang N, *et al*. Comparing the Rates of Further Resection After Intraoperative MRI Visualisation of Residual Tumour Between Brain Tumour Subtypes: A 17-Year Single-Centre Experience. Brain Sciences. 2025; 15: 45. https://doi.org/10.3390/brainsci15010045.

[233] Mirzayeva LS, Uçar M, Budak SN, Kaymaz AM, Yaylı N. Pushing the boundaries of neurosurgical oncology: evaluating the superiority of supratotal resection over gross total resection in intraoperative MRI-guided glioma surgery. Neurosurgical Review. 2025; 48: 200. https://doi.org/10.1007/s10143-025-03301-x.

[234] Shimizu T, Tanaka S, Kitagawa Y, Sakaguchi Y, Kamiya M, Takayanagi S, *et al*. Advancement of fluorescent aminopeptidase probes for rapid cancer detection-current uses and neurosurgical applications. Frontiers in Surgery. 2024; 11: 1298709. https://doi.org/10.3389/fsurg.2024.1298709.

[235] Valerius AR, Webb LM, Thomsen A, Lehrer EJ, Breen WG, Campian JL, *et al*. Review of Novel Surgical, Radiation, and Systemic Therapies and Clinical Trials in Glioblastoma. International Journal of Molecular Sciences. 2024; 25: 10570. https://doi.org/10.3390/ijms251910570.

[236] Gerritsen JKW, Broekman MLD, De Vleeschouwer S, Schucht P, Nahed BV, Berger MS, *et al*. Safe surgery for glioblastoma: Recent advances and modern challenges. Neuro-oncology Practice. 2022; 9: 364–379. https://doi.org/10.1093/nop/npac019.

[237] Cavallo C, De Laurentis C, Vetrano IG, Falco J, Broggi M, Schiariti M, *et al*. The utilization of fluorescein in brain tumor surgery: a systematic review. Journal of Neurosurgical Sciences. 2018; 62: 690–703. https://doi.org/10.23736/S0390-5616.18.04480-6.

[238] Muster RH, Young JS, Woo PYM, Morshed RA, Warrier G, Kakaizada S, *et al*. The Relationship Between Stimulation Current and Functional Site Localization During Brain Mapping. Neurosurgery. 2021; 88: 1043–1050. https://doi.org/10.1093/neuros/nyaa364.

[239] Soloukey S, Vincent AJPE, Satoer DD, Mastik F, Smits M, Dirven CMF, *et al*. Functional Ultrasound (fUS) During Awake Brain Surgery: The Clinical Potential of Intra-Operative Functional and Vascular Brain Mapping. Frontiers in Neuroscience. 2020; 13: 1384. https://doi.org/10.3389/fnins.2019.01384.

[240] Seidel K, Schucht P, Beck J, Raabe A. Continuous Dynamic Mapping to Identify the Corticospinal Tract in Motor Eloquent Brain Tumors: An Update. Journal of Neurological Surgery. Part A, Central European Neurosurgery. 2020; 81: 105–110. https://doi.org/10.1055/s-0039-1698384.

[241] Crowe LA, Boëx C, Lorton O, Bérard N, Boudabbous S, Vallée JP, *et al*. Brain surgery with safe intraoperative 3-T MRI and neuromonitoring. Journal of Neurosurgery. 2025; 143: 578–587. https://doi.org/10.3171/2024.11.JNS241382.

[242] Sharma M, Scott VA, Ball T, Castle JR, Neimat J, Williams BJ. Feasibility of Transcranial Motor Evoked Potentials and Electromyography during MRI-Guided Laser Interstitial Thermal Therapy for Glioblastoma. World Neurosurgery. 2023; 171: 108–113. https://doi.org/10.1016/j.wneu.2022.12.135.

[243] Hallett M, DelRosso LM, Elble R, Ferri R, Horak FB, Lehericy S, *et al*. Evaluation of movement and brain activity. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2021; 132: 2608–2638. https://doi.org/10.1016/j.clinph.2021.04.023.

[244] Larkin CJ, Yerneni K, Karras CL, Abecassis ZA, Zhou G, Zelano C, *et al*. Impact of intraoperative direct cortical stimulation dynamics on perioperative seizures and afterdischarge frequency in patients undergoing awake craniotomy. Journal of Neurosurgery. 2022; 137: 1853–1861. https://doi.org/10.3171/2022.3.JNS226.

[245] Saito T, Tamura M, Chernov MF, Ikuta S, Muragaki Y, Maruyama T. Neurophysiological Monitoring and Awake Craniotomy for Resection of Intracranial Gliomas. Progress in Neurological Surgery. 2018; 30: 117–158. https://doi.org/10.1159/000464387.

[246] Simon MV. Neurophysiologic intraoperative monitoring of the vestibulocochlear nerve. Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society. 2011; 28: 566–581. https://doi.org/10.1097/WNP.0b013e31823da494.

[247] Li Q, Chen S, Wang J, Wang Y, Zhou Y, Yan Z, *et al*. An adaptive stacking generalization integrated with Raman spectroscopy feature enhancement algorithm for fine glioma grading identification. Spectrochimica Acta. Part A, Molecular and Biomolecular Spectroscopy. 2025; 335: 125980. https://doi.org/10.1016/j.saa.2025.125980.

[248] Daoust F, Dallaire F, Tavera H, Ember K, Guiot MC, Petrecca K, *et al*. Preliminary study demonstrating cancer cells detection at the margins of whole glioblastoma specimens with Raman spectroscopy imaging. Scientific Reports. 2025; 15: 6453. https://doi.org/10.1038/s41598-025-87109-1.

[249] Leblond F, Dallaire F, Ember K, Le Moël A, Blanquez-Yeste V, Tavera H, *et al*. Quantitative assessment of the generalizability of a brain tumor Raman spectroscopy machine learning model to various tumor types including astrocytoma and oligodendroglioma. Journal of Biomedical Optics. 2025; 30: 010501. https://doi.org/10.1117/1.JBO.30.1.010501.

[250] Kim MM, Aryal MP, Suresh K, Rosen BS, Parmar H, You D, *et al*. A Phase 2 Study of Multiparametric Magnetic Resonance Imaging-Guided High-Dose Response-Adaptive Radiation Therapy With Concurrent Temozolomide in Patients With Newly Diagnosed Glioblastoma: Results From an Interim Analysis. International Journal of Radiation Oncology, Biology, Physics. 2025; 122: 605–610. https://doi.org/10.1016/j.ijrobp.2025.02.020.

[251] Hau E, Shen H, Clark C, Graham PH, Koh ES, L McDonald K. The evolving roles and controversies of radiotherapy in the treatment of glioblastoma. Journal of Medical Radiation Sciences. 2016; 63: 114–123. https://doi.org/10.1002/jmrs.149.

[252] Aiyappa-Maudsley R, Chalmers AJ, Parsons JL. Factors affecting the radiation response in glioblastoma. Neuro-oncology Advances. 2022; 4: vdac156. https://doi.org/10.1093/noajnl/vdac156.

[253] Wee CW. Radiotherapy for Newly Diagnosed Glioblastoma in the Elderly: What Is the Standard? Brain Tumor Research and Treatment. 2022; 10: 12–21. https://doi.org/10.14791/btrt.2022.10.e34.

[254] Mazarakis NK, Robinson SD, Sinha P, Koutsarnakis C, Komaitis S, Stranjalis G, *et al*. Management of glioblastoma in elderly patients: A review of the literature. Clinical and Translational Radiation Oncology. 2024; 46: 100761. https://doi.org/10.1016/j.ctro.2024.100761.

[255] Kim N, Shin H, Lim DH, Nam DH, Lee JI, Seol HJ, *et al*. Treatment Outcomes after Dose-Escalated Moderately Hypofractionated Radiotherapy for Frail Patients with High-Grade Glioma. Cancers. 2023; 16: 64. https://doi.org/10.3390/cancers16010064.

[256] Mann J, Ramakrishna R, Magge R, Wernicke AG. Advances in Radiotherapy for Glioblastoma. Frontiers in Neurology. 2018; 8: 748. https://doi.org/10.3389/fneur.2017.00748.

[257] Won YK, Kim ES, Jo IY, Oh HJ, Lee SM, Yoo ID, *et al*. Comparative analysis of hypofractionated short-course versus standard radiation therapy in elderly patients with glioblastoma: analysis of nationwide database. Journal of Neuro-oncology. 2025; 171: 463–472. https://doi.org/10.1007/s11060-024-04853-6.

[258] Jiang C, Mogilevsky C, Belal Z, Kurtz G, Alonso-Basanta M. Hypofractionation in Glioblastoma: An Overview of Palliative, Definitive, and Exploratory Uses. Cancers. 2023; 15: 5650. https://doi.org/10.3390/cancers15235650.

[259] Mayo ZS, Billena C, Suh JH, Lo SS, Chao ST. The dilemma of radiation necrosis from diagnosis to treatment in the management of brain metastases. Neuro-oncology. 2024; 26: S56–S65. https://doi.org/10.1093/neuonc/noad188.

[260] Redmond KJ, Mehta M. Stereotactic Radiosurgery for Glioblastoma. Cureus. 2015; 7: e413. https://doi.org/10.7759/cureus.413.

[261] Lehrer EJ, Kowalchuk RO, Ruiz-Garcia H, Merrell KW, Brown PD, Palmer JD, *et al*. Preoperative stereotactic radiosurgery in the management of brain metastases and gliomas. Frontiers in Surgery. 2022; 9: 972727. https://doi.org/10.3389/fsurg.2022.972727.

[262] Bunevicius A, Pikis S, Kondziolka D, Patel DN, Bernstein K, Sulman EP, *et al*. Stereotactic radiosurgery for glioblastoma considering tumor genetic profiles: an international multicenter study. Journal of Neurosurgery. 2021; 137: 42–50. https://doi.org/10.3171/2021.7.JNS211277.

[263] Margulies A, Sahki N, Rech F, Vogin G, Blonski M, Peiffert D, *et al*. Pattern of recurrence after fractionated stereotactic reirradiation in adult glioblastoma. Radiation Oncology (London, England). 2025; 20: 28. https://doi.org/10.1186/s13014-025-02611-0.

[264] Morris SAL, Zhu P, Rao M, Martir M, Zhu JJ, Hsu S, *et al*. Gamma Knife Stereotactic Radiosurgery in Combination with Bevacizumab for Recurrent Glioblastoma. World Neurosurgery. 2019; 127: e523–e533. https://doi.org/10.1016/j.wneu.2019.03.193.

[265] Trifiletti D. Preoperative Radiosurgery for the Treatment of High Grade Glioma. The NeoGlioma Study. NCT05030298. Available at: https://clinicaltrials.gov/search?term=NCT05030298 (Accessed: 9 April 2025).

[266] Waqar M, Roncaroli F, Djoukhadar I, Akkari L, O'Leary C, Hewitt L, *et al*. Study protocol: PreOperative Brain Irradiation in Glioblastoma (POBIG) - A phase I trial. Clinical and Translational Radiation Oncology. 2023; 39: 100585. https://doi.org/10.1016/j.ctro.2023.100585.

[267] Fernandez-Gil BI, Schiapparelli P, Navarro-Garcia de Llano JP, Otamendi-Lopez A, Ulloa-Navas MJ, Michaelides L, *et al*. Effects of PreOperative radiotherapy in a preclinical glioblastoma model: a paradigm-shift approach. Journal of Neuro-oncology. 2024; 169: 633–646. https://doi.org/10.1007/s11060-024-04765-5.

[268] Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, *et al*. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. The New England Journal of Medicine. 2017; 376: 1027–1037. https://doi.org/10.1056/NEJMoa1611977.

[269] Stupp R, Taillibert S, Kanner A, Read W, Steinberg D, Lhermitte B, *et al*. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. JAMA. 2017; 318: 2306–2316. https://doi.org/10.1001/jama.2017.18718.

[270] Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, Al-Tamimi Y, Collis SJ. Tumour treating fields therapy for glioblastoma: current advances and future directions. British Journal of Cancer. 2021; 124: 697–709. https://doi.org/10.1038/s41416-020-01136-5.

[271] Liang L, Chen L, Ni C, Shi W, Zhou Z, Chen S, *et al*. Chemoradiation treatment with or without concurrent tumor-treating fields (TTFields) therapy in newly diagnosed glioblastoma (GBM) patients in China. Chinese Neurosurgical Journal.

2025; 11: 5. https://doi.org/10.1186/s41016-025-00391-w.

[272] Kissling C, Di Santo S. Tumor Treating Fields - Behind and Beyond Inhibiting the Cancer Cell Cycle. CNS & Neurological Disorders Drug Targets. 2020; 19: 599–610. https://doi.org/10.2174/1871527319666200702144749.

[273] Shah HA, Duehr J, Abramyan A, Mittelman L, Galvez R, Winby T, *et al*. Enhancing brain tumor surgery precision with multimodal connectome imaging: Structural and functional connectivity in language-dominant areas. Clinical Neurology and Neurosurgery. 2025; 249: 108760. https://doi.org/10.1016/j.clineuro.2025.108760.

[274] Sun S, Qian S, Wang R, Zhao M, Li R, Gu W, *et al*. Targeting GOLPH3L improves glioblastoma radiotherapy by regulating STING-NLRP3-mediated tumor immune microenvironment reprogramming. Science Translational Medicine. 2025; 17: eado0020. https://doi.org/10.1126/scitranslmed.ado0020.

[275] Ehinger E, Darabi A, Visse E, Edvardsson C, Tomasevic G, Cederberg D, *et al*. Antisecretory factor as add-on treatment for newly diagnosed glioblastoma, IDH wildtype: study protocol for a randomized double-blind placebo-controlled trial. Trials. 2025; 26: 86. https://doi.org/10.1186/s13063-025-08792-z.

[276] Carstam L, Vecchio TG, Lyczak M, Åberg H, Jakola AS, Jennische E, *et al*. Antisecretory factor for treatment of peritumoral edema in glioblastoma patients. Acta Neurochirurgica. 2025; 167: 64. https://doi.org/10.1007/s00701-025-06481-z.

[277] Gesundheit B, Srinivas Raju J, Brauns CY, Weisslein C, Schmoll H, Ellis R, *et al*. Oncolytic Virotherapy for Relapsed, IDH-Mutant, Grade 3 Astrocytoma: A New Promising Approach - A Case Report. Case Reports in Oncology. 2025; 18: 462–472. https://doi.org/10.1159/000545004.

[278] Ling AL, Solomon IH, Landivar AM, Nakashima H, Woods JK, Santos A, *et al*. Clinical trial links oncolytic immunoactivation to survival in glioblastoma. Nature. 2023; 623: 157–166. https://doi.org/10.1038/s41586-023-06623-2.

[279] Bhutani B, Sharma V, Ganguly NK, Rana R. Unravelling the modified T cell receptor through Gen-Next CAR T cell therapy in Glioblastoma: Current status and future challenges. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2025; 186: 117987. https://doi.org/10.1016/j.biopha.2025.117987.

[280] Chen W, Hong L, Lin S, Xian N, Yan C, Zhao N, *et al*. Enhanced anti-tumor efficacy of "IL-15 and CCL19" -secreting CAR-T cells in human glioblastoma orthotopic xenograft model. Frontiers in Oncology. 2025; 15: 1539055. https://doi.org/10.3389/fonc.2025.1539055.

[281] Grewal EP, Nahed BV, Carter BS, Gerstner ER, Curry WT, Maus MV, *et al*. Clinical progress in the development of CAR T cells to treat malignant glioma. Journal of Neuro-oncology. 2025; 171: 571–579. https://doi.org/10.1007/s11060-024-04909-7.

[282] Choi BD, Gerstner ER, Frigault MJ, Leick MB, Mount CW, Balaj L, *et al*. Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma. The New England Journal of Medicine. 2024; 390: 1290–1298. https://doi.org/10.1056/NEJMoa2314390.

[283] Bagley SJ, Logun M, Fraietta JA, Wang X, Desai AS, Bagley LJ, *et al*. Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results. Nature Medicine. 2024; 30: 1320–1329. https://doi.org/10.1038/s41591-024-02893-z.

[284] Deshors P, Kheil Z, Ligat L, Gouazé-Andersson V, Cohen-Jonathan Moyal E. FGFR inhibition as a new therapeutic strategy to sensitize glioblastoma stem cells to tumor treating fields. Cell Death Discovery. 2025; 11: 265. https://doi.org/10.1038/s41420-025-02542-5.

[285] Ziani-Zeryouh A, Wouters R, Thirion G, Vandenbrande K, Vankerckhoven A, Berckmans Y, *et al*. Toward more accurate preclinical glioblastoma modeling: Reverse translation of clinical standard of care in a glioblastoma mouse model. Methods in Cell Biology. 2024; 183: 381–397. https://doi.org/10.1016/bs.mcb.2023.07.003.

[286] Lucchini S, Nicholson JG, Zhang X, Househam J, Lim YM, Mossner M, *et al*. A novel model of glioblastoma recurrence to identify therapeutic vulnerabilities. EMBO Molecular Medicine. 2025; 17: 1325–1354. https://doi.org/10.1038/s44321-025-00237-z.

[287] Wöllner A, Paul A, Arquilla M, Cao J, Lotsch C, Jungwirth G, *et al*. Use of Tissue Specimens from Stereotactic Biopsies for Patient-Derived GBM Organoid-Based Drug Testing. Cells. 2025; 14: 701. https://doi.org/10.3390/cells14100701.

[288] Hicks WH, Bird CE, Pernik MN, Haider AS, Dobariya A, Abdullah KG, *et al*. Large Animal Models of Glioma: Current Status and Future Prospects. Anticancer Research. 2021; 41: 5343–5353. https://doi.org/10.21873/anticanres.15347.

[289] Nieves J, Gil G, Gonzalez A. A bird's eye view to the homeostatic, Alzheimer and Glioblastoma attractors. Heliyon. 2025; 11: e42445. https://doi.org/10.1016/j.heliyon.2025.e42445.

[290] Cai J, Ye L, Hu Y, Ye Z, Gao L, Wang Y, *et al*. Exploring the inverse association of glioblastoma multiforme and Alzheimer's disease via bioinformatics analysis. Medical Oncology (Northwood, London, England). 2022; 39: 182. https://doi.org/10.1007/s12032-022-01786-w.

[291] Fetcko-Fayad K, Batich K, Reitman ZJ, Walsh KM, Chamberlin G, Smith V, *et al*. Coexisting Biopsy-Diagnosed Dementia and Glioblastoma. Brain Sciences. 2024; 14: 143. https://doi.org/10.3390/brainsci14020143.

[292] Pradeep S, Sai Chakith MR, Sindhushree SR, Reddy P, Sushmitha E, Purohit MN, *et al*. Exploring shared therapeutic targets for Alzheimer's disease and glioblastoma using network pharmacology and protein-protein interaction approach. Frontiers in Chemistry. 2025; 13: 1549186. https://doi.org/10.3389/fchem.2025.1549186.

[293] Zhang C, Zhong X, Yi L, Zhao Z, Zhang Y, Tan G, *et al*. Exploring the Associations between Alzheimer's Disease and GBM Mediated by Microglia Based on Network Analysis. The Journal of Prevention of Alzheimer's Disease. 2023; 10: 267–275. https://doi.org/10.14283/jpad.2023.23.

[294] Xu X, Wang J, Chen T, Wang S, Wang F, He J, *et al*. Deciphering novel mitochondrial signatures: multi-omics analysis uncovers cross-disease markers and oligodendrocyte pathways in Alzheimer's disease and glioblastoma. Frontiers in Aging Neuroscience. 2025; 17: 1536142. https://doi.org/10.3389/fnagi.2025.1536142.

[295] Chen L, Zhang H, Shang C, Hong Y. The Role and Applied Value of Mitochondria in Glioma-Related Research. CNS Neuroscience & Therapeutics. 2024; 30: e70121. https://doi.org/10.1111/cns.70121.

[296] Reiss AB, Gulkarov S, Jacob B, Srivastava A, Pinkhasov A, Gomolin IH, *et al*. Mitochondria in Alzheimer's Disease Pathogenesis. Life (Basel, Switzerland). 2024; 14: 196. https://doi.org/10.3390/life14020196.

[297] Cómitre-Mariano B, Vellila-Alonso G, Segura-Collar B, Mondéjar-Ruescas L, Sepulveda JM, Gargini R. Sentinels of neuroinflammation: the crucial role of myeloid cells in the pathogenesis of gliomas and neurodegenerative diseases. Journal of Neuroinflammation. 2024; 21: 304. https://doi.org/10.1186/s12974-024-03298-y.

[298] Liu H, Sun Y, Zhang Q, Jin W, Gordon RE, Zhang Y, *et al*. Pro-inflammatory and proliferative microglia drive progression of glioblastoma. Cell Reports. 2021; 36: 109718. https://doi.org/10.1016/j.celrep.2021.109718.

[299] Greutter L, Miller-Michlits Y, Klotz S, Reimann R, Nenning

KH, Platzek S, *et al*. Frequent Alzheimer's disease neuropathological change in patients with glioblastoma. Neuro-oncology Advances. 2024; 6: vdae118. https://doi.org/10.1093/noajnl/vdae118.

[300] Su Z, Zhang G, Li X, Zhang H. Inverse correlation between Alzheimer's disease and cancer from the perspective of hypoxia. Neurobiology of Aging. 2023; 131: 59–73. https://doi.org/10.1016/j.neurobiolaging.2023.07.002.

[301] Toader C, Dumitru AV, Eva L, Serban M, Covache-Busuioc RA, Ciurea AV. Nanoparticle Strategies for Treating CNS Disorders: A Comprehensive Review of Drug Delivery and Theranostic Applications. International Journal of Molecular Sciences. 2024; 25: 13302. https://doi.org/10.3390/ijms252413302.