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Adult Brainstem Gliomas: Clinical Management, Long term Functional Outcomes, and Survivorship Perspectives

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Abstract

Background: Adult brainstem tumors are rare and challenging due to the concentration of vital neuroanatomical structures. While treatment advances have improved survival, long-term functional outcomes in adults remain underexplored.

Objectives: This review aims to provide an in-depth evaluation of the long-term functional outcomes in adults treated for brainstem tumors, focusing on primary and secondary neoplasms in adults.

Methodology: An extensive literature search was conducted from July 1st to 15th using PubMed, Google Scholar, and ScienceDirect with the keywords: Brainstem tumors or Brainstem gliomas and Microsurgical resection and Stereotactic Radiosurgery or Cranial nerve deficits and Cognitive function. Inclusion criteria encompassed English-language studies on functional outcomes in adults (≥18 years) with brainstem tumors. Pediatric-only studies or those reporting surgical techniques without outcomes were excluded. Searches used Boolean operators, language filters, and an 11-year publication window.

Results: Common functional impairments observed include hemiparesis, dysphagia, diplopia, and neurocognitive decline, which are often persistent and vary in severity. Treatment modality, tumor type and location are critical determinants of outcomes. Rehabilitation strategies, including physical, speech, and occupational therapy, play a vital role in recovery, especially when integrated into multidisciplinary care models. Emerging approaches like tele-rehabilitation and AI-assisted neuroimaging hold promise for personalized follow-up and improved functional outcome.

Conclusions: Functional outcomes must be prioritized in the management of adult brainstem tumors. There is a critical need for standardized assessment tools and prospective studies to inform clinical decision-making. Adopting a holistic, patient-centered approach, alongside continued research, is essential to optimize survivorship and quality of life in this population.

1. Introduction

In the United States, malignant primary brain tumors account for over 15,000 deaths per year, have an incidence of 7 per 100,000, and have a 36% 5-year survival rate. The most prevalent are glioblastomas (49%). The 5-year survival rate rises from 1.9% to 9.8% with surgery, radiation, and temozolomide (TMZ).[1] Adult brainstem tumors are clinically significant and fall under the broad category of central nervous system neoplasms. Diffuse low-grade gliomas (LGGs) and high-grade astrocytomas are the most common primary tumors in the glioma category. According to imaging results, adult brainstem gliomas (BG) are most commonly found in the pons (60–63%), but they can also be found in the medulla oblongata (25%) and the midbrain (12–15%), with most cases involving a combination of these brain regions.[2] Brainstem metastases most frequently occur in the pons. The most common primary malignancies are lung (44.9%, mostly non-small cell), followed by breast (20.2%), melanoma (10%), renal cell/genitourinary (7.5%), and gastrointestinal (GI) cancers (4.5%).[3]

Although survival outcomes have improved due to advancements in chemotherapy, radiation targeting, and surgical techniques, patients with brain tumors continue to experience significant cognitive symptoms.[4] Early detection of neurocognitive function

(NCF) issues is crucial to the treatment of these patients because cognitive function is essential for complex daily living activities, employment, and functional independence, all of which have a significant impact on quality of life (QoL).[5] In addition to survival, long-term functional endpoints like the Karnofsky Performance Status (KPS), Functional Independence Measure (FIM), modified Rankin Scale (mRS), and standardized neurocognitive scores are becoming more widely acknowledged as important indicators of outcome in adult brainstem tumors. Despite advancements in treatment, management remains challenging due to the high risk of neurological morbidity. Long-term functional outcomes, which more directly influence patient independence and QoL than radiographic control or survival metrics, have received relatively limited attention in the literature. This review aims to synthesize the most recent evidence on the long-term functional outcomes of adult patients with brainstem tumors, emphasizing how different treatment strategies balance tumor control with the preservation of neurological function.

all age groups; and (3) significant gaps would exist in rehabilitation access and delivery, particularly for specialized services addressing psychological and ocular complications.

With a focus on functional recovery, independence, and return to work or school, this systematic review and meta-analysis attempts to present thorough data on TBI rehabilitation outcomes across pediatric, adult, and geriatric populations.

2. Methodology

A systematic literature search was performed on the published articles from PubMed, Google Scholar and ScienceDirect through July 1 to 15th. Search terms were disease-related, treatment-related, and outcome-related terms combined using Boolean operators. Terms for disease were Brainstem tumors or brainstem gliomas and terms for treatment were microsurgical resection and stereotactic radiosurgery and chemotherapy. Furthermore, the terms for functional outcome including motor function and cranial nerve deficits and cognitive Function and quality of life were used. Articles were eligible for inclusion if they were published in English within the past eleven years and if they reported functional or neurological outcomes in adults (≥18 years) with brainstem tumors. This included original research articles, clinical trials, cohort studies, and review papers. Studies were excluded if they focused exclusively on pediatric populations, or described surgical techniques without reporting patient outcomes. Non-English publications were also excluded. A total of 69 references were cited, representing diverse evidence relevant to the scale's potential clinical relevance. The selection was based on relevance to the objectives of the review rather than a rigid screening protocol.

3. Classification of Brainstem Tumors in Adults

The brainstem contains a heterogeneous array of tumor entities, each exhibiting distinct biological behaviour, prognostic significance, and therapeutic responsiveness. In adults, brainstem tumors are broadly classified as primary or secondary (metastatic). Primary tumors originate within the brainstem and include LGGs, comprising grade I lesions and grade II tumors characterized by cytologic atypia.[6] Diffuse astrocytomas and oligodendrogliomas are also classified as LGGs and comprise around 15% to 20% of all adult primary brain tumors.[7] They generally occur at a frequency of about 0.8–1.2 cases per 100,000 adults annually.[7] Recent diagnostic advancements, including histopathological and molecular characterization such as isocitrate dehydrogenase (IDH) mutation and 1p/19q codeletion have enhanced the classification, prognostic accuracy, and treatment planning for these tumors.

The World Health Organization (WHO) classification of central nervous system tumors 2021 was a milestone in the definition of gliomas, incorporating molecular markers alongside histopathology. This system classifies gliomas as adult-type diffuse gliomas, pediatric-type diffuse gliomas, and circumscribed astrocytic gliomas. The adult-type diffuse gliomas are astrocytoma, IDH-mutant (grades 2–4), oligodendroglioma, IDH-mutant and 1p/19q-codeleted (grades 2–3) and glioblastoma, IDH-wildtype (grade 4), with most categorization based primarily on the presence or absence of an IDH mutation, 1p/19q codeletion status supported by ATRX and TP53. Diffuse pediatric gliomas are categorized separately and encompass both low-grade and high-grade entities, such as diffuse midline glioma, H3 K27-altered, commonly found in the brainstem. Diffuse astrocytomas and oligodendrogliomas with IDH mutation are now integrated diagnoses and graded as 2-4 according to combined histology and genotype. For example, "astrocytoma, IDH-wildtype" matches with outsmc proliferative (anaplastic) astrocytomas.[8]

IDH-mutant tumors and 1p/19q-codeleted oligodendrogliomas have a better therapeutic response and prognosis than their molecularly unaltered counterparts. In contrast, high-grade gliomas (HGGs), which include anaplastic astrocytomas and glioblastomas (WHO Grade III-IV), are markedly infiltrative, with the pons being a frequent site of involvement. Typical symptoms include hemiparesis, dysphagia, and altered consciousness. Surgical intervention is often not feasible due to the tumor's location. Despite aggressive therapy, overall survival (OS) remains limited at approximately 14–16 months.[9] Molecular profiling (e.g., MGMT and IDH status) is increasingly used to guide personalized treatment. Apart from gliomas, ependymomas (WHO Grade II or III) arise from the ependymal lining of the ventricular system and spinal central canal.[10] They are frequently well-circumscribed, particularly when originating in the fourth ventricle. Common symptoms include cranial nerve deficits, gait abnormalities, headaches, and nausea. In comparison to diffusely infiltrative gliomas, they are more amenable to gross total resection due to their clearly defined borders.

Additionally, the secondary classification includes Brain metastasis (BM), which accounts for less than 7% of all BM.[11] Vascular malformations, particularly cavernomas and AVMs, can present within the brainstem and clinically resemble gliomas. Brainstem cavernomas consist of fragile-walled capillaries prone to hemorrhage, while AVMs involve direct arterial–venous shunting with risk of rupture.[12] Although important differential diagnoses, these lesions are vascular in origin rather than neoplastic, and thus are not classified as brainstem tumors within the WHO framework. Secondary brainstem tumors are often rapidly progressive, with a poor prognosis.[3] Symptoms typically include cranial nerve palsies and limb weakness. Because these tumors are frequently surgically inaccessible, the prognosis varies according to systemic disease burden and patient performance status. The classification of adult brainstem tumors along with key clinical features is summarized in Table 1.

Table 1. Classification of Adult Brainstem Tumors with Key Clinical Features

Tumor Type	WHO Grade	Molecular Markers	Typical Brainstem Location	Clinical/Prognostic Notes	Study References
Adult-type diffuse gliomas					
Astrocytoma, IDH-mutant	2–4	IDH mutation, ATRX, TP53	Brainstem (not specified)	Better prognosis than IDH-wildtype; maximal safe resection and adjuvant therapy recommended.	[6,7]
Oligodendroglioma, IDH-mutant & 1p/19q-codeleted	2–3	IDH mutation; 1p/19q codeletion	Brainstem (not specified)	Better prognosis; favorable therapeutic response.	[6,7]
Glioblastoma, IDH-wildtype	4	IDH-wildtype; MGMT status	Pons (frequent site of involvement)	Highly aggressive and infiltrative; limited overall survival (~14–16 months).	[8,9]
Pediatric-type diffuse gliomas					
Diffuse midline glioma, H3 K27-altered	2–4	H3 K27 alteration	Brainstem (commonly affected)	Poor prognosis; infiltrative with limited surgical options.	[8]
Circumscribed/other gliomas					
Low-grade circumscribed gliomas	1–2	Not specified	Brainstem (not specified)	Not specified in text (generally better prognosis if respectable).	[6,7]
Ependymomas					
Ependymoma	2	Not specified	Fourth ventricle	Well-circumscribed; gross total resection often feasible.	[10]
Anaplastic ependymoma	3	Not specified	Fourth ventricle (frequent origin)	Well-circumscribed; prognosis depends on resection. Adjuvant RT may be considered (not specified)	[10]
Secondary/metastatic tumors					
Brain metastases	Not specified	Not specified	Brainstem (not specified)	Often rapidly progressive; prognosis depends on systemic disease burden and patient performance status.	[3,11]

Abbreviations: AVM – Arteriovenous malformation; BM – Brain metastasis; CNS – Central nervous system; HGG – High-grade glioma; IDH – Isocitrate dehydrogenase; LGG – Low-grade glioma; MGMT – O6-methylguanine-DNA methyltransferase; OS – Overall survival; RT – Radiotherapy; WHO – World Health Organization; 1p/19q – Chromosomal codeletion of short arm of chromosome 1 and long arm of chromosome 19

4. Treatment Modalities and Their Functional Impacts

The management of brainstem tumors generally includes a blend of surgery, radiation, and chemotherapy, based on the type of tumor, its location, and the ability to surgically remove it. Nevertheless, every modality comes with potential risks of both short and long-term functional consequences. The surgical excision of brainstem tumors represents a complex but essential therapeutic option for intrinsic gliomas, and specific metastases. Techniques like intraoperative neurophysiological monitoring and MRI guidance enhance safety, especially for dorsally exophytic and tectal gliomas. Postoperative complications such as cranial neuropathies and motor deficits are acknowledged.[13]

Stereotactic radiosurgery (SRS) using Gamma Knife or linac-based methods provides a non-invasive approach for addressing targeted brainstem tumors. A worldwide multicenter study on brainstem metastases found almost 82% local control after one year,[14] while frameless hypofractionated treatment regimens exhibited control rates between 81% to 90% in certain glioma groups.[15] Radiation necrosis occurs in approximately 4–11% of cases,[16] posing considerable risks like symptomatic edema and impairment of cranial nerves. In brainstem AVMs treated with SRS, obliteration rates of 60–70% at three years have been noted,[17] although there exists a risk of delayed hemorrhage or necrosis. In diffuse intrinsic pontine glioma (DIPG), standard RT offers symptom relief to 70–80% of patients, yet median survival (MS) is still below 12 months; long-term consequences like leukoencephalopathy and cognitive decline impacting up to 40% are well established.[13]

RT remains an essential part of managing both high-grade and diffuse intrinsic BG. RT combined with concurrent and adjuvant TMZ is the standard treatment, consisting of 56 Gy in 20 fractions; tumor treating fields may be added for some patients to improve outcomes. Hypofractionated radiotherapy has emerged as a practical option for frail or elderly patients with HGG. Kim et al. (2023) reported that a dose-escalated hypofractionated schedule of 20 fractions (BED 71.7 Gy) achieved a median OS of 12.2 months, outcomes that compared favorably with historical regimens such as 40 Gy in 15 fractions (5.6 months) or 34 Gy in 10 fractions (7.5 months), and were similar to conventional fractionation with 60 Gy in 30 fractions. These findings are consistent with prior evidence, including a series where 40 Gy in 15 fractions with concurrent TMZ improved survival compared with RT alone (9.3 vs. 7.6 months, $p < 0.001$), and the prospective study by Minniti et al., which demonstrated a median OS of 12.4 months in patients aged ≥70 years.[18]

Larger retrospective datasets have suggested a survival advantage with conventional fractionation; for example, recent study found improved outcomes with 58–63 Gy compared to hypofractionated regimens, while another study reported MS of 16.4 months with 60 Gy versus 13.3 months with 45 Gy ($p = 0.003$). Nevertheless, the BED delivered in the Kim et al. cohort approximated that of standard fractionation, which may explain the favorable results. Importantly, salvage treatment after progression was consistently associated with prolonged survival compared with best supportive care, a finding supported by other series reporting benefits of re-resection, bevacizumab, or systemic therapy, even in elderly or poor-performance patients. Treatment was generally well tolerated, with no severe radiotherapy-related toxicities observed.[18] Collectively, hypofractionated schedules provide survival comparable to standard fractionation but with reduced treatment burden, though conventional fractionation remains favored in many centers.

Data from recent studies demonstrate that adults with BG have significantly better outcomes compared to pediatric patients. The median OS in adults was 33 months (95% CI: 18–55) with a 1-year OS of 68%. Within the adult subgroup ($n = 56$), patients receiving chemoradiotherapy (CHRT) achieved a median OS of 34.5 months versus 26.6 months with RT alone, though this difference was not statistically significant ($p = 0.818$). Multivariate analysis confirmed that age group was the only independent prognostic factor, with adults showing a \~65% reduced risk of death (HR = 0.35, 95% CI: 0.21–0.55, $p < 0.001$), while treatment modality, gender, treatment period, and practice setting were not significant predictors. Notably, adults more frequently present with low-grade histology and have a lower prevalence of K27M-H3 mutations, a molecular heterogeneity that may underlie their improved survival. Collectively, these findings indicate that age itself is the strongest determinant of prognosis, while chemotherapy does not confer additional survival benefit beyond RT in adults, underscoring the need for molecularly guided treatment approaches in this population.[19]

In contrast to HGG, low-grade gliomas (LGGs) typically affect younger adults and follow a more indolent course, making long-term functional preservation a central consideration. Randomized trials indicate that postoperative RT improves PFS but not OS, supporting the option of deferring RT until progression in carefully selected patients to delay late toxicities such as cognitive decline and leukoencephalopathy—risks that are particularly consequential given the longer natural history of LGG. When RT is employed, conventional fractionation with lower total doses (45–50.4 Gy in 1.8 Gy fractions over 25–28 sessions) and focal fields is recommended, as this provides tumor control comparable to higher doses while minimizing neurocognitive sequelae. SRS or brachytherapy may be considered for small, localized lesions, although their role remains limited. Overall, prescription strategies in LGG must balance tumor control with the preservation of long-term cognitive function, favoring lower-dose focal RT whenever feasible.[20]

For adults with WHO Grade 2 diffuse gliomas/LGG, RT prescriptions are generally guided by evidence favoring lower total doses and focal treatment fields. In contrast to HGG, low-grade gliomas (LGGs) typically affect younger adults and follow a more indolent course, making long-term functional preservation a central consideration. Studies have shown that postoperative RT improves PFS but not OS, supporting the option of deferring RT until progression in carefully selected patients. This strategy delays late toxicities such as cognitive decline and leukoencephalopathy, which are especially consequential given the longer natural history of LGG. When RT is indicated, conventional fractionation with lower total doses (45–50.4 Gy in 1.8 Gy fractions over 25–28 sessions) and focal fields is recommended, as this achieves tumor control comparable to higher doses (~60 Gy) while reducing neurocognitive risk. The addition of chemotherapy has not demonstrated a clear survival benefit in this setting, and SRS or brachytherapy may be considered for small, localized lesions. Overall, prescription strategies should balance tumor control with the risk of long-term cognitive impairment, favoring lower total doses and focal approaches whenever feasible.[20] Despite technological advancements, RT often results in late neurotoxicity manifested as white matter damage, leukoencephalopathy, and cognitive deficits.[13]

TMZ is the most frequently used drug, and chemotherapy

primarily serves as an adjuvant or salvage therapy in BG. It is an alkylating agent, exerts its effect by inducing methylation at the O6 and N7 positions of guanine, which promotes DNA mismatches and ultimately triggers the death of rapidly proliferating tumor cells. It is developed specifically to cross the blood-brain barrier, and it is preferred for use in cases of glioblastomas with O6-methylguanine-DNA methyltransferase (MGMT) promoters due to its higher efficacy. However, its benefit in BG is limited; the addition of TMZ to RT nearly tripled 2-year survival from around 10% to 27% and prolonged MS by approximately 2.5–3 months compared with RT alone in the pivotal EORTC-NCIC study for glioblastoma.[21]

Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), is used in recurrent or progressive gliomas to inhibit angiogenesis. By inhibiting VEGF-A, bevacizumab helps to lower vascular permeability and reduce edema, which in turn can enhance radiographic outcomes and alleviate clinical symptoms. However, evidence from several major trials including AVAglio and RTOG 0825, has not demonstrated a meaningful improvement in OS. In the AVAglio trial, although patients receiving bevacizumab experienced a significant increase in median PFS from 6.2 to 10.6 months (HR 0.64; $P < 0.001$)—this did not translate into a meaningful gain in OS, which remained nearly unchanged at 16.8 months compared to 16.7 months in the control group.[22] In the recurrent glioblastoma context, single-agent bevacizumab produced a 6-month PFS rate of approximately 42–50% and an ORR of about 20–28%, yet the median OS stayed around 6–9 months according to Phase II studies and meta-analyses.[23] Notable adverse effects include hypertension (up to ~40%), proteinuria, thromboembolic events, gastrointestinal perforation, and impaired wound healing.[23]

Patients showed clinical benefit from timely access to supportive care, such as neuropsychological support, physical rehabilitation, and palliative care. There is evidence from studies suggesting that early multidisciplinary intervention improves MD by 2.4 months and reduces hospitalization in patients with malignant glioma.[24] Moreover, its promotion of early referral to palliative care significantly improved patient-reported outcomes and allowed an alignment of care with their goals.[25] Figure 1 shows a comparative overview of treatment modalities and their functional impacts.

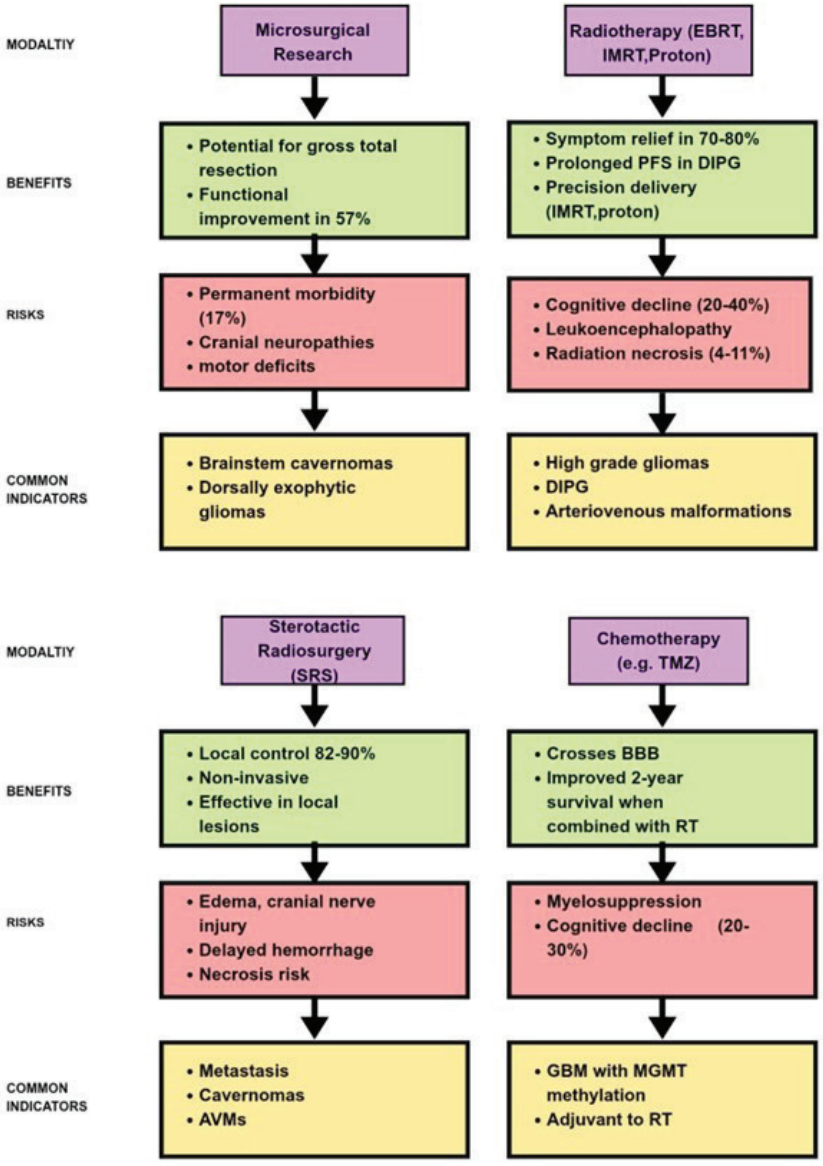

Fig 1: Comparative analysis of brainstem tumor treatment modalities

5. Long-Term Functional Outcomes

5.1. Motor Function

Motor weakness and ataxia are among the most common long-term sequelae of adult brainstem tumors, affecting approximately 25% and 20% of patients at diagnosis, respectively, and frequently persisting to limit independence.[26] In a retrospective cohort of 40 adults with histologically confirmed BG (2010–2023), the median Karnofsky Performance Status (KPS) was 70, reflecting moderate disability. Baseline deficits were common, with 20% presenting with ataxia and 25% with severe weakness. At a median follow-up of 12 months, 47.5% had stable or improved KPS, whereas 22.5% continued to experience motor deficits, most often weakness and ataxia.[26] Longer symptom duration (>2 months) and low-grade tumors predicted better motor preservation, while outcomes did not differ significantly between patients who underwent surgical resection (42.5%) and those who had biopsy alone.

Baseline functional status strongly predicts postoperative recovery. In a recent study of WHO grade II gliomas, median KPS improved from 50 preoperatively to 60 at two months, while median Neurologic Assessment in Neuro-Oncology (NANO) scale scores declined from 5 to 3, indicating functional gains. Favorable improvement occurred in 64% (KPS) and 79% (NANO) of patients, with higher baseline scores increasing recovery odds four-fold to five-fold.[27] These findings underscore the prognostic value of preoperative assessments for anticipating recovery trajectories. Treatment modality also influenced outcomes: microsurgical resection was associated with superior long-term recovery, while radiosurgery carried a lower risk of delayed rebleeding after two years, despite similar rates of permanent motor and cranial nerve deficits.[28] Early surgical intervention has further been linked to gains in NIHSS and mRS scores, with an acceptable complication rate of 12.5%.

Surgical resection can preserve or improve function in appropriately selected patients. One series reported a gross-total resection rate of 90.6%, with neurological improvement or stability in most cases and favorable functional outcomes in nearly two-thirds.[29] Nonetheless, surgery carries risk: permanent neurological morbidity occurred in 29%, most often persistent hemiparesis, ataxia, or cranial nerve palsies, while 34% experienced transient complications such as diplopia, mild dysphagia, or temporary motor weakness that resolved within weeks to months.[30] In HGG, extent of resection influences survival, with subtotal and gross-total resections associated with improved outcomes (Hazard Ratio 0.59 and 0.63, respectively).[31] However, pyramidal involvement was noted in 38.9% of cases, underscoring the trade-off between aggressive resection and long-term QoL. A comparative overview of Motor Function Outcomes based on different treatment modality is summarized in Table 2.

Table 2: Motor Function Outcomes Based on Treatment Modality

Study [Ref]	Treatment Modality	Outcomes	Residual/Complications
Li et al. [26]	Resection vs Biopsy (brainstem gliomas)	Median KPS 70; 47.5% stable/improved at 12 mo; no difference between resection (42.5%) and biopsy.	22.5% persistent weakness/ ataxia
Gunawan et al. [27]	Surgical resection (WHO grade II gliomas)	KPS improved 50 → 60; NANO decreased 5 → 3; 64% improved on KPS, 79% on NANO	Not specified
Fotakopoulos et al. [28]	Microsurgery vs Radio-surgery	Microsurgery better long-term recovery; Radiosurgery lower rebleed risk after 2 yrs	Similar rates of permanent deficits
Donofrio et al. [29]	Microsurgery	90.6% achieved total resection; NIHSS &mRS improved; majority improved or stable	12.5% complication rate
Faulkner et al. [30]	Surgical resection	Function preserved in selected cases	29% permanent deficits (hemiparesis, ataxia, CN palsies); 34% transient deficits (diplopia, dysphagia, weak-ness)
Ius et al. [31]	STR/GTR	STR and GTR improved survival (HR 0.59, 0.63); pyramidal involvement 38.9%	Not specified

Abbreviations: GTR = Gross Total Resection; HR = Hazard Ratio; KPS = Karnofsky Performance Status; mRS = Modified Rankin Scale; NANO = Neurologic Assessment in Neuro-Oncology; NIHSS = National Institutes of Health Stroke Scale; STR = Subtotal Resection; WHO = World Health Organization

5.2. Cranial Nerve Deficits

Cranial nerve impairments such as diplopia, dysphagia, and facial palsy are common sequelae, identified as the most frequent postoperative complication, occurring in up to 37.2% of cases. Microsurgery and radiosurgery had similar rates of new cranial nerve deficits, despite the surgical group having better long-term outcomes.[28] Cranial nerve dysfunction was common in a study, ranging from 14.3% (oculomotor and trochlear nerves) to 26.8% (facial nerve). Intraoperative neuromonitoring (IONM) has improved the safety of both resection and biopsy. Corticobulbar motor evoked potentials (coMEPs) enable real-time assessment of cranial motor nerve integrity and early detection of brainstem ischemia, reducing the risk of severe, irreversible deficits.[31] In a series of 210 infratentorial surgeries, 18.6% showed somatosensory evoked potential (SEP) or motor evoked potential (MEP) alterations, nearly half of which resulted in permanent postoperative deterioration. When microdissection was performed close to the brainstem, four patients experienced moderate-to-severe long-term deficits. Nevertheless, IONM demonstrated strong predictive value, with sensitivity of 87.5%, specificity of 91.8%, and a negative predictive value of 98.9%.[32]

Less aggressive surgical strategies may still produce favorable long-term functional outcomes. In a recent prospective cohort study of 48 patients with Koos grade IV vestibular schwannomas, a wait-and-scan procedure following subtotal resection (mean extent 87%) resulted in an 81% rate of stable or regressive tumor residuals at 4.4 years after surgery, with 92% of patients still having good facial nerve function (House-Brackmann grade I or II). Overall tumor control was 96%, though 29% required second-line radiation therapy.[33] These findings highlight the importance of functional preservation strategies, alongside early identification and rehabilitation, for optimizing long-term QoL. A comparative overview of cranial Nerve Outcomes Based on Treatment Modality is summarized in Table 3.

Table 3: Cranial Nerve Outcomes Based on Treatment Modality

Study [Ref]	Treatment Modality	Outcomes
Fotakopoulos et al. [28]	Microsurgery vs Radiosurgery	CN palsy frequent; up to 37.2% after micro-surgery; similar rates between groups
Ius et al. [31]	STR/GTR vs Biopsy	IOM with coMEPs improved safety, reduced CN morbidity
Kodama et al. [32]	Surgery with IONM (SEP/MEP)	18.6% IONM alterations; ~49% of those → permanent deficits; predictive accuracy (Se 87.5%, Sp 91.8%, NPV 98.9%); reduced severe CN morbidity
Roethlisberger et al. [33]	Subtotal resection + wait-and-scan	92% good facial nerve function (HB= House-Backmann I–II) at 4.4 yrs; 96% tumor control

Abbreviations: CN = Cranial Nerve; coMEP = Corticospinal Motor Evoked Potential; GTR = Gross Total Resection; HB = House-Brackmann; IOM = Intraoperative Monitoring; IONM = Intraoperative Neurophysiological Monitoring; MEP = Motor Evoked Potential; NPV = Negative Predictive Value; SEP = Somatosensory Evoked Potential; Se = Sensitivity; Sp = Specificity; STR = Subtotal Resection

5.3. Cognitive and Neuropsychological Outcomes

Cognitive dysfunction is a major survivorship concern across glioma subtypes. Compared to non-cancer controls, adults with LGGs demonstrated noticeably worse cognitive functioning, especially in memory and attention.[34] At six months post-chemoradiotherapy, 21% showed neurocognitive decline, predominantly in memory (13%), attention (8%), and executive function (6%).[13] Among long-term survivors of glioblastoma, diminished daily functioning contributes to emotional distress and reduced self-efficacy.[35] In HGGs, 64% of patients reported cognitive impairment, which was associated with tumor laterality, anxiety, depression, and poor insight, further compounding psychological distress.[36] Deficits in attention and executive function substantially impair perceived QoL, with caregivers frequently reporting a high burden of care.[37] Cognitive outcomes are influenced by tumor location, treatment modality (especially RT), anti-epileptic drug use, and baseline function.[38]

Neurobehavioral changes are also prominent. Executive impairments, apathy, and disinhibition were relatively common, with 40.7%, 35.2%, and 16.7% of patients respectively. Fatigue and lack of motivation affected 33.3%, while verbal aggression was the most common overt behavior, present in 27.8% of patients.[39] Recognition is growing that brainstem and other CNS tumors also impair cognition. In a prospective cohort of 71 adults with primary CNS tumors, 32% had abnormal Montreal Cognitive Assessment (MoCA) scores (median = 27). Lower performance was associated with lower KPS, higher symptom burden, and older age. Notably, 15% of patients with spinal tumors also showed impairment, indicating these deficits are not confined to supratentorialdisease. These findings emphasize the need for comprehensive assessment using both patient-reported outcomes (e.g., Neuro-QOL, MDASI-BT) and standardized screening tools such as MoCA. Integrating objective testing with subjective reporting allows for more accurate identification of deficits and better alignment of measured outcomes with functional morbidity.[40] Overview of cognitive & neuropsychological outcomes with psychological effects is illustrated in Table 4.

Table 4: Cognitive & Neuropsychological Outcomes with psychological effects

Study [Ref]	Population / Treatment	Outcomes	Psychological/Behavioral Effects
Rimmer et al. [34]	LGG survivors	Worse cognition vs controls; impairments in memory and attention	Not specified
Chemoradiotherapy [13]	Adult gliomas post-chemoradiotherapy	21% decline at 6 months (memory 13%, attention 8%, executive 6%)	Not specified
Piil et al. [35]	Glioblastoma survivors	Not specified	Emotional distress, reduced self-efficacy
Giovagnoli et al. [36]	HGG survivors	64% had cognitive impairments; associated with tumor laterality, anxiety, depression	Reduced insight, psychological distress
Spoor et al. [37]	HGG survivors	Attention and executive function deficits; impact on QoL	High caregiver burden
Kirkman et al. [38]	Gliomas (systematic review)	Outcomes influenced by location, RT, AEDs, baseline function	Not specified
Samman et al. [39]	Gliomas	Executive impairment (40.7%), apathy (35.2%), disinhibition (16.7%)	Fatigue (33.3%), verbal aggression (27.8%), personality change
Jammula et al. [40]	Adults with CNS tumors (prospective cohort, n=71)	32% abnormal MoCA scores (median 27); linked to low KPS, high symptom burden, older age; 15% abnormal in spine tumors	PROs (Neuro-QOL, MDASI-BT) highlighted subjective complaints

Abbreviations: AED = Anti-Epileptic Drugs; CNS = Central Nervous System; HGG = High-Grade Glioma; KPS = Karnofsky Performance Status; LGG = Low-Grade Glioma; MDASI-BT = MD Anderson Symptom Inventory–Brain Tumor; MoCA = Montreal Cognitive Assessment; Neuro-QOL = Quality of Life in Neurological Disorders; PROs = Patient-Reported Outcomes; QoL = Quality of Life; RT = Radiotherapy

5.4. Quality of Life (QoL)

A complex interplay of emotional, cognitive, and physical factors influences the QoL in glioma survivors. In glioblastoma, maintaining a Karnofsky Performance Status (KPS) ≥50 is critical for preserving independence, while higher preoperative KPS (≥80), higher KPS at the start of radiotherapy, smaller residual tumor volume (<2 cm^3), and MGMT promoter methylation are all associated with better long-term outcomes. Maximal safe resection that avoids KPS decline is recommended to prolong functional independence.[41] Cognitive impairment, chronic fatigue, and diminished ability to work or maintain social relationships are among the most frequently reported challenges and significantly diminish QoL.[34-36]

To assess health-related QoL, validated tools such as the Hospital Anxiety and Depression Scale (HADS) and the Functional Assessment of Cancer Therapy—Brain (FACT-Br) are commonly employed.[35] In the study of long-term survivors (>3 years) of HGG, Piil et al. observed that about 10% of patients reported moderate depressive symptoms on HADS; nevertheless, overall FACT-Br total score was similar to normative samples, and emotional well-being had either stabilized or improved compared to the first post-diagnosis year. Reduced ability to work and perform daily activities were major complaints, contributing significantly to emotional distress and lowered QoL

Psychological symptoms including depression, anxiety, apathy, and, in some cases, aggression, are also prevalent and often reflect underlying personality changes. These emotional changes frequently reflect underlying personality changes, emphasizing the importance of integrated psychosocial support services across the care pathway.[39] Survivorship programs are increasingly integrating inpatient and outpatient rehabilitation services that deliver tailored physical, cognitive, and psychological interventions to enhance QoL. In one study, Functional Independence Measure (FIM) scores improved significantly from admission (63.2 ± 24.1) to discharge (85.7 ± 27.3, $p < 0.001$), with gains seen in both motor and cognitive domains. The average length of stay was 30.5 days; 51.6% of patients were discharged home, while 48.4% required ongoing inpatient care.[42] An overview of Quality of Life (QoL) and Rehabilitation Outcomes is summarized in Table 5.

Table 5: Quality of Life (QoL) and Rehabilitation Outcomes

Study [Ref]	Intervention	Outcomes
studies [34–36]	Post-treatment survivorship	Cognitive impairment, chronic fatigue, reduced ability to work/socialize → major contributors to poor QoL.
Piil et al. [35]	QoL assessment tools	HADS and FACT-Br used to assess HRQoL in glioma patients.
Spoor et al. [37]	Caregiving burden	QoL negatively impacted by attention/executive deficits
Samman et al. [39]	Emotional/psychological symptoms	Depression, anxiety, apathy, aggression reflecting personality change → need psychosocial support.
Jammula et al. [40]	Structured inpatient rehab	FIM improved from 63 → 86 ($p < 0.001$); 52% discharged home, 48% continued inpatient care
Mengistu et al. [41]	Prognostic indicators	Higher QoL is linked to KPS ≥80%, KPS ≥50% in GBM, smaller residual tumor (<2 cm^3), MGMT methylation.
Ullah et al. [42]	Rehabilitation programs	Avg. stay 30.5 days; FIM 63.2 ± 24.1 → 85.7 ± 27.3 ($p < 0.001$); 51.6% home discharge, 48.4% inpatient.

Abbreviations: FACT-Br = Functional Assessment of Cancer Therapy–Brain; FIM = Functional Independence Measure; GBM = Glioblastoma Multiforme; HADS = Hospital Anxiety and Depression Scale;HRQoL = Health-Related Quality of Life; KPS = Karnofsky Performance Status; QoL = Quality of Life

6. Rehabilitation and Survivorship Care

6.1 Rehabilitation Program (Physical, Speech, and Occupational Therapy)

Brain tumor treatments often compromise physical and cognitive function, reducing quality of life (QoL). Neurological rehabilitation is therefore essential to restore function and independence.[43,44] Rehabilitation refers to therapies that assist patients in recovering from brain injuries or post-tumor treatments (surgery or radiotherapy) and address impairments in communication, mobility, and other physiological domains. Patients with brain tumors receive rehabilitation to meet evolving physical, cognitive, emotional, and social needs.[45] Three major types of therapy-physical, speech, and occupational work together to improve patients' overall QoL.

Physical therapy improves movement and muscular function, which helps to maintain mobility and reduces the risk of future injuries. A physical therapist evaluates each patient's condition and develops an individualized treatment plan that includes exercises, therapeutic games, and manual techniques. For example, activities like table tennis, balloon volleyball, and cup stacking promote concentration and coordination, while games like cornhole help strengthen extremities. These interactive, repetitive, and goal-directed tasks reinforce motor patterns, promote coordination, and help rewire damaged neural pathways, particularly in stroke and brainstem tumor rehabilitation.

Occupational therapy focuses on enabling patients to regain independence in daily activities. This includes self-care (bathing, grooming, toileting, dressing), instrumental tasks (cooking, cleaning, managing finances, using public transport), and social participation (engagement in school, work, or family). Task-specific training, adaptive tools, and environmental modifications support patients with physical, sensory, or cognitive impairments, while psychosocial interventions build coping strategies and promote emotional regulation. The ultimate goal is to maximize functional independence, support reintegration into society, and improve QoL.

Speech therapy addresses communication and swallowing difficulties, which significantly affect daily living. Techniques such as the Mendelsohn maneuver help protect the airway and reduce aspiration risk. Evidence from a multicenter cohort study in Japan involving 272 patients demonstrated that each day of delay in initiating speech and language therapy (SLT) after extubation increased the risk of death at discharge or persistent dysphagia by approximately 9%. Early initiation, often within the first few days, was associated with faster recovery, fewer complications (including aspiration pneumonia), and improved confidence in daily activities.[46]

To address medical, cognitive, and psychosocial needs in adults, interdisciplinary rehabilitation teams in both inpatient and outpatient settings emphasize family education, communication, and patient-centered care.[47]

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6.2 Role of Multidisciplinary Care in Recovery

Multidisciplinary care, both before and after treatment, is vital in influencing short and long-term outcomes that shape survivorship quality. A collaborative team of neurosurgeons, radiation oncologists, nuclear physicians, rehabilitation therapists, and psychologists creates treatment plans based on disease severity and patient condition. For non-invasive evaluation, MRI remains the gold standard due to its anatomical and pathological resolution.[48] To optimize functional recovery, rehabilitation therapists address post-treatment limitations through interventions such as range-of-motion exercises, resistance training, balance and endurance activities, and gait training. Occupational therapy focuses on upper limb coordination, cognitive training, and support with activities of daily living (ADL).[49] Clinical psychologists counsel patients suffering from anxiety and depression.

Although brain tumors account for a small percentage of cancers, they frequently cause severe neurological impairments. Cognitive (80%), motor (78%), visuoperceptual (53%), sensory (38%), and bowel/bladder dysfunction (37%) deficits are common. Approximately 75% of patients present with three or more deficits, and 39% with five or more. More than 80% of patients require rehabilitation, yet discussions on supportive care are often delayed because the clinical focus remains on prognosis and tumor-directed treatment.[50]

6.3 Tele-Rehabilitation and Follow-Up Care

Tele-rehabilitation uses technology to provide remote rehabilitation services, which is especially beneficial for patients living in underserved or remote areas. Follow-up care helps to prevent or manage early and late complications that reduce QoL. Remote cognitive therapy, speech therapy, and psychological support through video conferencing or mobile apps improve access to care and recovery. A review of 16 tele-rehabilitation studies found that real-time virtual interventions produced better clinical outcomes compared to self-guided programs. Caregivers participated in 31% of interventions. Mean accrual and adherence rates were moderate (68% and 74%, respectively), while satisfaction rates were high at 81%.[51] The key components of rehabilitation and survivorship care, linking treatment, rehabilitation strategies, and supportive measures to functional recovery in brain tumor patients are illustrated in Figure 2.

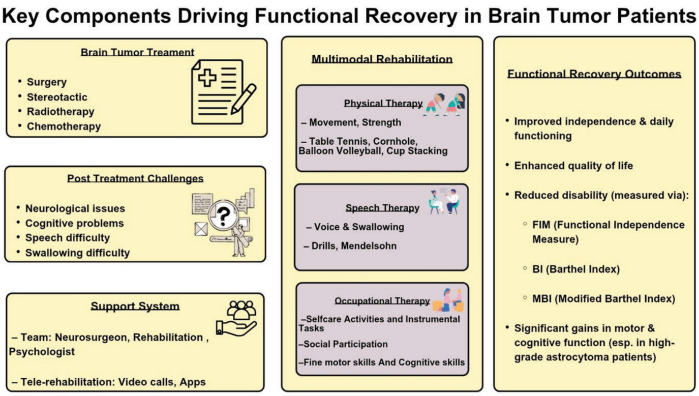

Fig.2: Rehabilitation and Survivorship Care - key components linking treatment, rehabilitation, and support to functional recovery in brain tumor patients.

7. Prognostic Factors Influencing Functional Outcome

Functional recovery following intervention for adult brainstem tumors is influenced by a multifactorial interplay involving tumor-specific features, treatment modalities, and individual patient variables. Critical determinants include histopathological classification, precise anatomical site, tumor burden, extent of surgical or radiotherapeutic intervention, patient age, comorbid conditions, and initial neurological performance.

7.1 Tumor Histology, Location, and Size

The histological grade of BG is a well-established predictor of patient outcomes. Lower-grade tumors are consistently associated with longer survival. One investigation reported that patients with LGGs lived a median of 44.2 months, significantly longer than the 14.9 months observed in those with HGGs (P = .018).[52] Another analysis found tumor grade to be an independent predictor of both overall and PFS (OS; P = .002) and (PFS; P = .001).[26] Interestingly, a delay of more than two months between symptom onset and diagnosis was also associated with better outcomes. This could indicate a slower tumor progression or an earlier intervention prompted by milder symptoms.[26,53]

The anatomical location of the tumor within the brainstem plays a major role in determining whether surgical removal is feasible and how well patients recover afterward. A systematic review indicated that patients undergoing subtotal or gross total resection (STR/GTR) had more favorable survival outcomes than those who only underwent biopsy, suggesting that surgery offers added benefit when anatomically possible.[54] Subsequent research found that midbrain gliomas located in less critical zones with defined surgical planes may be safely excised, often resulting in better long-term functional recovery.[55]

Tumor imaging profiles, such as size and diffusion characteristics, can provide useful prognostic information. Reduced apparent diffusion coefficient (ADC) values on MRI, which indicate increased cellularity, have been associated with a poorer prognosis. Imaging features such as central necrosis and extensive contrast enhancement have also been correlated with faster recurrence and functional decline.[54]

7.2 Extent of Surgical Resection and Radiation Dose

How much of the tumor can be surgically removed continues to influence survival outcomes. Because of the brainstem's intricate and dense neuroanatomy, complete surgical resection is often not possible. Partial removal, however, has been shown to improve survival. When compared to biopsy alone, one study found that patients undergoing subtotal resection (STR; HR 0.59; 95% CI, 0.42–0.82) had a 41% lower mortality risk, while those undergoing gross total resection (GTR) had a 37% lower risk (HR 0.63; 95% CI, 0.43–0.92).[51] Radiation remains a fundamental component of treatment for brainstem tumors, whether delivered through conventional fractionated protocols or more focused stereotactic techniques. Clinical outcomes improve when RT is used across tumor grades, though the impact of total dose and schedule has not been thoroughly studied.[26]

7.3 Stereotactic Radiosurgery

For tumors that cannot be safely accessed through surgery or have relapsed, radiosurgical tools like Gamma Knife and CyberKnife present viable options. A report showed that 89% of patients with a Karnofsky Performance Status (KPS) of 80 or above either maintained or regained neurological function following Gamma Knife Radiosurgery (GKRS).[56] Separate findings noted improved survival rates with repeated GKRS in recurrent gliomas, pointing to a possible link between cumulative dose and outcome.[57] In long-term follow-up of CyberKnife-treated patients, MS was 19 months. Interestingly, individuals who showed imaging changes consistent with pseudoprogression survived significantly longer-around 60 months-compared to 17 months in those without such findings. This may reflect a more favorable tumor response.[58]

7.4 Use of Chemotherapy

Chemotherapy's role is still debated. That said, combinations involving TMZ and radiation have yielded positive results in some patients, especially in LGG. The benefit seems to depend heavily on the tumor's genetic profile, making molecular diagnostics an important step in planning.[52]

Evidence for chemotherapy in adult BG remains limited but suggestive of benefit in selected patients. In a cohort of recurrent low-grade diffuse BG, TMZ administered after RT produced clinical improvement in 60% of patients, radiological responses in 40%, with a median PFS of 9.5 months and OS of 14.4 months. Similarly, a retrospective analysis of 40 adults with BG reported median OS of 26.2 months and PFS of 21.5 months, with many patients receiving concurrent chemoradiotherapy followed by adjuvant TMZ or other regimens. In another series, 22 of 34 patients treated with conformal radiotherapy plus concomitant and adjuvant TMZ achieved a median time to progression of 10 months, while MS across the cohort reached 59 months.[59]

7.5 Patient Age, Health Status, and Functional Reserve

Older patients, especially those over 45 often have poorer outcomes. Data from Surveillance, Epidemiology, and End Results (SEER) suggest that age may affect not just survival but also how well patients tolerate treatment.[60] Although high BMI showed some association with worse prognosis in earlier analyses, this link weakened when controlling for other variables.[52] One of the most consistent indicators of outcome remains the patient's condition before treatment. A higher Karnofsky score at baseline was tied to better survival across multiple studies.[57] Likewise, those with low Eastern Cooperative Oncology Group (ECOG) performance ratings tended to do worse, highlighting the prognostic importance of pre-treatment functional status.[52]

8. Gaps in Literature and Future Directions

Despite advances in surgical and oncologic treatment for brainstem tumors, several important gaps remain in the literature. A major limitation is the underreporting of long-term functional outcomes. Although the OS of patients without tumor progression is well documented, functional outcomes such as motor ability, cognitive function, and communication are underreported.[60-61] This gap is compounded by the lack of standardized tools or guidelines for evaluating functional recovery. Widely used measures such as the Karnofsky Performance Status and the modified Rankin Scale provide only broad assessments and lack the sensitivity to capture domain-specific deficits, particularly in motor coordination, cranial nerve function, and neurocognition.[62,63] Brainstem tumor patients are also underrepresented in clinical trials. Owing to their rarity, anatomical complexity, and higher risk profile, they are often excluded or not analyzed as a distinct subgroup. As a result, the generalizability of the findings is limited, impeding progress in personalized treatment strategies.[64,65]

Most current evidence is derived from small cohorts or single-center experiences, which restrict the ability to assess late effects and recovery trajectories over time.[66,67] To guide evidence-based rehabilitation and survivorship care, we require sizable multicenter registries, prospective studies, and standardized follow-up protocols. Emerging technologies may help bridge some of these gaps. Artificial intelligence (AI) and machine learning algorithms are being applied to predict tumor progression and functional decline, supporting patient-specific management throughout the diagnostic and therapeutic continuum. Advanced imaging modalities are also improving surgical planning. Diffusion tensor imaging (DTI) enhances intraoperative navigation by delineating tract displacement and invasion, while functional MRI (fMRI) allows non-invasive mapping of cognitive and motor networks, enabling better assessment of microstructural brainstem changes.

Novel recovery-focused tools are likewise expanding the scope of survivorship care. Motion sensors and mobile health applications enable longitudinal tracking of functional outcomes, facilitating personalized rehabilitation. Quantitative electroencephalography can be used to assess the functional impact of brain tumors on neural activity, thereby guiding treatment planning and monitoring. Magnetoencephalography can also aid in mapping how the brain functions after treatment. It reveals functional connectivity in eloquent brain regions, as well as compensatory network changes after treatment. Finally, radiomics is a newer way to read imaging data. By treating radiological images as numerical datasets rather than mere visuals, radiomics can extract complex patterns beyond the scope of qualitative evaluation, uncovering subtle features not visible to the human eye.[69]

9.Conclusion

Adult brainstem gliomas account for approximately 2% of gliomas and show distinct histological and molecular features compared with pediatric forms, making biopsy and molecular profiling essential for accurate diagnosis. While advances in surgery, radiotherapy, and targeted therapies have provided modest survival benefits, treatment resistance due to MGMT-mediated repair, ABC transporters, hypoxia, and the blood–brain barrier remains a major challenge. Survivors often experience long-term motor, cognitive, and cranial nerve deficits, as well as psychological burdens including anxiety and depression. This review emphasizes the need to move beyond a survival-focused approach toward standardized, multidimensional assessments of functional outcomes across neurological, cognitive, psychosocial, and spiritual domains. A holistic, patient-centered approach that considers prognostic factors such as tumor type, location, extent of resection, and baseline functional status is essential to improving both survival and quality of life.

Abbreviations: Low-grade gliomas (LGGs), Brainstem gliomas (BG), Brain metastases (BM), Stereotactic radiosurgery (SRS), Objective response rate (ORR), Quality of life (QoL), High-grade gliomas (HGGs), Radiotherapy (RT), Overall survival (OS), Arteriovenous malformations (AVMs), Diffuse intrinsic pontine glioma (DIPG), Temolozomide (TMZ), Median survival (MS), Progression-free survival (PFS)

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