

Review Article

BUTTERFLY GLIOBLASTOMA MULTIFORME: HISTOLOGICAL ORIGIN, MOLECULAR PATHOLOGY AND CONTEMPORARY MANAGEMENT

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ABSTRACT

Glioblastoma multiforme (GBM), now classified "glioblastoma, IDH-wildtype" in the fifth edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System, is the most prevalent and deadly primary malignant brain tumour of adulthood. A distinctive and unusually aggressive anatomical presentation is the so-called "butterfly glioma" involving the corpus callosum which extends symmetrically or asymmetrically into both cerebral hemispheres to produce a wing-like, bat-shaped configuration on cross-sectional imaging. This review synthesises current understanding of the histological origin, molecular pathogenesis, diagnostic classification, histopathological features, and evolving management of glioblastoma, with particular emphasis on the butterfly variant and on developments reported in 2025-2026 including tumour-treating fields combined with immunotherapy, oncolytic viral therapy, and novel cell-of-origin research implicating subventricular zone neural stem cell.

INTRODUCTION

Central nervous system malignancies, though comparatively uncommon relative to other solid tumours, carry a disproportionate burden of morbidity and mortality since their location within a functionally indispensable and surgically unforgiving organ. Among primary brain tumours, diffuse gliomas dominate and glioblastoma is both the most frequent and the most aggressive of these, accounting for roughly half of all malignant CNS neoplasms in adults ^[1,2]. Median survival with maximal contemporary therapy remains under two years and for a rare but recognisable subset of patients the tumour does not remain confined to one hemisphere but tracks along the white-matter commissures — mainly the corpus callosum — to invade the contralateral side. When this bihemispheric spread produces a symmetrical or near-symmetrical mass with the visual appearance of butterfly wings on axial imaging the lesion is termed a "butterfly glioma" or, when the underlying histology is glioblastoma, "butterfly glioblastoma" (bGBM) ^[17,18,25]. This entity is not a separate WHO diagnostic category but rather a descriptive, anatomically defined pattern of an otherwise conventionally classified tumour and is widely regarded as representing one of the most treatment-resistant presentations of an already formidable disease ^[22,23].

HISTOLOGICAL ORIGIN AND HISTOGENESIS

Glial tumours were traditionally believed to arise through dedifferentiation of mature astrocytes but accumulating molecular and lineage-tracing evidence over the past decade has shifted this paradigm toward a stem-and-progenitor-cell model of gliomagenesis. The adult human brain retains two neurogenic niches capable of continuous cell division throughout life: the subventricular zone (SVZ) lining the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus ^[11,13,14]. SVZ neural stem cells (NSCs) are astrocyte-like in morphology and are considered developmental descendants of embryonic radial glia, retaining the capacity to generate both neuronal and glial progenitors postnatally ^[11,12].

A landmark genomic study using deep sequencing of tumour tissue, grossly normal cortex, and grossly normal SVZ tissue from patients with IDH-wildtype glioblastoma demonstrated that low-allele-frequency driver mutations identical to those found in the tumour itself — including alterations in TP53, PTEN, EGFR, and TERT promoter mutations — were already present in histologically normal, astrocyte-like SVZ cells located remote from the radiographically evident mass ^[10]. When these mutations were introduced experimentally into murine SVZ NSCs the animals developed tumours that were often anatomically distant from the SVZ itself, closely mirroring the pattern seen in human glioblastoma, and lineage analysis implicated migrating oligodendrocyte-precursor-like cells as an intermediate population contributing to tumour formation ^[10]. This body of work supports a model in which a mutated SVZ neural stem cell migrates away from its niche of origin, undergoes clonal evolution, and ultimately manifests as a mass lesion in the frontal, temporal, or periventricular white matter — a migratory pathway that plausibly explains why gliomas, and glioblastoma in particular, so readily invade white-matter tracts such as the corpus callosum en route to the contralateral hemisphere ^[13,45,48].

Comparative studies of SVZ versus hippocampal NSCs have further asked why the SVZ niche disproportionately gives rise to glioma while the hippocampal niche rarely does; proposed explanations include differences in the proliferative kinetics, microenvironmental signalling, and susceptibility to genotoxic stress between the two niches, as well as the physical proximity of periventricular white matter to sites of tumour growth [14]. Glioblastoma stem cells (GSCs) isolated from resected tumours share numerous phenotypic and molecular features with normal SVZ NSCs including expression of stemness transcription factors, telomerase activity, and self-renewal capacity, reinforcing the hypothesis of a shared cellular ancestry and offering a rationale for SVZ-directed radiotherapy strategies now under clinical investigation ^[11,15,16]. It should be noted that not every glioblastoma is thought to originate from the SVZ; oligodendrocyte precursor cells and mature astrocytes retain some capacity for reactive proliferation and may also serve as cells of origin in a subset of tumours, particularly those arising outside the

periventricular region ^[15,57].

MOLECULAR PATHOLOGY AND THE WHO CNS5 CLASSIFICATION

The 2021 fifth edition of the WHO Classification of Tumours of the Central Nervous System (WHO CNS5) has fundamentally restructured the diagnosis of diffuse gliomas, making the molecular status, rather than the histological grade, central to tumour typing ^[1,2,3]. Adult-type diffuse gliomas are now divided into three integrated types: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype ^[1,2]. Critically, the term "glioblastoma" is now reserved exclusively for IDH-wildtype tumours; an IDH-mutant astrocytoma that displays high-grade histological features (necrosis, microvascular proliferation) is classified as "astrocytoma, IDH-mutant, CNS WHO grade 4," not glioblastoma ^[1,4].

The histological hallmarks that permit a morphological diagnosis of glioblastoma are diffuse infiltration by a hypercellular, pleomorphic astrocytic proliferation together with microvascular proliferation and/or necrosis, the latter frequently arranged as serpentine or geographic zones bordered by radially oriented, densely packed tumour cell nuclei — the classic "pseudopalisading necrosis" ^[1,25,32,37]. A major innovation of WHO CNS5 is that these classic histological criteria are no longer strictly required: a diffusely infiltrating, IDH-wildtype astrocytic glioma lacking necrosis or microvascular proliferation can nonetheless be assigned the diagnosis "glioblastoma, IDH-wildtype, CNS WHO grade 4" if it demonstrates any one of three molecular alterations — TERT promoter mutation, EGFR gene amplification, or the combined whole-chromosome-7 gain with whole-chromosome-10 loss (+7/−10) signature — even in the setting of otherwise lower-grade morphology ^[1,4,37,39]. This so-called "molecular glioblastoma" designation has meaningfully expanded the diagnostic category and altered epidemiological and prognostic estimates ^[7,8,9].

Beyond these defining alterations, MGMT (O6-methylguanine-DNA methyltransferase) promoter methylation status remains the single most important predictive biomarker in clinical use, since epigenetic silencing of this DNA-repair gene sensitises tumour cells to alkylating chemotherapy such as temozolomide and is strongly associated with more durable response and prolonged survival ^[3,38]. CDKN2A/B homozygous deletion has separately been incorporated as a grade-4-defining criterion for IDH-mutant astrocytomas, reflecting its association with an aggressive clinical course independent of histological appearance ^[1,37,39]. Taken together, an accurate contemporary diagnosis of glioblastoma is an integrated histomolecular exercise requiring IDH1/2 mutation testing, assessment of 1p/19q co-deletion status where relevant, TERT promoter sequencing, EGFR amplification and chromosome 7/10 copy-number analysis, and MGMT promoter methylation testing, alongside conventional light-microscopic evaluation ^[1,3,4].

Proposed histogenesis, molecular evolution and anatomical progression of butterfly glioblastoma

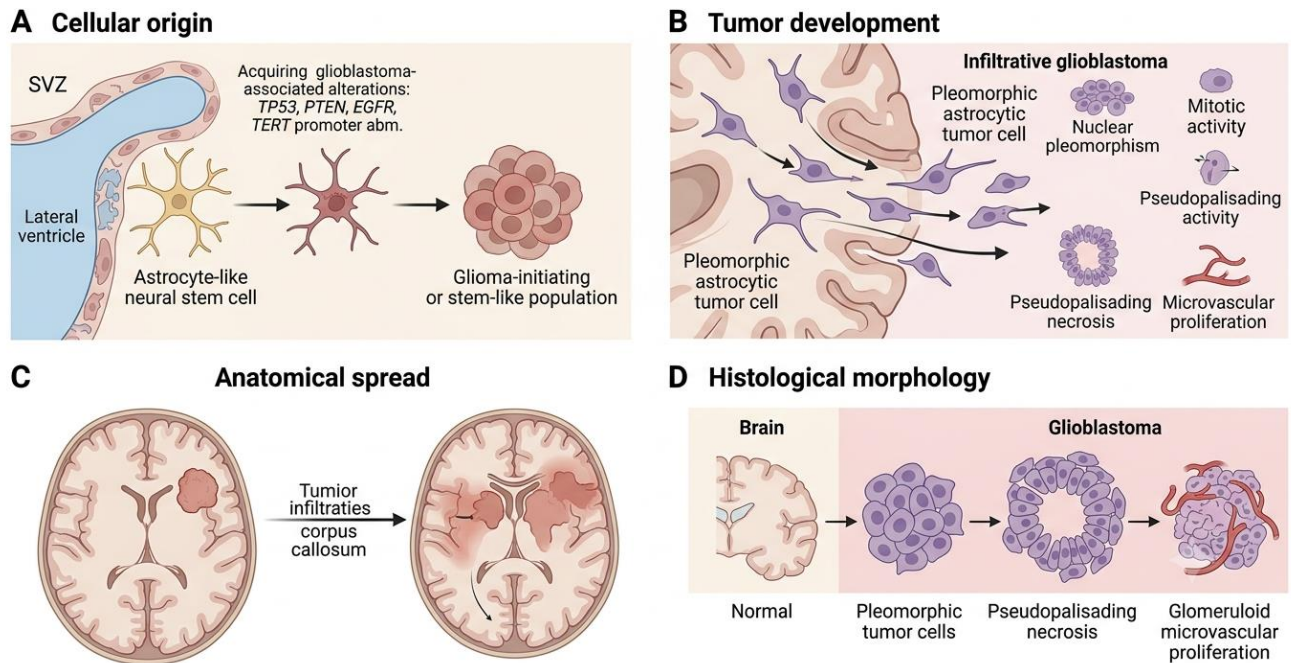


Figure 1 Histogenesis, molecular evolution and butterfly morphology.

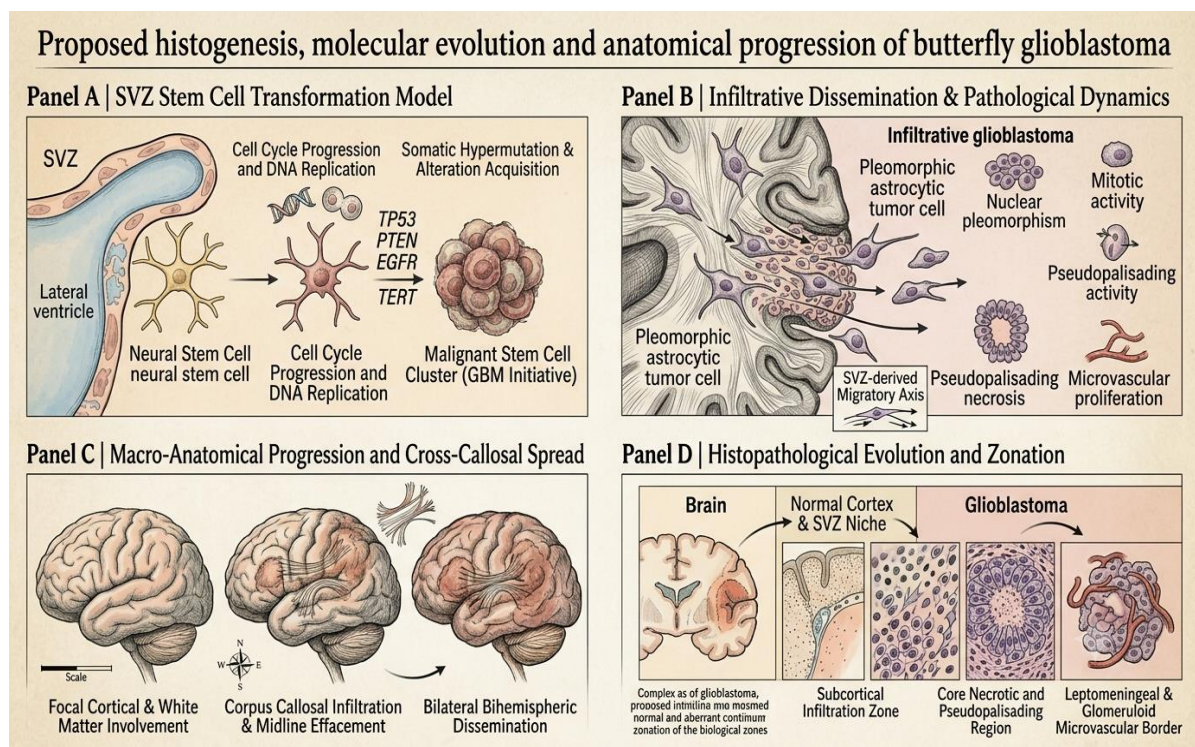


Figure 2 Histogenesis, molecular evolution and butterfly morphology.

Butterfly Glioblastoma: Definition, Epidemiology and Anatomical Basis

The corpus callosum is the largest commissural white-matter tract in the brain and functions, unfortunately, as a highly efficient conduit for glioma spread between hemispheres ^[24,29]. When a high-grade glioma infiltrates the genu, body, or splenium of the corpus callosum and extends contiguously into both cerebral hemispheres the resulting lesion may assume a bilateral, roughly symmetrical, wing-shaped morphology on axial MRI or CT — the appearance from which the descriptive term "butterfly glioma" derives ^[17,18,25]. Historically, WHO texts described this pattern chiefly in reference to glioblastoma, noting that extension through the corpus callosum into the contralateral hemisphere creating a bilateral symmetric lesion was a recognised, if uncommon, feature of the tumour's spread ^[18].

Reported incidence figures vary depending on the strictness of the imaging or histological definition applied, with corpus callosum involvement noted in roughly one-quarter of newly diagnosed glioblastomas overall, while the specifically bilateral, butterfly-pattern subset accounts for a smaller fraction, on the order of 2 to 14 percent of glioblastoma cohorts in different series ^[10,19]. No single, universally accepted set of radiological or histopathological criteria exists to formally define what qualifies as a "butterfly" lesion, which has historically complicated cross-study comparison and pooled analysis ^[18]. Typical demographic features mirror those of glioblastoma generally: a predominance in middle-aged and older adults, a slight male preponderance, and presenting symptoms that often include progressive headache, hemiparesis, and — distinctively for the butterfly pattern given its frequent frontal and bifrontal involvement — cognitive and behavioural change, confusion, and personality alteration, reflecting bilateral frontal lobe and interhemispheric connectivity disruption ^[9,14,26,27].

HISTOPATHOLOGICAL AND IMAGING FEATURES

Microscopically, butterfly glioblastoma reproduces the full morphological spectrum of conventional IDH-wildtype glioblastoma. Sections typically show a densely cellular, diffusely infiltrating astrocytic proliferation composed of markedly pleomorphic cells with hyperchromatic, irregular nuclei, brisk mitotic activity, and a high Ki-67 proliferation index ^[1,25,37]. Necrosis is characteristically serpentine or geographic, with tumour cells arranged in a pseudopalisading pattern around necrotic foci, a configuration thought to reflect intratumoural hypoxia and consequent centrifugal migration of viable, hypoxia-adapted tumour cells away from a dying vascular-deprived core ^[1,32]. Florid microvascular proliferation, with glomeruloid tufts of endothelial and pericytic cells, is a second cardinal diagnostic feature reflecting the markedly pro-angiogenic microenvironment of the tumour ^[1,37]. Within the corpus callosum itself, histological sections in reported butterfly cases have specifically documented invasion of callosal white-matter tracts by neoplastic astrocytes tracking along myelinated fibre bundles, providing the structural substrate for the bihemispheric spread ^[2,3,17].

On MRI, butterfly glioblastoma typically presents as a heterogeneously T1-hypointense, T2/FLAIR-hyperintense bihemispheric mass centred on or extending through the corpus callosum, with variable and often irregular ring or heterogeneous contrast enhancement, substantial perilesional vasogenic oedema, and frequent central necrosis; symmetry between the two hemispheric components may be striking or, in many cases, distinctly asymmetric ^[2,3,26]. Diffusion-weighted and perfusion imaging, along with advanced techniques such as proton MR spectroscopy, are increasingly used to distinguish butterfly glioblastoma from its principal radiological mimics, which include primary CNS lymphoma, metastatic disease, demyelinating pseudotumour, and, rarely, infectious processes such as toxoplasmosis, each of which can also produce a callosal, bihemispheric lesion and therefore requires careful differentiation before a treatment pathway is chosen ^[16,25].

Diagnostic and contemporary management pathway for butterfly glioblastoma

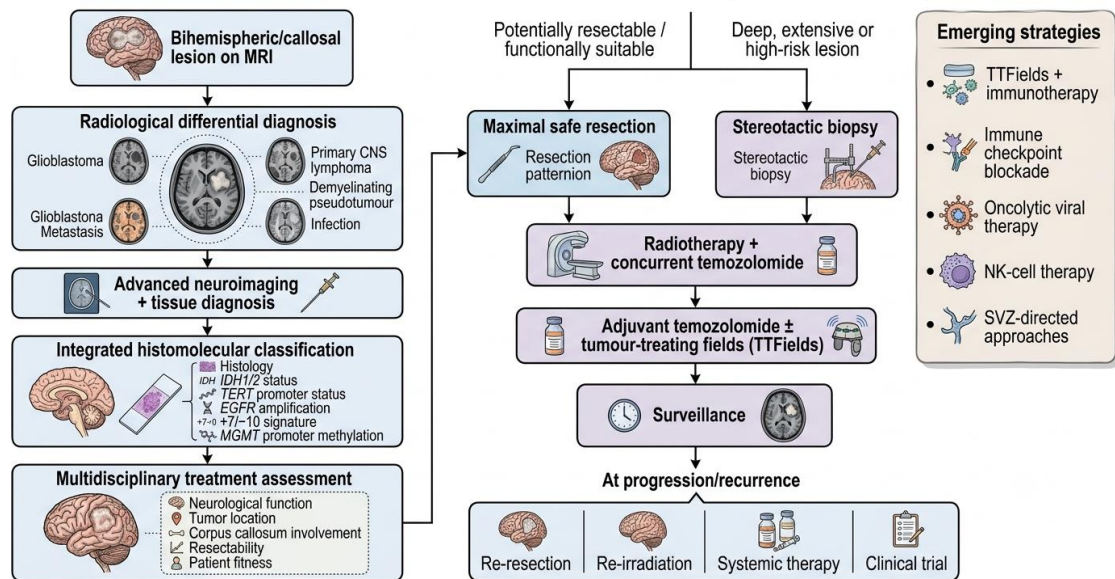


Figure 3 Diagnostic and contemporary management algorithm

Clinical Management

Management of butterfly glioblastoma has historically been more conservative than that of unilateral glioblastoma, due to a longstanding perception that aggressive resection of a bilateral, deep, callosal lesion carries prohibitive risk of neurological morbidity with little survival benefit; as a result, many patients have been offered biopsy alone followed by radiotherapy and chemotherapy, or, in some cases, best supportive care ^[18,22]. This conservative stance has, however, been increasingly challenged by more recent comparative outcome data. A systematic review and meta-analysis pooling seven studies and 293 patients found that surgical resection, whether radical or partial, was associated with significantly longer overall survival than biopsy alone, without a statistically significant increase in postoperative complications, and this survival advantage persisted across both higher and lower extent-of-resection subgroups ^[20]. Population-based cohort data from Western Norway similarly demonstrated that multimodal treatment incorporating radiotherapy with or without temozolomide was associated with meaningfully longer survival than best supportive care alone, even though overall outcomes for the group remained poor ^[6,19]. A separate German single-centre series further distinguished prognosis by extent of callosal involvement, showing that patients with fully bilateral corpus callosum infiltration fared worse than those with unilateral callosal extension, a finding with direct implications for surgical decision-making and counselling ^[11]. Standard-of-care treatment for fit patients therefore continues to follow the Stupp protocol established for glioblastoma broadly: maximal safe resection or biopsy, followed by concurrent radiotherapy with daily low-dose temozolomide, and subsequently six or more cycles of adjuvant temozolomide ^[30]. Tumour-treating fields (TTFields), a non-invasive antimitotic modality delivered via scalp-mounted transducer arrays that generate low-intensity, alternating electric fields disrupting mitotic spindle formation and organelle assembly in dividing tumour cells, is now an established adjunct to maintenance temozolomide for newly diagnosed glioblastoma and has been used safely even in patients with implanted cardiac devices such as pacemakers, provided appropriate precautions are taken ^[34]. Reported median overall survival for butterfly glioblastoma specifically remains substantially shorter than for glioblastoma overall, with figures across recent series ranging from approximately 3 to 9 months depending on treatment intensity and patient selection, underscoring the continued need for individualised, multidisciplinary decision-making that weighs functional preservation against oncological benefit ^[9,19,22].

Table 1. Integrated diagnostic and molecular features of glioblastoma, IDH-wildtype

Feature	Key findings	Clinical/diagnostic significance
WHO classification	Glioblastoma, IDH-wildtype, CNS WHO grade 4	Diagnosis is based on integrated histomolecular criteria
IDH status	IDH1/IDH2 wildtype	Essential for distinguishing glioblastoma from IDH-mutant astrocytoma
Histological appearance	Hypercellularity, nuclear pleomorphism, atypia and brisk mitotic activity	Supports recognition of a high-grade infiltrating astrocytic neoplasm
Necrosis	Geographic or serpentine necrosis, frequently with pseudopalisading tumour cells	Classic histological hallmark of glioblastoma
Microvascular proliferation	Glomeruloid or multilayered endothelial proliferation	Major histological criterion for grade 4 morphology
TERT promoter mutation	Common in IDH-wildtype glioblastoma	Can establish glioblastoma diagnosis in an appropriate diffuse IDH-wildtype astrocytic tumour even without necrosis or microvascular proliferation
EGFR amplification	Frequent molecular alteration	One of the WHO CNS5 molecular criteria supporting glioblastoma diagnosis
Chromosome 7/10 alterations	Combined whole-chromosome 7 gain and whole-chromosome 10 loss (+7/-10)	Molecular criterion supporting glioblastoma diagnosis
MGMT promoter methylation	Epigenetic silencing of MGMT	Predictive biomarker associated with greater sensitivity to temozolomide
CDKN2A/B deletion	Homozygous deletion is associated with aggressive biology	Particularly important for grading IDH-mutant astrocytomas
MRI characteristics	T1 hypointensity, T2/FLAIR hyperintensity, heterogeneous or ring enhancement, oedema and necrosis	Defines tumour extent and guides biopsy/resection planning
Corpus callosum involvement	Infiltration through genu, body or splenium	Provides the anatomical substrate for interhemispheric tumour spread
Butterfly pattern	Bilateral contiguous hemispheric involvement through the corpus callosum	Descriptive radiological phenotype rather than a separate WHO tumour entity

RECENT ADVANCES AND EMERGING THERAPIES (2024–2026)

The past two years have brought several notable developments relevant to glioblastoma management generally, with early signals of applicability to aggressive, treatment-resistant presentations such as the butterfly variant. Immunotherapy, long disappointing in glioblastoma due to its markedly immunosuppressive, "cold" tumour microenvironment and the restrictive blood-brain barrier, has seen renewed clinical momentum [31,32,33]. A 2025 clinical-trial update highlighted encouraging results for neoadjuvant immune checkpoint blockade with pembrolizumab in recurrent glioblastoma, where preoperative dosing produced measurable tumour reduction and prompted a confirmatory phase IV study, along with early evidence that combining checkpoint inhibition with laser interstitial thermal therapy may improve outcomes through blood-brain barrier disruption [31].

Table 2. Recent advances and emerging therapeutic strategies in glioblastoma

Emerging approach	Current evidence / rationale	Potential significance
TTFields + immunotherapy	TTFields may enhance immune-cell infiltration and improve responsiveness to checkpoint blockade	May convert an immunologically “cold” tumour into a more treatment-responsive environment
Oncolytic viral therapy	Engineered viruses selectively infect tumour cells while stimulating antitumour immunity	Promising strategy for overcoming tumour heterogeneity and immune suppression
NK-cell therapy + TTFields	Early clinical studies are evaluating NK-cell activation in combination with TTFields	Potentially enhances immune-mediated tumour killing
Checkpoint inhibitors	Neoadjuvant and combination approaches are being investigated in recurrent glioblastoma	May improve efficacy compared with checkpoint blockade alone
SVZ-directed strategies	Increasing evidence implicates neural stem/progenitor cells in gliomagenesis	May provide future opportunities for early detection or targeted prevention

A particularly notable 2025 finding from investigators at the University of Southern California demonstrated that TTFields therapy recruits tumour-infiltrating T cells into and around the glioblastoma microenvironment, and that sequencing TTFields with immune checkpoint blockade and chemotherapy substantially prolonged survival compared with standard therapy alone in a mouse model, suggesting that TTFields may act as a priming step that renders an otherwise immunologically "cold" tumour more responsive to subsequent immunotherapy — a combination now advancing toward clinical evaluation [35]. Complementing this, early-phase human data reported in 2025 from a regimen combining an interleukin-15 agonist (to expand and activate natural killer cells), adoptive natural killer cell therapy, and TTFields in recurrent glioblastoma achieved disease control in all five initially treated patients, with two achieving near-complete radiographic response [as reported in industry and institutional communications during 2025].

Oncolytic viral therapy has also re-emerged as a promising strategy: a single intratumoural injection of an engineered virus designed to infect and lyse glioblastoma cells while simultaneously recruiting and sustaining activation of tumour-infiltrating immune cells was associated with improved survival in a recent clinical trial reported by investigators at Mass General Brigham and the Dana-Farber Cancer Institute, offering a mechanistic explanation for how a single dose can convert an immunologically cold tumour into one accessible to immune attack [as reported in 2026]. Separately, a gene-therapy approach using an engineered adeno-associated viral vector that selectively activates within aggressive glioblastoma cells to trigger both direct cytotoxicity and immune activation is progressing toward first-in-human testing, illustrating the breadth of combinatorial and precision strategies now under active investigation for this historically intractable tumour [32,33].

Alongside these therapeutic developments, refinements in molecular diagnostics continue to reshape epidemiological understanding of glioblastoma. A 2025 Spanish regional study applying the WHO CNS5 molecular criteria found that both IDH-wildtype glioblastoma and IDH-mutant astrocytoma incidence rose significantly over the study period — very likely reflecting improved molecular ascertainment rather than a true rise in disease occurrence — and confirmed a stark survival divergence between the two entities, with median overall survival of 12.3 months for IDH-wildtype glioblastoma versus 38.4 months for IDH-mutant astrocytoma, reinforcing the prognostic importance of accurate molecular subtyping at diagnosis [9].

PROGNOSIS AND CONCLUDING REMARKS

Glioblastoma, IDH-wildtype, remains one of the most lethal human malignancies, and the butterfly phenotype represents an especially aggressive anatomical subset associated with shorter survival than unilateral disease, reflecting both the biological aggressiveness implied by bihemispheric, commissural spread and the practical surgical limitations such a distribution imposes [9,19,22,23]. Nonetheless, accumulating evidence that carefully selected patients benefit from resection rather than biopsy alone, together with a rapidly expanding pipeline of immunotherapeutic, viral, and device-based combination strategies, suggests that the historically nihilistic approach to this tumour subtype is being reappraised [20,31,35]. Advances in understanding the subventricular-zone stem-cell origin of glioblastoma may in time open avenues for niche-directed prevention or early-intervention strategies, while the WHO CNS5 molecular framework has already sharpened diagnostic precision and prognostic stratification [1,10,45]. Continued accrual of butterfly-specific outcome data, ideally through multi-institutional registries given the rarity of the entity, will be essential to defining an evidence-based, individualised standard of care for these patients.

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