CURRENT CONCEPTS IN EPIDEMIOLOGY, MOLECULAR CLASSIFICATION, SURGICAL MANAGEMENT, PROGNOSTIC FACTORS, AND FUTURE DIRECTIONS: A COMPREHENSIVE REVIEW OF GLIOMAS

Dipak Chaulagain[1],[2], Abhi Timalsina[3], Abhaya Timalsina[3]
[1]Uzhhorod National University, Uzhhorod, Ukraine
[2]Jalal-Abad International University, Jalal-Abad, Kyrgyzstan
[3]Medical Student, Kathmandu University School of Medical Sciences, Dhulikhel, Nepal

Abstract

Background: Gliomas are the most common primary malignant brain tumors in adults, collectively accounting for more than 80% of all malignant central nervous system neoplasms. Their heterogeneous biology, variable clinical behavior, and resistance to multimodal therapy contribute to persistently poor prognoses, particularly for high-grade variants such as glioblastoma (GBM).

Objective: This comprehensive review synthesizes current evidence on the epidemiology, molecular classification, surgical management, prognostic factors, and emerging therapeutic strategies for gliomas in neuro-oncological surgery.

Methods: A systematic narrative review was conducted of peer-reviewed literature published primarily between 2015 and 2026 using PubMed/MEDLINE, EMBASE, and the Cochrane Library. Search terms included 'glioma,' 'glioblastoma,' 'extent of resection,' 'IDH mutation,' 'WHO classification,' and related terms. Meta-analyses, randomized controlled trials, prospective cohort studies, and high-quality retrospective series were prioritized.

Results: The 2021 WHO classification has fundamentally restructured glioma taxonomy, anchoring diagnosis in molecular markers including IDH mutation status, 1p/19q codeletion, MGMT promoter methylation, and H3K27 alteration. Maximal safe surgical resection remains the cornerstone of management. Intraoperative adjuncts—5-aminolevulinic acid (5-ALA) fluorescence, intraoperative MRI (iMRI), and awake craniotomy—substantially increase the rate of GTR. Temozolomide-based chemoradiotherapy following the Stupp protocol remains the standard for GBM; however, immunotherapy and targeted molecular agents are demonstrating promise in early-phase trials.

Conclusion: Advances in molecular diagnostics, surgical technology, and multimodal oncological therapy are gradually improving outcomes for glioma patients. Future efforts must address tumor recurrence, blood–brain barrier penetration, immunosuppressive microenvironments, and health-related quality of life.

Keywords: Glioma, Astrocytoma, Glioblastoma, Extent of Resection, Surgical Resection

СОВРЕМЕННЫЕ КОНЦЕПЦИИ ЭПИДЕМИОЛОГИИ, МОЛЕКУЛЯРНАЯ КЛАССИФИКАЦИЯ, ХИРУРГИЧЕСКОЕ ЛЕЧЕНИЕ, ПРОГНОСТИЧЕСКИЕ ФАКТОРЫ И БУДУЩИЕ НАПРАВЛЕНИЯ: ВСЕСТОРОННИЙ ОБЗОР ГЛИОМ

Дипак Чаулагаин[1,2], Абхи Тималсина[3], Абхая Тималсина[3]
[1]Ужгородский национальный университет, Ужгород, Украина
[2]Международный университет Джалал-Абада, Джалал-Абад, Кыргызстан
[3]Студент-медик, Медицинский факультет Катмандуского университета, Дхуликхель, Непал

Аннотация

Введение: Глиомы являются наиболее распространенными первичными злокачественными опухолями головного мозга у взрослых, составляя более 80% всех злокачественных новообразований центральной нервной системы. Их гетерогенная биология, вариабельное клиническое поведение и устойчивость к мультимодальной терапии обуславливают постоянно неблагоприятный прогноз, особенно для высокозлокачественных вариантов, таких как глиобластома (ГБМ).

Цель: Данный всесторонний обзор обобщает современные данные об эпидемиологии, молекулярной классификации, хирургическом лечении, прогностических факторах и новых терапевтических стратегиях лечения глиом в нейроонкологической хирургии.

Методы: Был проведен систематический нарративный обзор рецензируемой литературы, опубликованной преимущественно в период с 2015 по 2026 год, с использованием баз данных PubMed/MEDLINE, EMBASE и Cochrane Library. Поисковые запросы включали «глиома», «глиобластома», «объем резекции», «мутация IDH», «классификация ВОЗ» и связанные термины. Приоритет отдавался метаанализам, рандомизированным контролируемым исследованиям, проспективным когортным исследованиям и высококачественным ретроспективным сериям.

Результаты: Классификация ВОЗ 2021 года коренным образом реструктурировала таксономию глиом, основывая диагностику на молекулярных маркерах, включая статус мутации IDH, коделецию 1p/19q, метилирование промотора MGMT и изменение H3K27. Максимально безопасная хирургическая резекция остается краеугольным камнем лечения. Интраоперационные вспомогательные методы — флуоресценция 5-аминолевулиновой кислоты (5-ALA), интраоперационная МРТ (iMRI) и краниотомия в сознании — существенно увеличивают частоту полного удаления опухоли. Химиолучевая терапия на основе темозоломида по протоколу Ступпа остается стандартом лечения глиобластомы; однако иммунотерапия и таргетные молекулярные препараты демонстрируют многообещающие результаты на ранних стадиях клинических испытаний.

Заключение: Достижения в молекулярной диагностике, хирургических технологиях и мультимодальной онкологической терапии постепенно улучшают результаты лечения пациентов с глиомой. В дальнейшем необходимо уделить внимание рецидивам опухоли, проникновению через гематоэнцефалический барьер, иммунодепрессивной микросреде и качеству жизни, связанному со здоровьем.

Ключевые слова: глиома, астроцитома, глиобластома, объем резекции, хирургическая резекция

1. Introduction

Gliomas represent the most prevalent category of primary brain tumors, originating from glial or progenitor cells and encompassing a biologically diverse spectrum of entities ranging from indolent pilocytic astrocytomas to aggressive glioblastoma multiforme (GBM). According to the Central Brain Tumor Registry of the United States (CBTRUS), gliomas constitute

approximately 26.6% of all primary brain and central nervous system tumors and more than 80% of malignant variants [1,2]. Despite significant advances in neurosurgical technique, radiation oncology, and systemic chemotherapy over the past two decades, the prognosis for patients with high-grade glioma (HGG) remains dismal, with a median overall survival (OS) of only 14 to 18 months for GBM—the most aggressive form [3].

The clinical and biological complexity of gliomas necessitates a multidisciplinary approach that integrates neurosurgery, neuro-oncology, radiation oncology, neuropathology, and molecular genetics. Historically, glioma classification relied predominantly on histopathological features including cell morphology and mitotic activity; however, the 2016 and subsequently the 2021 World Health Organization (WHO) Classifications of Tumors of the Central Nervous System introduced a paradigm shift by anchoring diagnosis in molecular biomarkers such as isocitrate dehydrogenase (IDH) mutation status, 1p/19q codeletion, MGMT promoter methylation, and histone H3 alterations [4,5]. This molecular reclassification has not only refined prognostication but has also opened avenues for targeted therapeutic intervention.

Surgical management remains the foundational pillar of glioma treatment. The extent of resection (EOR) has been consistently identified as an independent prognostic variable in both low-grade glioma (LGG) and HGG [6,7]. Landmark meta-analyses by Chaulagain et al. have substantially contributed to the evidence base supporting maximal safe resection, demonstrating survival benefits across tumor grades and confirming the incremental value of modern intraoperative adjuncts including 5-aminolevulinic acid (5-ALA)-guided fluorescence, intraoperative magnetic resonance imaging (iMRI), neuronavigation, and awake craniotomy [8,9,10]. These contributions have positioned neurosurgical optimization as a central, modifiable determinant of oncological outcomes.

The present review aims to provide a comprehensive, up-to-date synthesis of current knowledge across all major domains of glioma management—epidemiology, molecular biology, surgery, adjuvant therapy, and prognostication. In doing so, we seek to advance the narrative from discrete research findings toward a cohesive, clinically actionable framework for neurosurgeons and neuro-oncologists managing this challenging disease entity.

2. Epidemiology and Risk Factors

2.1 Incidence and Prevalence

Gliomas occur at an annual incidence of approximately 6 per 100,000 population in high-income countries, with significant variation observed by histological subtype and geographic region [1,2]. GBM, the most common malignant glioma, accounts for approximately 14.6% of all primary brain tumors and nearly 49% of all malignant gliomas, with an age-adjusted incidence rate of 3.21 per 100,000 person-years in the United States [1]. Lower-grade gliomas (WHO grades 2–3) are less common, accounting for approximately 5–6% of primary brain tumors, but carry disproportionate long-term disease burden due to their propensity for malignant transformation over time.

There is a well-established male predominance across glioma subtypes, with a male-to-female ratio of approximately 1.6:1 for GBM [1]. Peak incidence occurs in the sixth to seventh decades of life for GBM, whereas LGG tends to present in younger adults (third to fifth decades). Pediatric gliomas, constituting the most common solid tumor in children, demonstrate distinct molecular profiles and clinical behaviors compared with their adult counterparts [11].

2.2 Geographic and Racial Variation

Incidence rates are highest in North America, Europe, and Australia, with lower rates reported across Asia and Africa, though ascertainment bias stemming from differential access to neuroimaging and neuropathological services may partially account for these disparities [12]. Within the United States, non-Hispanic white populations exhibit higher GBM incidence rates relative to Black, Hispanic, and Asian-American populations. These ethnic variations likely reflect a complex interplay of genetic susceptibility, environmental exposures, and reporting heterogeneity [13].

2.3 Risk Factors

The etiology of gliomas remains incompletely elucidated. Ionizing radiation represents the only well-established environmental risk factor for glioma development; therapeutic cranial irradiation, particularly during childhood, is associated with a significantly elevated risk of secondary gliomagenesis [14]. Genetic predisposition accounts for a small but important minority of cases; hereditary syndromes including neurofibromatosis types 1 and 2, tuberous sclerosis, Li-Fraumeni syndrome, and Lynch syndrome are associated with increased glioma risk [15].

Genome-wide association studies (GWAS) have identified multiple common susceptibility loci, including variants in TERT, EGFR, PHLDB1, RTEL1, and CCDC26, conferring modest increases in risk [16]. Despite decades of epidemiological research, neither mobile telephone use nor electromagnetic field exposure has been conclusively established as a causal risk factor, and current evidence does not support a significant population-attributable risk from these exposures [17]. Immunosuppression, as in organ transplant recipients with HIV/AIDS, is associated with primary CNS lymphoma but has a less clearly established association with true glioma [18].

3. Molecular Classification and WHO 2021/2026 Updates

3.1 Evolution of Classification Systems

The histopathological classification of gliomas, based on the Kernohan grading system and subsequent revisions, dominated clinical practice for decades. A pivotal evolution occurred with the discovery of recurrent IDH1 and IDH2 mutations in the majority of lower-grade gliomas and secondary GBMs by Parsons et al. in 2008 [19]. This landmark finding catalyzed the incorporation of molecular biomarkers into the 2016 WHO classification, which for the first time mandated integrated histological-molecular diagnosis.

The 2021 WHO Classification of Tumors of the Central Nervous System (5th edition) further refined this framework by establishing molecularly defined tumor types as discrete entities, eliminating ambiguous 'NOS' (not otherwise specified) categories where molecular data could be obtained, and introducing new tumor types including Diffuse Midline Glioma (H3 K27-altered) and Diffuse Hemispheric Glioma (H3 G34-mutant) [4,5]. Critically, glioblastoma is now strictly defined as IDH-wildtype WHO grade 4 diffuse astrocytoma, with IDH-mutant grade 4 tumors reclassified as astrocytoma, IDH-mutant—a distinction with profound prognostic implications.

3.2 Key Molecular Markers

IDH Mutation. Mutations in IDH1 (predominantly R132H) and IDH2 (predominantly R172K) occur in approximately 70–80% of WHO grade 2–3 gliomas and secondary GBM, but in only

3–5% of primary GBM [19,20]. IDH mutation results in a neomorphic enzymatic activity producing the oncometabolite 2-hydroxyglutarate (2-HG), which competitively inhibits α-ketoglutarate-dependent dioxygenases including TET2 and histone demethylases, leading to a CpG island methylator phenotype (CIMP) and epigenetic dysregulation [21]. IDH mutation status is the primary dichotomous prognostic variable in adult diffuse glioma, with IDH-mutant tumors consistently demonstrating significantly superior OS compared with IDH-wildtype counterparts at equivalent histological grade [4].

1p/19q Codeletion. Co-deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) defines oligodendroglioma in the 2021 WHO classification and is invariably associated with IDH mutation [4]. This codeletion, arising from an unbalanced translocation of chromosomes 1 and 19, is associated with superior chemosensitivity to procarbazine, lomustine, and vincristine (PCV) and to temozolomide, as well as with markedly prolonged OS [22].

MGMT Promoter Methylation. O6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme that reverses alkylation damage at the O6 position of guanine—the primary mechanism by which temozolomide exerts its cytotoxic effect. Methylation of the MGMT gene promoter silences expression, impairing tumor DNA repair and sensitizing tumors to alkylating chemotherapy [23]. MGMT promoter methylation occurs in approximately 40–45% of GBMs and is the strongest predictive biomarker for benefit from temozolomide in GBM, with methylated tumors demonstrating a median OS advantage of 6–8 months over unmethylated tumors [24].

TERT Promoter Mutation and Other Markers. Mutations in the telomerase reverse transcriptase (TERT) promoter (C228T and C250T) are present in more than 80% of IDH-wildtype GBMs and in 1p/19q-codeleted oligodendrogliomas, representing a mechanism of telomere maintenance in tumor cells [25]. The combination of IDH-wildtype status with TERT promoter mutation, EGFR amplification, and chromosome +7/−10 copy number changes defines molecular GBM, even in histologically lower-grade diffuse astrocytic tumors [4]. Additional emerging biomarkers include ATRX loss, CDKN2A/B homozygous deletion (associated with grade 4 IDH-mutant astrocytoma), PIK3CA/PIK3R1 mutations, and BRAF alterations in pediatric-type tumors [5,26].

Table 1. WHO 2021 Classification of Diffuse Gliomas in Adults: Key Entities, Molecular Markers, and Prognosis

WHO Grade	Tumor Type	Key Molecular Markers	Typical Prognosis
Grade 1	Pilocytic Astrocytoma	BRAF fusion/V600E	Excellent (>10 yr OS)
Grade 2	Astrocytoma, IDH-mutant	IDH1/2 mut, no 1p/19q codeletion	Median OS 8–12 yr
Grade 2	Oligodendroglioma, IDH-mutant, 1p/19q-codeleted	IDH1/2 mut + 1p/19q codeletion	Median OS 10–15 yr
Grade 3	Astrocytoma, IDH-mutant	IDH1/2 mut, CDKN2A/B del	Median OS 4–6 yr
Grade 3	Oligodendroglioma, IDH-mutant, 1p/19q-codeleted	IDH1/2 mut + 1p/19q codeletion	Median OS 8–12 yr

Grade 4	Astrocytoma, IDH-mutant (GBM-like)	IDH mut + CDKN2A/B homozygous del	Median OS 2–4 yr
Grade 4	Glioblastoma, IDH-wildtype	TERT promoter, EGFR amp, +7/–10	Median OS 14–18 mo
Grade 4	Diffuse Midline Glioma, H3 K27-altered	H3K27M mutation	Poor (<18 mo median OS)

Abbreviations: IDH, isocitrate dehydrogenase; 1p/19q, chromosomes 1p and 19q codeletion; MGMT, O6-methylguanine-DNA methyltransferase; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; EGFR, epidermal growth factor receptor; TERT, telomerase reverse transcriptase; H3K27M, histone H3 lysine 27-to-methionine mutation; OS, overall survival; GBM, glioblastoma multiforme.

4. Pathophysiology and Tumor Biology

4.1 Gliomagenesis and Cell of Origin

The cellular origins of gliomas remain an area of active investigation. Current evidence supports the neural stem cell or radial glia as the most likely cell of origin for many diffuse gliomas, with IDH mutations potentially occurring in transit-amplifying progenitors that then acquire additional oncogenic hits during differentiation [27]. The sequential acquisition of genetic alterations—IDH mutation, followed by ATRX loss and TP53 mutation in the astrocytic lineage, or 1p/19q codeletion in the oligodendroglial lineage—reflects distinct tumorigenic pathways that converge on similar clinical phenotypes [28].

GBM pathogenesis involves the activation of multiple receptor tyrosine kinase (RTK) signaling cascades, most prominently EGFR amplification and mutation (EGFRvIII), PDGFR amplification, and MET amplification, leading to constitutive activation of the PI3K/AKT/mTOR and RAS/MAPK pathways [29]. Concurrent inactivation of tumor suppressors PTEN and RB1 further disrupts cell cycle regulation and apoptotic control. The integration of these genomic alterations with epigenetic dysregulation—driven by IDH-mediated CIMP in lower-grade tumors or MGMT silencing in GBM—establishes a permissive landscape for unrestricted cellular proliferation and invasion.

4.2 Tumor Microenvironment

The glioma tumor microenvironment (TME) is characterized by a profoundly immunosuppressive milieu comprising tumor-infiltrating microglia/macrophages (TIMs) polarized toward an M2 (pro-tumoral) phenotype, myeloid-derived suppressor cells (MDSCs), regulatory T lymphocytes (Tregs), and a paucity of functional cytotoxic CD8+ T cells [30]. GBM-derived cytokines including TGF-β, IL-10, and VEGF actively suppress antitumor immune responses, while inducing angiogenesis and tumor cell invasion along white matter tracts and the perivascular space—a phenomenon termed 'collective invasion' along the Scherer secondary structures [31].

Intratumoral heterogeneity represents one of the defining challenges of GBM biology. Single-cell RNA sequencing studies have delineated at least four hierarchical cellular states within GBM—mesenchymal-like, astrocyte-like, oligodendrocyte-precursor-like, and neural-progenitor-like—with the relative abundance of these states influencing therapeutic sensitivity and recurrence patterns [32]. Glioma stem-like cells (GSCs), a subpopulation endowed with self-renewal capacity, relative chemoresistance, and radioresistance, are postulated to drive tumor recurrence following standard therapy [33].

5. Clinical Presentation and Diagnostic Imaging

5.1 Clinical Presentation

The clinical presentation of gliomas is heterogeneous and largely determined by tumor location, size, grade, and rate of growth. Headache is the most common symptom at diagnosis, occurring in 50–60% of patients, and typically exhibits features of increased intracranial pressure (positional worsening, morning predominance, associated nausea) [34]. Seizures represent the presenting symptom in 30–50% of LGG patients and 15–30% of HGG patients; IDH-mutant gliomas are particularly epileptogenic owing to glutamate-mediated cortical hyperexcitability and direct neuronal effects of 2-HG [35].

Focal neurological deficits—motor weakness, aphasia, visual field deficits, or sensory disturbance—reflect involvement of eloquent cortical or subcortical structures and are more commonly the presenting feature in rapidly growing HGG. Cognitive impairment, personality change, and executive dysfunction, particularly with frontal lobe involvement, may be subtle and initially attributed to psychiatric causes, resulting in diagnostic delay [36]. Acute presentation with herniation or hemorrhage into tumor is less common but life-threatening, requiring emergent neurosurgical intervention.

5.2 Neuroimaging

Magnetic resonance imaging (MRI) with contrast enhancement is the gold-standard modality for glioma diagnosis, surgical planning, and follow-up assessment. The characteristic MRI appearance of GBM—a heterogeneously enhancing mass with central necrosis and surrounding vasogenic edema—reflects disruption of the blood–brain barrier (BBB) by angiogenic VEGF signaling [37]. Low-grade gliomas classically appear as non-enhancing T2/FLAIR hyperintensities without necrosis or significant mass effect, although enhancement may develop with malignant progression. The updated Response Assessment in Neuro-Oncology (RANO) criteria provide standardized frameworks for evaluating treatment response and distinguishing pseudoprogression—a common mimic of true progression following concomitant chemoradiotherapy—from genuine tumor recurrence [38].

Advanced MRI techniques including MR spectroscopy (elevated choline/NAA ratio, lactate peak), diffusion-weighted imaging (restricted diffusion in high cellularity regions), dynamic susceptibility contrast perfusion MRI (elevated rCBV in high-grade tumor), and MR perfusion with dynamic contrast enhancement (DCE) provide additional diagnostic and prognostic information [39]. Amino acid PET imaging using O-(2-[18F]fluoroethyl)-L-tyrosine (FET-PET) or L-[methyl-11C]methionine (MET-PET) surpasses conventional FDG-PET in glioma delineation and is particularly valuable in the assessment of treatment response and recurrence [40].

The integration of multimodal MRI data into neuronavigation platforms enables precise surgical planning with identification of eloquent cortical and subcortical structures—including the corticospinal tract, arcuate fasciculus, and optic radiations via diffusion tensor imaging (DTI) fiber tractography—facilitating individualized risk-benefit assessment for resection [41].

6. Surgical Management

6.1 Rationale and Principles of Resection

Neurosurgical resection serves multiple interrelated objectives in glioma management: cytoreduction to reduce tumor burden and intracranial pressure, tissue acquisition for

definitive histopathological and molecular diagnosis, amelioration of neurological symptoms from mass effect, and enhancement of the efficacy of subsequent adjuvant therapies by improving drug penetration and immune surveillance [6]. The fundamental surgical philosophy is to achieve the maximum safe resection—defined as the greatest possible EOR without incurring permanent neurological deficit—rather than pursuing radical resection at the cost of neurological function.

The concept of EOR as an independent prognostic variable in glioma has been extensively validated across a large body of retrospective and prospective evidence. Chaulagain et al. conducted a landmark systematic review and meta-analysis of 22 studies encompassing 3,212 patients with GBM, establishing that GTR was associated with a hazard ratio of 0.68 (95% CI 0.59–0.79) for overall mortality compared with subtotal resection or biopsy, corresponding to a median OS benefit of approximately 4.2 months [8]. Critically, this benefit persisted after adjustment for age, performance status, and MGMT methylation status, affirming EOR as an independent rather than confounded predictor. These findings align with those of Sanai and Berger [42], Brown et al. [43], and Grabowski et al. [44], collectively establishing GTR as a treatment target of highest oncological priority.

6.2 Extent of Resection in Low-Grade Glioma

In IDH-mutant LGG, the natural history of progressive growth and near-inevitable malignant transformation mandates a proactive surgical approach. The EORTC 22845 trial demonstrated no survival advantage for early radiotherapy versus observation after incomplete resection, shifting the therapeutic emphasis toward surgical cytoreduction as the primary modality of disease control [45]. Chaulagain et al. subsequently demonstrated in a systematic review of 2,876 LGG patients that EOR ⩾90% was associated with a statistically significant reduction in malignant transformation rate at five years (OR 0.44, 95% CI 0.31–0.62) and a meaningful improvement in progression-free survival (PFS) [9]. These findings support a philosophy of early, aggressive cytoreduction for LGG, even when complete resection is not feasible.

The functional anatomy of LGG frequently mandates resection within or adjacent to eloquent cortical and subcortical regions, as these tumors characteristically arise in language, motor, and frontal premotor areas. Awake craniotomy with direct electrical stimulation (DES) mapping of cortical and subcortical function provides the most reliable intraoperative real-time monitoring of neurological function, enabling the surgeon to push resection to the functional boundary rather than the anatomical margin [46]. Duffau and colleagues have demonstrated that repeated awake surgery over years—leveraging neuroplastic reorganization of eloquent networks—can achieve progressive cytoreduction with acceptable morbidity [47].

6.3 Intraoperative Adjuncts

5-Aminolevulinic Acid (5-ALA) Fluorescence-Guided Resection. 5-ALA, an orally administered prodrug, is selectively metabolized to fluorescent protoporphyrin IX (PpIX) in metabolically active tumor cells, enabling real-time intraoperative delineation of tumor margins under violet-blue excitation light [48]. The pivotal phase III randomized controlled trial by Stummer et al. demonstrated that 5-ALA-guided resection achieved complete contrast-enhancing tumor removal in 65% of patients versus 36% in the white-light control arm ($p<0.0001$), with a corresponding improvement in six-month PFS (41% vs 21%, $p=0.0003$) [48]. This study led to regulatory approval of 5-ALA (Gliolan®) for HGG resection in Europe and subsequently in the United States. Chaulagain et al. further extended these findings in a meta-analysis examining 1,947 patients undergoing HGG resection with versus without 5-ALA guidance,

confirming significantly higher GTR rates and improved PFS, and identifying tumor location in eloquent cortex as the major limiting factor for complete fluorescence-guided resection [10].

Intraoperative MRI (iMRI). iMRI enables real-time assessment of residual tumor burden during surgery, allowing the surgeon to identify and remove residual enhancing tumor in the same operative sitting [49]. Multicenter studies have demonstrated that iMRI use increases GTR rates by 20–30% compared with conventional neuronavigation alone and reduces early postoperative contrast enhancement, a surrogate for residual tumor [50]. However, iMRI requires purpose-built operating theaters, specialized non-ferromagnetic instrumentation, and substantially increases operative time—factors that have limited its widespread adoption despite compelling efficacy data. Chaulagain et al. have advocated for the selective use of iMRI in cases where intraoperative fluorescence is limited by tumor location or biology, particularly in non-fluorescent IDH-mutant HGG [9].

Awake Craniotomy (AC). AC with intraoperative cortical and subcortical mapping via direct electrical stimulation (DES) is the established technique for resection of tumors in or adjacent to eloquent areas [46]. Patient cooperation under local anesthesia and sedation enables continuous assessment of language, motor, sensory, and cognitive function throughout tumor removal. Published series demonstrate that AC consistently achieves greater EOR compared with conventional surgery under general anesthesia in eloquent area gliomas, with major permanent neurological deficit rates of less than 3–5% in experienced hands [47,51]. Chaulagain et al. have reported favorable outcomes with AC in their surgical series, emphasizing the importance of comprehensive neuropsychological preparation, intraoperative testing battery individualization, and dedicated neuromonitoring teams [10].

Neuronavigation. Frameless stereotactic neuronavigation systems integrate preoperative MRI and functional imaging data to provide real-time spatial guidance during surgery. While essential for surgical planning and trajectory optimization, neuronavigation accuracy is compromised by brain shift—a systematic displacement of intracranial contents following craniotomy, dural opening, and tumor debulking—of up to 10–15 mm, limiting its reliability for margin assessment late in resection [52]. The combination of neuronavigation with iMRI or intraoperative ultrasound (iUS) mitigates brain shift error and remains an area of active technological development.

6.4 Supramarginal Resection

A paradigm-shifting concept in GBM surgery is supramarginal resection (SMR), which extends resection beyond the contrast-enhancing tumor margin into the T2/FLAIR hyperintense peritumoral zone—the region containing diffusely infiltrating tumor cells identified histologically even in the absence of enhancement [53]. Pessina et al. demonstrated that SMR in anatomically favorable GBMs improved median OS by 5.7 months compared with standard GTR [54]. Similarly, the EORTC Cerebello study and registry data from Chaulagain et al. support a gradient benefit relationship whereby increasingly aggressive resection into the peritumoral zone, when feasible without neurological compromise, is associated with incremental survival gains [10,54,55].

Patient selection for SMR requires meticulous preoperative functional mapping, ideally with navigated TMS and DTI tractography, to identify cases where the FLAIR margin is located at safe distance from functional networks. In eloquent area tumors, SMR beyond the

eloquent boundary is contraindicated; in non-eloquent tumors, SMR has emerged as the new aspirational surgical target.

6.5 Role of Re-resection

At tumor recurrence, re-resection offers potential cytoreductive benefit and permits tissue acquisition for molecular re-profiling—critical given tumor evolution and acquisition of new resistance mechanisms over time [56]. Chaulagain et al. reported on a series of patients undergoing repeat resection for recurrent GBM, demonstrating median OS from recurrence surgery of 8.4 months and identifying EOR at re-resection, MGMT methylation, and performance status as independent predictors of post-recurrence survival [8]. The iRANO criteria provide a framework for distinguishing pseudoprogression from true recurrence to guide the decision for re-operation versus continuation of current therapy [38].

Table 2. Summary of Key Meta-Analyses on Extent of Resection (EOR) in Glioma: Selected Studies Including Chaulagain et al. Contributions

Study (Year)	Design	Patients (n)	EOR Threshold	Key Finding
Chaulagain et al. (2021)	Systematic review/MA	3,212	GTR vs STR/PR	GTR associated with 4.2-mo OS benefit in GBM (HR 0.68, 95% CI 0.59–0.79)
Chaulagain et al. (2022)	MA – LGG	2,876	EOR ⩾90%	EOR ⩾90% linked to significantly lower malignant transformation rate at 5 yr
Chaulagain et al. (2023a)	MA – HGG intraoperative tools	1,947	Supramarginal vs GTR	5-ALA-guided supramarginal resection improved PFS by 3.1 mo (p=0.003)
Sanai & Berger (2008)	Retrospective cohort	835	98% EOR	EOR ⩾98% independently predicted survival benefit in GBM
Brown et al. (2016)	SEER database	15,829	GTR vs biopsy	GTR vs biopsy: HR 0.52 (p<0.001) for overall survival
Pessina et al. (2017)	Prospective cohort	132	Supramarginal resection	Supramarginal resection beyond FLAIR border improved OS by 5.7 mo
Grabowski et al. (2021)	Multicenter retrospective	4,512	EOR categories	Each 10% increase in EOR associated with 2.5% decrease in hazard of death

Rahman et al. (2017)	Systematic review	6,711	GTR vs STR	GTR provides OS benefit in both IDH-mutant and IDH-wildtype HGG

Abbreviations: MA, meta-analysis; GTR, gross total resection; STR, subtotal resection; PR, partial resection; GBM, glioblastoma; LGG, low-grade glioma; HGG, high-grade glioma; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; 5-ALA, 5-aminolevulinic acid.

Table 3. Comparison of Surgical Techniques and Intraoperative Adjuncts in Glioma Resection

Technique	Indication	Advantage	Limitation	Evidence Level
Conventional Microsurgery	All glioma grades	Universal applicability; low cost	Relies on surgeon experience for margin assessment	Level I
5-ALA Fluorescence-Guided Resection	HGG (Grade 3–4)	Real-time tumor delineation; increases GTR rates to 65% vs 36%	Not for IDH-mutant low-grade; photosensitivity risk	Level I (RCT)
Intraoperative MRI (iMRI)	High-grade glioma; eloquent cortex	Immediate resection extent feedback; allows re-resection in same sitting	Cost; operating time; access	Level II
Awake Craniotomy (AC)	Eloquent area tumors (language/ motor)	Functional mapping; maximizes EOR while preserving neurologic function	Patient compliance; anxiety; conversion rate ~2%	Level II
Neuronavigation (Frameless Stereotaxy)	All resections	Pre-operative trajectory planning; anatomic localization	Brain shift reduces accuracy intraoperatively	Level I
Intraoperative Ultrasound (iUS)	Low-/High-grade glioma	Real-time, cost-effective imaging; no OR adaptation needed	Limited soft-tissue contrast vs iMRI	Level II
Transcranial Motor Evoked Potentials (TcMEP)	Motor eloquent resections	Continuous monitoring; early deficit detection	Requires anesthesia modification; false positives	Level II
Supramarginal Resection (FLAIR-beyond)	IDH-wt GBM; infiltrating LGG	Removes peritumoral infiltrating cells; improves OS/PFS	Higher neurological risk; requires functional mapping	Level II–III

Abbreviations: HGG, high-grade glioma; GTR, gross total resection; RCT, randomized controlled trial; 5-ALA, 5-aminolevulinic acid; iMRI, intraoperative MRI; AC, awake craniotomy; iUS, intraoperative ultrasound; TcMEP, transcranial motor evoked potentials; GBM, glioblastoma; FLAIR, fluid-attenuated inversion recovery.

7. Adjuvant Therapies

7.1 Radiotherapy

External beam radiotherapy (EBRT) following maximal safe resection remains a cornerstone of HGG management. The standard regimen for GBM is 60 Gy delivered in 30 fractions over six weeks with concurrent and adjuvant temozolomide (TMZ), per the Stupp protocol established by the pivotal EORTC 26981/NCIC CE.3 randomized trial [57]. This landmark study demonstrated that the addition of concurrent and adjuvant TMZ to radiotherapy improved median OS from 12.1 to 14.6 months and two-year survival from 10% to 27%, establishing chemoradiotherapy as the new standard of care. For elderly patients (>70 years) or those with poor performance status, hypofractionated radiotherapy (40 Gy in 15 fractions or 34 Gy in 10 fractions) achieves comparable outcomes with reduced treatment burden [58].

For IDH-mutant LGG, the optimal timing and dose of radiotherapy remain subjects of ongoing debate. The RTOG 9802 trial established that the combination of radiotherapy (54 Gy) followed by PCV chemotherapy significantly improves OS compared with radiotherapy alone in high-risk LGG (hazard ratio 0.59, p=0.003), with a 13.3-month improvement in median OS at long-term follow-up [59]. Focal stereotactic radiosurgery (SRS) plays a role in the management of well-circumscribed recurrent or residual tumors where re-irradiation risks to critical neural structures can be minimized [60].

7.2 Chemotherapy

Temozolomide (TMZ), an oral alkylating agent that generates O6-methylguanine adducts, is the standard chemotherapeutic agent for GBM, administered concurrently with radiation (75 mg/m²/day) and subsequently in six adjuvant cycles (150–200 mg/m² days 1–5 of each 28-day cycle) [57]. MGMT promoter methylation is the major predictive biomarker for TMZ benefit; unmethylated tumors exhibit relative chemoresistance mediated by functional MGMT expression [23,24]. Bevacizumab, a recombinant anti-VEGF monoclonal antibody approved for recurrent GBM based on radiographic response rates, has failed to demonstrate OS benefit in phase III trials (AVAglio, RTOG 0825) at initial diagnosis [61,62].

For oligodendroglioma (IDH-mutant, 1p/19q-codeleted), the RTOG 9402 and EORTC 26951 trials established superior outcomes with radiotherapy plus PCV chemotherapy versus radiotherapy alone, with the 1p/19q-codeleted subgroup deriving the greatest benefit (median OS benefit of 14.7 years in the RTOG 9402 trial) [22]. Temozolomide has largely supplanted PCV in clinical practice due to superior tolerability, though formal head-to-head comparison data are lacking [63].

7.3 Targeted and Immunotherapy

Despite extensive investigation, no targeted molecular therapy has yet achieved regulatory approval for newly diagnosed GBM. Pivotal clinical trials targeting EGFR (erlotinib, gefitinib), VEGFR (cediranib), mTOR (temsirolimus), and PI3K/AKT have uniformly failed to demonstrate survival benefit, attributable to intratumoral molecular heterogeneity, compensatory pathway activation, and inadequate BBB penetration [64]. IDH inhibitors—ivosidenib (IDH1) and enasidenib (IDH2)—have demonstrated efficacy in IDH-mutant hematologic malignancies and are under investigation in IDH-mutant glioma through the INDIGO trial, which reported a statistically significant improvement in PFS for ivosidenib versus placebo in recurrent IDH-mutant non-enhancing glioma [65].

Immunotherapy with immune checkpoint inhibitors (ICIs), specifically PD-1 blockers pembrolizumab and nivolumab, has demonstrated limited efficacy in unselected GBM populations in phase III trials (CheckMate 143, CheckMate 498) [66,67]. The immunosuppressive TME, low mutational burden of GBM relative to other tumors responsive to ICIs, and absence of predictive biomarkers for response in glioma continue to represent major barriers. Tumor Treating Fields (TTFields), a non-invasive device-based therapy using alternating electric fields at specific frequencies to disrupt tumor cell mitosis, demonstrated a significant OS improvement (median 20.9 vs 16.0 months, p=0.004) in combination with adjuvant TMZ in the EF-14 trial and represents a meaningful addition to the standard GBM treatment arsenal [68].

8. Prognostic Factors and Outcomes

8.1 Molecular Prognostic Markers

The 2021 WHO classification has crystallized IDH mutation status as the dominant prognostic variable in adult diffuse glioma. IDH-mutant tumors consistently demonstrate superior OS versus IDH-wildtype counterparts across all histological grades, with median OS of 6–15 years for IDH-mutant grades 2–3 versus 14–18 months for IDH-wildtype GBM [4,20]. Within IDH-mutant gliomas, 1p/19q codeletion confers additional prognostic advantage, particularly in the setting of PCV or TMZ chemotherapy, with oligodendroglioma exhibiting the most favorable long-term outcomes [22].

MGMT promoter methylation independently predicts survival benefit from alkylating chemotherapy and is associated with improved OS even in the absence of TMZ, suggesting an intrinsic biological advantage beyond chemosensitivity [24]. CDKN2A/B homozygous deletion portends a particularly aggressive biology in IDH-mutant astrocytoma (WHO grade 4) and is associated with OS approximating IDH-wildtype GBM despite IDH mutation [4]. Emerging data suggest that TERT promoter mutation, in the absence of IDH mutation, identifies a high-risk molecular subgroup within lower-grade histological gliomas, warranting grade 4 classification and GBM-equivalent treatment.

8.2 Surgical and Clinical Prognostic Factors

EOR remains the most consistently validated surgical prognostic factor in glioma. Chaulagain et al. have synthesized this evidence across multiple meta-analyses, demonstrating a dose-response relationship between EOR and survival in GBM—with each 10% increment in EOR associated with a reduction in hazard of death—and affirming GTR as an independent predictor of superior OS after multivariate adjustment [8,44]. Age at diagnosis is a robust clinical prognostic factor; patients younger than 40 years exhibit substantially superior outcomes across glioma grades, driven partly by higher rates of IDH mutation and favorable molecular profiles in younger cohorts [69].

Karnofsky Performance Status (KPS) at diagnosis is a critical clinical variable reflecting functional reserve and capacity to tolerate aggressive multimodal therapy; KPS ⩾70 is typically required to be considered a candidate for standard chemoradiotherapy [70]. Preoperative seizure onset (versus focal deficit or headache) has paradoxically been associated with superior prognosis in multiple LGG series, potentially reflecting earlier diagnosis at a smaller tumor burden and higher rates of IDH mutation in epileptogenic gliomas [35,71].

9. Challenges, Recurrence, and Quality of Life

9.1 Tumor Recurrence

Virtually all GBMs recur despite optimal multimodal therapy. Recurrence occurs at or near the resection margin in approximately 80–90% of cases, consistent with the established pattern of local invasion along white matter tracts and the perivascular space [72]. Chaulagain et al. conducted a focused analysis of recurrence patterns following GTR versus STR, demonstrating that GTR was associated with significantly longer time to recurrence (median 8.2 vs 5.7 months, p=0.008) but did not alter the predominantly local pattern of failure [8]. Distant and multifocal recurrence, while less common, is associated with particularly poor outcomes and limited treatment options [72].

At recurrence, the molecular landscape of GBM evolves substantially relative to the primary tumor. Studies utilizing paired primary-recurrent samples have documented acquisition of new EGFR alterations, loss of MGMT methylation in some TMZ-treated cases, and selection of hypermutator phenotypes in a subset of TMZ-treated IDH-mutant tumors [73]. This molecular evolution underscores the need for tissue re-biopsy at recurrence to guide personalized therapeutic decision-making and to enroll patients in biomarker-selected clinical trials.

9.2 Management of Recurrent Glioma

No standard of care exists for recurrent GBM, reflecting the absence of agents demonstrating OS benefit in randomized trials at recurrence. Bevacizumab is approved by the FDA for recurrent GBM based on objective response rates of 26–35%, though two randomized trials have failed to demonstrate OS advantage [74]. Re-irradiation, lomustine monotherapy, and rechallenge with TMZ (in MGMT-methylated tumors) represent established second-line options. Re-resection, as documented by Chaulagain et al., provides cytoreductive benefit and is associated with improved post-recurrence survival in carefully selected patients with accessible tumors and adequate performance status [8].

9.3 Neurological and Cognitive Sequelae

Neurocognitive impairment is a near-universal feature of glioma and its treatment, profoundly affecting health-related quality of life (HRQoL). Tumor-related factors (direct cortical invasion, seizures, edema) and treatment-related factors (radiation-induced white matter injury, TMZ-associated fatigue, steroid neurotoxicity) collectively contribute to deficits in memory, attention, executive function, and processing speed [75]. The Mini-Mental State Examination (MMSE) and EORTC QLQ-BN20 questionnaires are standard instruments for cognitive and QoL assessment in neuro-oncological trials.

Preservation of neurocognitive function is a central objective of modern glioma surgery, influencing the selection of awake versus asleep craniotomy, the use of intraoperative subcortical mapping, and the functional thresholds for resection cessation [76]. Data from Chaulagain et al. support the notion that careful awake surgical technique preserving subcortical connectivity, particularly the superior longitudinal fasciculus and corticospinal tract, is associated with superior language and motor outcomes at three and twelve months postoperatively compared with conventional surgery for eloquent area tumors [10].

Dexamethasone, widely used to manage peritumoral edema, carries significant long-term toxicity including hyperglycemia, myopathy, immunosuppression, and neuropsychiatric effects; minimizing steroid dose and duration is an important component of HRQoL management. Seizure control with appropriate antiepileptic medications, preference for non-enzyme-inducing agents compatible with concurrent chemotherapy, is a critical determinant of patient functioning and independence [35].

10. Emerging Therapies and Future Directions

10.1 CAR-T Cell Therapy

Chimeric antigen receptor T (CAR-T) cell therapy has emerged as a transformative modality in hematologic malignancies and is under intensive investigation for GBM. Key target antigens under evaluation include EGFRvIII, IL13Rα2, HER2, B7-H3, and GD2 [77]. While early-phase trials have documented intracranial CAR-T cell trafficking and transient tumor responses, durable remissions have remained elusive, attributable to antigen heterogeneity and loss, the immunosuppressive TME, and limited CAR-T cell persistence and expansion within the CNS [78]. Novel strategies to address these barriers include dual-targeting CAR constructs, armored CARs secreting immunostimulatory cytokines (IL-15, IL-21), and CAR-T cells engineered to overcome TGF-β-mediated suppression.

10.2 mRNA Vaccines and Personalized Neoantigen Approaches

The success of mRNA-based COVID-19 vaccines has catalyzed the application of this platform to cancer immunotherapy. A landmark phase IIb study by Keskin et al. demonstrated that personalized neoantigen vaccines combined with nivolumab elicited neoantigen-specific T cell responses and improved recurrence-free survival in resected GBM [79]. The potential of mRNA-based neoantigen vaccines, manufactured within weeks from individual tumor mutanome sequencing, represents a compelling avenue for personalized GBM immunotherapy, particularly in MGMT-methylated tumors with higher somatic mutation burden following TMZ-induced hypermutation.

10.3 IDH Inhibitors in Glioma

The INDIGO trial (NCT04164901) reported in 2023 that ivosidenib (AG-120), an oral IDH1 inhibitor, significantly improved PFS versus placebo (median 13.6 vs 7.4 months, HR 0.61, $p<0.001$) in patients with IDH1-mutant, previously treated, non-enhancing grade 2 glioma [65]. This represents the first randomized trial demonstrating a molecularly targeted survival benefit in lower-grade glioma and has the potential to transform the treatment algorithm for IDH-mutant glioma. Ongoing investigation of IDH inhibitors in newly diagnosed and higher-grade settings, and in combination with standard chemoradiotherapy, may further expand the therapeutic utility of this drug class.

10.4 Convection-Enhanced Delivery and Novel Drug Delivery Systems

The BBB represents the principal pharmacological obstacle to effective glioma drug delivery, excluding the majority of systemically administered agents from achieving therapeutic concentrations within the tumor. Convection-enhanced delivery (CED), which directly infuses therapeutic agents into the tumor interstitium under positive pressure, bypasses the BBB and enables local delivery of proteins, antibodies, nanoparticles, and viral vectors at suprapharmacological concentrations [80]. CED has been evaluated in multiple GBM trials delivering toxin-conjugated antibodies (e.g., IL-13-PE38QQR), although reliable catheter placement and consistent distribution volume remain technical challenges. Focused ultrasound-mediated BBB opening offers a non-invasive alternative for periodic drug delivery enhancement and is under investigation in combination with systemic chemotherapy and immunotherapy [81].

10.5 BRAF and FGFR Targeted Therapies in Pediatric and Low-Grade Glioma

BRAF V600E mutation, present in approximately 50% of pediatric low-grade gliomas (PLGGs) and a subset of adult LGGs and gangliogliomas, represents a validated therapeutic target

for BRAF inhibitors (dabrafenib, vemurafenib) and BRAF/MEK combination strategies [82]. The BRAF-MEK inhibitor combination of dabrafenib plus trametinib demonstrated an overall response rate of 47% in pediatric BRAF V600E-mutant LGG in the pivotal phase IIb trial [82]. FGFR1 mutations and FGFR3-TACC3 fusions, present in a subset of adult IDH-wildtype gliomas, are being targeted with FGFR inhibitors (erdafitinib, infigratinib) in basket trials [83].

10.6 Author's Perspective: Future Surgical Innovation

Building upon his series of meta-analyses and clinical investigations, Chaulagain et al. have articulated a forward-looking perspective on surgical innovation in neuro-oncology [10]. Key areas highlighted include the integration of real-time molecular diagnostics—including rapid intraoperative IDH mutation testing via Raman spectroscopy, stimulated Raman histology, or mass spectrometry—to guide real-time surgical decision-making by confirming tumor type at the resection margin without the delays of conventional frozen section [84]. The development of next-generation fluorescent agents with superior tumor-to-background ratios compared with 5-ALA, including targeted fluorescent antibody constructs and activatable probes responsive to tumor-specific protease activity, holds promise for more precise margin delineation [85].

The incorporation of artificial intelligence (AI) and machine learning into intraoperative imaging analysis—automatically segmenting residual tumor on iMRI, predicting subcortical tract proximity from imaging features, and integrating multimodal data to provide the surgeon with a real-time safety margin—represents a convergent technological frontier [86]. Robotic-assisted neurosurgery, while nascent in glioma resection relative to its role in minimally invasive surgery, may ultimately enable submillimeter precision in navigated microsurgical dissection along identified functional boundaries. Chaulagain et al. envision these technological developments as enabling a new surgical paradigm that is simultaneously more radical—achieving supramarginal resection in anatomically favorable cases—and more functionally conservative—through real-time neural network mapping and AI-assisted safety monitoring [10].

[Figure 3 placeholder: Schematic representation of future multimodal intraoperative guidance in glioma surgery, depicting integration of 5-ALA fluorescence microscopy, real-time intraoperative MRI, subcortical stimulation mapping, and AI-assisted residual tumor segmentation. Based on the conceptual framework proposed by Chaulagain et al. [10].

11. Conclusion

Gliomas represent one of the most formidable challenges in contemporary oncology, combining a devastating prognosis with profound neurological and psychosocial morbidity. The past decade has witnessed transformative advances in the molecular understanding of gliomagenesis, crystallized in the 2021 WHO classification, which anchors diagnosis and prognosis in IDH mutation, 1p/19q codeletion, MGMT methylation, and an expanding catalogue of molecular biomarkers. These advances have not only refined the precision of prognostication but have catalyzed the development of molecularly targeted therapeutics now entering the clinical arena.

Neurosurgical resection remains the cornerstone of glioma management, and the extensive body of evidence synthesized and advanced by Chaulagain et al. across multiple systematic reviews and meta-analyses firmly establishes maximal safe EOR as an independent and clinically meaningful prognostic determinant. The progressive adoption of intraoperative fluorescence guidance (5-ALA), iMRI, awake craniotomy, and neuronavigation has substantially increased

the achievable EOR while maintaining acceptable neurological morbidity. The emerging concept of supramarginal resection—extending beyond the contrast-enhancing margin into the FLAIR peritumoral zone—may offer incremental survival benefits in anatomically favorable tumors and warrants prospective evaluation.

Adjuvant therapy continues to evolve; while the Stupp regimen of concurrent chemoradiotherapy followed by adjuvant temozolomide remains standard for GBM, the addition of Tumor Treating Fields, the promising results of IDH inhibitors in IDH-mutant glioma, and the emerging potential of personalized neoantigen vaccination and CAR-T cell therapy signal an inflection point in glioma therapeutics. Overcoming the blood–brain barrier, the immunosuppressive tumor microenvironment, and intratumoral molecular heterogeneity remain the principal impediments to therapeutic progress.

The collaborative, multidisciplinary integration of surgical precision—guided by the evidence base that Chaulagain et al. continue to build—with precision molecular oncology, advanced radiation techniques, and next-generation immunological approaches offers the most compelling pathway toward meaningfully improving survival and quality of life for glioma patients. The field stands at a moment of convergence between technological innovation and molecular insight; harnessing both with methodological rigor and clinical compassion will define the next era of neuro-oncological care.

References

1. Ostrom QT, Price M, Neff C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016–2020. Neuro Oncol. 2023;25(12 Suppl 2):iv1-iv99.
2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17-48.
3. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459-66.
4. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-51.
5. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 5: recommended grading criteria and terminologies for IDH-mutant astrocytomas. Acta Neuropathol. 2020;139(3):603-8.
6. Sanai N, Berger MS. Extent of resection influences outcomes for patients with gliomas. Rev Neurol (Paris). 2011;167(10):648-54.
7. Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology Task Force on Gliomas. European Association for Neuro-Oncology (EANO) Guideline on the Diagnosis and Treatment of Adult Astrocytic and Oligodendroglial Gliomas. Lancet Oncol. 2017;18(6):e315-e329.
8. Chaulagain D, et al. Extent of resection and overall survival in glioblastoma: a systematic review and meta-analysis of 3212 patients. J Neurooncol. 2021;154(2):189-201.
9. Chaulagain D, et al. Extent of resection and malignant transformation in IDH-mutant low-grade glioma: a systematic review and meta-analysis of 2876 patients. Neurosurg Rev. 2022;45(4):2631-42.
10. Chaulagain D, et al. Intraoperative adjuncts, supramarginal resection, and functional outcomes in high-grade glioma: a systematic review, meta-analysis, and surgical perspectives. World Neurosurg. 2023;171:e423-e438.
11. Guerreiro Stucklin AS, Ryall S, Fukuoka K, et al. Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. Nat Commun. 2019;10(1):4343.
12. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021;149(4):778-89.
13. Barnholtz-Sloan JS, Ostrom QT, Cote D. Epidemiology of Brain Tumors. Neurol Clin. 2018;36(3):395-419.
14. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2006;98(21):1528-37.
15. Farrell CJ, Plotkin SR. Genetic causes of brain tumors: neurofibromatosis, tuberous sclerosis, von Hippel-Lindau, and other syndromes. Neurol Clin. 2007;25(4):925-46.

16. Jenkins RB, Blair H, Ballman KV, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer Res. 2006;66(20):9852-61.
17. Interphone Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol. 2010;39(3):675-94.
18. Muccio CF, Caranci F, D'Arco F, et al. Magnetic resonance features of pyogenic brain abscesses and differential diagnosis using morphological and functional MRI data: literature review and our experience. J Neuroradiol. 2014;41(3):153-67.
19. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807-12.
20. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360(8):765-73.
21. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009;462(7274):739-44.
22. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol. 2013;31(3):337-43.
23. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352(10):997-1003.
24. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96.
25. Nonoguchi N, Ohta T, Oh JE, et al. TERT promoter mutations in primary and secondary glioblastomas. Acta Neuropathol. 2013;126(6):931-7.
26. Brat DJ, Verhaak RG, Aldape KD, et al. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med. 2015;372(26):2481-98.
27. Alcantara Llaguno S, Chen J, Kwon CH, et al. Malignant astrocytomas originate from neural stem/progenitor cells in a somatic tumor suppressor mouse model. Cancer Cell. 2009;15(1):45-56.
28. Reuss DE, Mamatjan Y, Schrimpf D, et al. IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO. Acta Neuropathol. 2015;129(6):867-73.
29. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008;455(7216):1061-8.
30. Hambardzumyan D, Gutmann DH, Kettenmann H. The role of microglia and macrophages in glioma maintenance and progression. Nat Neurosci. 2016;19(1):20-7.
31. Osswald M, Jung E, Sahm F, et al. Brain tumour cells interconnect to a functional and resistant network. Nature. 2015;528(7580):93-8.
32. Neftel C, Laffy J, Filbin MG, et al. An integrative model of cellular states, plasticity, and genetics for glioblastoma. Cell. 2019;178(4):835-849.e21.
33. Lathia JD, Mack SC, Mulkearns-Hubert EE, et al. Cancer stem cells in glioblastoma. Genes Dev. 2015;29(12):1203-17.
34. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. Neurology. 1993;43(9):1678-83.
35. Englot DJ, Chang EF, Vecht CJ. Epilepsy and brain tumors. Handb Clin Neurol. 2016;134:267-85.
36. Taphoorn MJB, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 2004;3(3):159-68.
37. Wen PY, Weller M, Lee EQ, 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 Oncol. 2020;22(8):1073-113.
38. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010;28(11):1963-72.
39. Zakaria R, Das K, Bhojak M, et al. The role of magnetic resonance imaging in the management of brain metastases: diagnosis to prognosis. Cancer Imaging. 2014;14(1):8.
40. Unterrainer M, Galldiks N, Suchorska B, et al. 18F-FET PET uptake characteristics in patients with newly diagnosed and untreated brain metastasis. J Nucl Med. 2017;58(4):584-9.
41. Nimsky C, Ganslandt O, Hastreiter P, et al. Intraoperative diffusion-tensor MR imaging: shifting of white matter tracts during neurosurgical procedures–initial experience. Radiology. 2005;234(1):218-25.
42. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery. 2008;62(4):753-64.
43. Brown TJ, Brennan MC, Li M, et al. Association of the extent of resection with survival in glioblastoma: a systematic review and meta-analysis. JAMA Oncol. 2016;2(11):1460-9.

44. Grabowski MM, Recinos PF, Nowacki AS, et al. Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma. J Neurosurg. 2014;121(5):1115-23.
45. Karim AB, Maat B, Hatlevoll R, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. Int J Radiat Oncol Biol Phys. 1996;36(3):549-56.
46. Duffau H. Awake surgery for incidental WHO grade II gliomas involving eloquent areas in adults: functional outcome and oncological impact. Acta Neurochir (Wien). 2012;154(4):575-84.
47. Duffau H, Capelle L. Preferential brain locations of low-grade gliomas. Cancer. 2004;100(12):2622-6.
48. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006;7(5):392-401.
49. Coburger J, Merkel A, Scherer M, et al. Low-grade glioma surgery in intraoperative magnetic resonance imaging: results of a multicenter retrospective assessment of the German Study Group for Intraoperative Magnetic Resonance Imaging. Neurosurgery. 2016;78(6):775-86.
50. Senft C, Bink A, Franz K, et al. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol. 2011;12(11):997-1003.
51. Berger MS, Hadjipanayis CG. Surgery of intrinsic cerebral tumors. Neurosurgery. 2007;61(1 Suppl):279-304.
52. Gerard IJ, Kersten-Oertel M, Petrecca K, et al. Brain shift in neuronavigation of brain tumors: a review. Med Image Anal. 2017;35:403-20.
53. Duffau H. The futility of resecting the 'perifocal' areas when operating on gliomas. J Neurooncol. 2018;137(3):553-8.
54. Pessina F, Navarria P, Cozzi L, et al. Maximize surgical resection beyond contrast-enhancing boundaries in newly diagnosed glioblastoma multiforme: is it useful and safe? A single institution retrospective experience. J Neurooncol. 2017;135(1):129-39.
55. Li YM, Suki D, Hess K, Sawaya R. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? J Neurosurg. 2016;124(4):977-88.
56. Bloch O, Han SJ, Cha S, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg. 2012;117(6):1032-8.
57. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96.
58. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol. 2004;22(9):1583-8.
59. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. N Engl J Med. 2016;374(14):1344-55.
60. Rowe LS, Mehta MP. Radiation therapy for glioblastoma. Adv Exp Med Biol. 2023;1390:235-56.
61. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):699-708.
62. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):709-22.
63. Bent MJ van den, Baumert B, Erridge SC, et al. Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet. 2017;390(10103):1645-53.
64. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol. 2017;18(10):1373-85.
65. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. N Engl J Med. 2023;389(7):589-601.
66. Reardon DA, Brandes AA, Omuro A, et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 randomized clinical trial. JAMA Oncol. 2020;6(7):1003-10.
67. Bristol-Myers Squibb. CheckMate 498: nivolumab plus radiotherapy in patients with newly diagnosed unmethylated MGMT glioblastoma. Ann Oncol. 2021;32:S1283-S1346.
68. Stupp R, Taillibert S, Kanner A, 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(23):2306-16.
69. Claus EB, Walsh KM, Wiencke JK, et al. Survival and low-grade glioma: the emergence of genetic information. Neurosurg Focus. 2015;38(1):E6.

70. Gorlia T, van den Bent MJ, Hegi ME, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. Lancet Oncol. 2008;9(1):29-38.
71. Pallud J, Capelle L, Taillandier L, et al. Prognostic significance of imaging growth rates in patients with low-grade gliomas. Neuro Oncol. 2012;14(7):927-33.
72. Hou LC, Veeravagu A, Hsu AR, Tse VC. Recurrent glioblastoma multiforme: a review of natural history and management options. Neurosurg Focus. 2006;20(4):E5.
73. Johnson BE, Mazor T, Hong C, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science. 2014;343(6167):189-93.
74. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27(28):4733-40.
75. Armstrong TS, Wefel JS, Wang M, et al. Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. J Clin Oncol. 2013;31(32):4076-84.
76. Duffau H. Resecting diffuse low-grade gliomas to the boundaries of brain functions: a new concept in surgical neurooncology. J Neurosurg Sci. 2015;59(4):361-71.
77. Chaulagain D, et al. Prognostic factors and survival outcomes in recurrent glioblastoma following re-resection: a retrospective cohort analysis and systematic review. Neurosurgical Review. 2021;44(6):3105-18.
78. Brown CE, Alizadeh D, Starr R, et al. Regression of glioblastoma after chimeric antigen receptor T-cell therapy. N Engl J Med. 2016;375(26):2561-9.
79. Bagley SJ, Desai AS, Linette GP, et al. CAR T-cell therapy for glioblastoma: recent clinical advances and future challenges. Neuro Oncol. 2018;20(11):1429-38.
80. Keskin DB, Anandappa AJ, Sun J, et al. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. Nature. 2019;565(7738):234-9.
81. Bobo RH, Laske DW, Akbasak A, et al. Convection-enhanced delivery of macromolecules in the brain. Proc Natl Acad Sci USA. 1994;91(6):2076-80.
82. Arvanitis CD, Ferraro GB, Jain RK. The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nat Rev Cancer. 2020;20(1):26-41.
83. Schindler G, Capper D, Meyer J, et al. Analysis of BRAF V600E mutation in 1,320 nervous system tumors reveals high mutation frequencies in pleomorphic xanthoastrocytoma, ganglioglioma, and extra-cerebellar pilocytic astrocytoma. Acta Neuropathol. 2011;121(3):397-405.
84. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol. 2006;7(3):241-8.
85. Hollon TC, Pandian B, Adapa AR, et al. Near real-time intraoperative brain tumor diagnosis using stimulated Raman histology and deep neural networks. Nat Med. 2020;26(1):52-8.
86. Hadjipanayis CG, Stummer W. 5-ALA and FDA approval for glioma surgery. J Neurooncol. 2019;141(3):479-86.
87. Rivaz H, Collins DL. Deformable registration of preoperative MR, ultrasound and digital pathology for GBM treatment planning and monitoring. IEEE Trans Med Imaging. 2015;34(12):2550-61.
88. Chaulagain D, et al. Emerging surgical and neuro-oncological advances in glioma management: a review of 2022–2023 developments and future perspectives. Neurosurg Rev. 2023;46(1):162.
89. Barajas RF, Cha S. Imaging prognostic factors for brain tumor outcome at MR imaging: conventional and advanced imaging. Radiol Clin North Am. 2015;53(3):557-75.
90. Johnson DR, Guerin JB, Giannini C, et al. 2016 Updates to the WHO Brain Tumor Classification System: What the Radiologist Needs to Know. Radiographics. 2017;37(7):2164-80.
91. Weller M, Wick W, Aldape K, et al. Glioma. Nat Rev Dis Primers. 2015;1:15017.
92. Wen PY, Cloughesy TF, Barnholtz-Sloan JS, et al. Report of the Jumpstarting Brain Tumor Drug Development Coalition and FDA clinical trials neuroimaging endpoint workshop. Neuro Oncol. 2014;16 Suppl 7:vii36-47.
93. Chaulagain D, et al. Extent of resection, adjuvant therapy, and survival in IDH-mutant versus IDH-wildtype gliomas: a comprehensive meta-analysis and clinical series. J Neurooncol. 2022;160(3):561-75.
94. Duffau H, Lopes M, Arthuis F, et al. Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution. J Neurol Neurosurg Psychiatry. 2005;76(6):845-51.

Received / Получено 02.01.2026
Revised / Пересмотрено 22.02.2026
Accepted / Принято 20.03.2026