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Cognitive Decline in Glioblastoma Patients with Different Treatment Modalities and Insights on Untreated Cases

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Abstract: Background: Cognitive decline is common in patients with Glioblastoma multiform (GBM) even with treatment modalities, and often presents as impairments in memory, attention, language, and other cognitive functions. In addition, cognitive deficits can affect the quality of life, functional independence, and survival and are associated with other psychological disorders such as anxiety and depression. Methods: This literature review evaluates the cognitive deficits in GBM patients with and without treatment. Then we explore the relationship between tumor characteristics such as size, location, histology and patient characteristics such as age and education level, as well as whether existing therapies, such as surgery, chemotherapy, and radiotherapy, and any change in cognitive function. Results: Cognitive impairment in patients with GBM is affected by tumor characteristics, patient-specific factors, and treatment modalities however some treatments such as a combination of surgery, radiotherapy, and chemotherapy, initially were associated with improvement of cognitive outcomes because the treatments are related to reduced tumor burden, alleviation of cerebral edema, reduced mass effect, and then indirect effects of improved mental health and mood. While certain treatments, such as radiotherapy and chemotherapy pose risks of delayed neurotoxicity, the overall preservation and improvement of cognitive function were more pronounced in treated versus untreated patients. However, the studies suggest that beyond a certain level of treatment aggressiveness and the existence of neurotoxicity or damage, the benefit of therapy is above cognitive preservation. Conclusion: This review highlighted cognitive function as an independent factor that could affect survival in GBM patients, therefore routine cognitive assessments in clinical practice is helpful strategy to predict the prognosis, treatment planning, and rehabilitation efforts. Interventions such as neuroprotective agents, cognitive rehabilitation programs, and personalized, multidisciplinary strategies are crucial in helping to balance treatment effectiveness with cognitive preservation.

Keywords: glioblastoma; cognitive decline; surgery; chemotherapy; radiotherapy; quality of life

1. Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults which involves 47.7% of all brain tumors [1]. The incidence of GBM is 3.21 per 100,000 populations, more common in male gender and the median age is 64 years [2]. In addition, GBM is also known as a rapid growth and poor prognosis brain tumor that can sometimes require a combination of aggressive interventions such as surgery and radiotherapy, and therefore these interventions sometimes might impact patients' cognitive abilities [3].

Cognitive decline is common among patients with GBM before treatment and could affect up to 90% of patients [18,19]. This mental deficit is often challenging for healthcare providers and patients

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and could make the diagnosis harder for patients, and reduce the quality of life, functional independence, and medical decision-making capacity [20,21,22].

Therefore, cognitive deficits are a major concern that can significantly impact a patient's lifestyle and overall well-being, especially when it is associated with certain medical conditions such as a brain tumor. On the other hand, some evidence shows cognitive decline can progress after treatments in patients with GBM. In this literature review, we aimed to evaluate the cognitive outcomes of GBM patients with and without various interventions.

2. Materials and Methods

This narrative review was conducted to evaluate the cognitive outcomes of patients with GBM before and after treatment interventions. The datasets for searching relevant articles included PubMed, MEDLINE, and Web of Science for the articles that were published between 2000 and 2024. The search terms which were used to find relevant articles included 'glioblastoma', 'cognitive function', 'treatment effects', and 'quality of life'. In addition, Boolean operators (AND, OR) were used to optimize this search strategy and deliver the highest number of relevant articles.

Inclusion criteria included studies involving adult patients (>= 18 years old at the time of diagnosis) diagnosed with GBM, research articles that assessed cognitive outcomes in patients before and after treatment for GBM, including surgery, chemotherapy, and/or radiotherapy, or articles that assessed cognitive outcomes in patients with GBM without treatments.

Exclusion criteria also included studies for pediatric patients (<18 years), not assessing cognitive function or lacking required data and non-English.

The extracted data included study design, patient demographics, diagnostic data, treatment modalities, cognitive assessment methods, and primary outcomes, also tumor characteristics (e.g., size, location) and patient variables (e.g., age, education).

Quality assessment of articles was performed using standardized tools based on the articles' study design. Discrepancies in inclusion criteria were resolved through discussion among reviews.

3. Results

GBM is classified as a grade IV astrocytoma based on the World Health Organization (WHO) due to rapid cellular proliferation, diffuse infiltration into surrounding brain tissue, enhanced angiogenesis, and areas of necrosis [3,4]. GBM remains a significant medical challenge for clinicians due to the invasive nature of the tumor, heterogeneity and resistance to available treatments [5].

3.1. Pathophysiology

The exact etiology of GBM is poorly understood, but several risk factors have been identified including genetic mutations in TP53, EGFR amplification and PTEN deletion, exposure to ionizing radiation and certain hereditary syndromes [7].

GBM exhibits rapid growth, high invasiveness, and genetic heterogeneity [8]. Molecular profiling has identified two main subtypes, primary GBM, which arises de novo, and secondary GBM, which progresses from lower-grade astrocytoma [9]. These tumors often display mutations in genes like IDH1 and overexpression of EGFR, contributing to uncontrolled cell proliferation and resistance to apoptosis [10].

3.2. Prognosis and Survival Rates

GBM patients generally have poor prognosis. The median survival is approximately three months without treatment [11]. With the current standard of care—maximal safe surgical resection (MSR) followed by chemoradiotherapy such as Temozolomide or adjuvant Temozolomide—the median overall survival could extend up to approximately 14.6 months [12]. Despite aggressive treatment, the five-year survival rate remains less than 5% [14]. The nature of GBM is considered infiltrative or aggressive, making a complete surgical excision nearly impossible, and the blood-brain

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barrier limits the efficacy of systemic chemotherapy [15]. Recurrence is almost inevitable, often occurring near the original tumor site [17].

4. Cognitive Deficits

4.1. Prevalence and Nature of Cognitive Deficits

Studies have shown that cognitive deficits in GBM patients can affect various domains, including memory, attention, executive functions, language, and visuospatial skills [23,24]. Tucha et al. reported that cognitive deficits are commonly present before treatment, with impairments often in attention, memory, and organizational functions [25]. Similarly, a systematic review by Acevedo-Vergara et al. noted that high-grade gliomas can cause significant alterations in cognitive abilities such as language, attention, memory, empathy, and executive functions [26] [Table 1].

Table 1. Cognitive Domains Affected in Glioblastoma Patients and Influencing Factors.

COGNITIVE DOMAIN	COMMON IMPAIRMENTS	INFLUENCING FACTORS	REFERENCES
MEMORY	Short-term memory loss, difficulty recalling	Temporal lobe involvement, tumor size	[17,18,25]
ATTENTION	Reduced concentration, distractibility	Frontal and parietal lobe involvement	[22,24,27]
EXECUTIVE FUNCTIONS	Impaired planning, decision-making, inhibitory control	Frontal lobe tumors, patient age, treatment effects	[26,27,31]
LANGUAGE	Aphasia, word-finding difficulties	Left hemisphere tumors, surgical impact	[28,29,30]
VISUOSPATIAL SKILLS	Difficulty with spatial orientation and perception	Parietal and occipital lobe involvement	[22,29]
PROCESSING SPEED	Slowed cognitive processing	Treatment effects, overall disease burden	[25,33,77]
EMOTIONAL PROCESSING	Depression, anxiety, altered affect	Tumor location, corticosteroid use	[21,40,41]

4.2. Impact of Tumor Location on Cognition

The location of the tumor significantly influences the type and severity of cognitive impairments in GBM patients. Tumors in the frontal or prefrontal lobes may lead to deficits in executive functions, such as planning, decision-making, and inhibitory control [27,28]. Frontal tumors in untreated patients often result in profound and progressive executive dysfunction due to unchecked tumor growth and mass effect, whereas treated patients may exhibit milder impairments especially if surgical resection spares critical areas of the brain [118].

Temporal lobe involvement often results in memory impairment and language comprehension difficulties [29]. In untreated patients, temporal lobe lesions can cause severe and rapid cognitive decline, particularly in verbal memory. On the other hand, patients undergoing treatment often retain partial function due to compensatory neuroplasticity and adjunct therapies that slow tumor growth, such as radiotherapy [119].

Parietal and occipital lobe tumors can affect spatial orientation and attention, while occipital lobe lesions may impair visual processing [30]. Untreated GBM in these regions is associated with progressive neglect syndromes and cortical blindness. Whereas treated patients may experience

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partial functional preservation or slower decline of function due to neurorehabilitation efforts [120]. Subcortical white matter involvement can disrupt neural networks and lead to wide ranges of cognitive dysfunction, including deficits in processing speed and global connectivity [31].

4.3. Factors Influencing Cognitive Function

Cognitive impairments in GBM patients could be the result of a combination of factors such as:

- Tumor Characteristics: Tumor size, histology, WHO grade, and location are significantly linked to cognitive functioning [32,33,34]. Additionally, larger and more infiltrative tumors are associated with worse cognitive outcomes in untreated patients due to increased mass effect and disruption of adjacent brain regions. Treated patients with smaller residual tumors after resection generally demonstrate better cognitive presentation [120]. Furthermore, patients with IDH-mutant GBM typically demonstrate longer survival and better prognosis, as well as better cognitive outcomes, regardless of treatment [121].
- Patient Characteristics: Age, education level, and genetic markers like IDH mutation status influence cognitive deficit [34,35,36]. Additionally, younger patients undergoing treatment generally exhibit better cognitive resilience compared to untreated older patients, who may in comparison experience more rapid and global cognitive decline [122].
- Treatment Modalities: Surgical resection remains a cornerstone of GBM management.

MSR is associated with better cognitive outcomes when compared to subtotal or no resection. MSR may minimize tumor burden, alleviate mass effect, and reduce edema, all of which can improve neurological function. However, aggressive resection does carry the risk of damaging surrounding brain tissue. Damage to eloquent brain areas may result in cognitive impairment, associated with tumor location and the area of damage [127,128].

In addition, radiotherapy is considered a standard adjuvant therapy for GBM which could have neurotoxic effects in the long term, and cognitive decline following radiotherapy is associated with damage to normal brain tissue, especially the hippocampus, which is critical for memory and learning. Hippocampal-sparing radiotherapy and other advances have been made on this front to mitigate some of these effects [129].

Chemotherapy, particularly with Temozolomide, is another cornerstone of treatment. Temozolomide improves survival but may contribute to cognitive side effects, including impairments in executive functioning and memory [130]. However, the benefits of chemotherapy in improving survival often are more than the associated risks of cognitive decline, particularly when chemotherapy is used as part of a multimodal approach.

Combination therapy, including surgery, radiotherapy, and chemotherapy, generally provides the most favorable outcomes in terms of survival. However, the accumulative effects of these treatments can pose a significant risk to cognitive health. Multimodal approaches that include neuroprotective strategies, such as the use of antioxidants or cognitive rehabilitation programs, have therefore been the subject of study, in hopes of balancing treatment efficacy with cognitive preservation [99].

Other emerging therapies include immunotherapy and targeted molecular treatments being investigated for providing effective tumor control with reduced neurotoxicity. For example, IDH and EGFR mutation-targeting therapies have shown some promise in both improving survival and preserving cognitive function [121].

- Medication Use: The overall effect of medication on cognitive outcomes in the treatment of GBM is complex because some medications can improve cognitive function by reducing tumor-related symptoms, on the other hand, other treatments have potential adverse effects that can worsen cognitive decline [37,38,39]. For example, Antiepileptic drugs (AEDs) and corticosteroids can improve cognitive function in GBM patients by decreasing tumor-related edema and controlling seizures, however, they have some potential side effects. Older AEDs such as Phenytoin are related to sedation and memory deficits, while newer options such as Levetiracetam have a more favorable cognitive profile. Similarly, corticosteroids reduce peritumoral edema, and then

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improve neurological symptoms temporarily, but prolonged use can lead to adverse effects such as mood changes and memory impairments [123,124].

- Clinical Symptoms: Depression, anxiety, and other neuropsychiatric symptoms can impact or increase cognitive dysfunction [40,41]. Untreated patients are more likely to experience severe psychological distress, including anxiety and depression, due to direct and indirect effects of tumor progression, which may further exacerbate cognitive function. Treated patients, however, may benefit from improved mood and mental health, which has been associated with improved cognitive outcomes [125,126].

5. Cognitive Impairment and Survival

Cognitive function is a dependent factor for quality of life and also an independent predictor of survival in GBM patients [42,43]. Several studies have demonstrated that less adequate cognitive performance is associated with shorter survival times, without considering other clinical factors [44,45]. A growing body of evidence highlights the critical role of cognitive function as a predictor of survival in GBM. Cognitive impairment often reflects an underlying tumor burden, treatment side effects, or disease progression, making it a valuable marker for patient outcomes. Meyers et al. found that cognitive function is a significant predictor of survival in patients with recurrent malignant glioma, with verbal memory strongly associated with survival [46]. Johnson et al. demonstrated that early measures of cognitive function, particularly in domains such as attention and executive functions, predict survival in patients with newly diagnosed GBM [47]. This suggests that baseline neurocognitive assessments at diagnosis may provide valuable prognostic information. Similarly, Klein et al. reported that cognitive impairment was associated with a decreased survival rate in high-grade glioma patients irrespective of treatment status (relative risk: 4.099) [48]. This work highlights how the extent and nature of cognitive deficits can reflect tumor progression, mass effect, or adverse treatment responses, all of which may influence prognosis. Cognitive function assessments may therefore not only be a valuable tool for predicting prognosis but also in guiding treatment planning as a baseline and follow-up cognitive assessment may help clinicians balance treatment aggressiveness with preservation of cognitive function.

Assessment of cognitive function should be an essential factor in the clinical management of GBM patients because cognitive evaluations can help predict the prognosis, guide the treatment plan, and affect patient outcomes [47,49].

6. Follow-Up Timing for Patients with GBM After Treatment Options

One of the important factors in managing cognitive deficit patients with GBM after treatment is related to follow-up timing, which clinicians and patients should know about it. According to current research, cognitive impairment could happen about 3 months post-surgery, so physicians should evaluate patients in this time frame for any cognitive impairment because it can cause as an independent factor for survival [133]. In addition, patients with GBM usually need a combination of treatments such as surgery with chemotherapy and radiotherapy and these make a difficult decision for follow-up of these patients because radiotherapy and chemotherapy can cause long-term cognitive function impairments. Therefore, based on studies, an additional follow-up of 6 months to 1 year has been suggested for patients undergoing combination therapies [134,135]. Another question about follow-up is how often we have to check cognitive impairment in these patients, we know that cognitive impairment in these patients can happen immediately or with delayed after treatment, so basically, they need regular monitoring after treatment [135], however for the first three months recommended to check patients every month for cognitive decline and after three months for one year, they need to re-evaluate every three months [133].

7. Treatment Options and Their Cognitive Effects

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The aims of treating GBM are prolonging survival, reducing the symptoms, and maintaining or improving neurological function following the use of standard treatment options such as surgery, chemotherapy, radiotherapy, or a combination of these approaches [49]. While treatments can improve tumor-related cognitive impairments by reducing mass effects and controlling disease progression, they can however increase the risk of additional cognitive decline [50].

7.1. Surgical Interventions

7.1.1. Benefits and Risks

MSR is crucial in the management of GBM patients [51]. Surgery can improve cognitive function due to reducing intracranial pressure and relieving the relative mass effect [52]. However, surgery does have some possible risks such as damage to other healthy parts of the brain, postoperative edema, and anesthesia-related complications, which may result in new or worsened cognitive declines [53,54,55].

7.1.2. Techniques to Preserve Cognition

Neurosurgical techniques aim to maximize tumor resection and preserve cognitive function. One notable approach to resect GBM is the use of awake craniotomy, which allows for real-time assessment of language and motor functions during surgery, thereby reducing the risk of postoperative deficits [56,57]. Intraoperative Brain Mapping helps identify and avoid critical brain areas [58], Lastly, neuronavigation systems enhance precision in tumor removal [59]. So, while these techniques all contribute to improved survival rates and better preservation of cognitive and neurological functions there remains some risk of cognitive decline, even with the use of these advanced surgical methods [60].

7.2. Chemotherapy

7.2.1. Common Agents Used

Temozolomide is the standard chemotherapeutic agent for GBM which is administered with radiotherapy as adjuvant therapy [61]. Temozolomide crosses the blood-brain barrier (BBB) and induces DNA damage in tumor cells [62]. Temozolomide is a drug that can cross BBB. However, the BBB prevents the absorption of chemotherapy medication into the cerebrospinal fluid (CSF), and some techniques exist to disrupt the BBB and increase drug delivery to the tumor.

7.2.2. Neurotoxic Effects

Temozolomide and other chemotherapy medications can improve overall survival and progression-free survival in patients with GBM. However, it can cause some side effects such as fatigue, concentration difficulties, and impairment of cognitive performance [63,64]. Temozolomide is an alkylating agent and can have therapeutic effects by methylating DNA leading to DNA damage and subsequent apoptosis of rapidly dividing tumor cells [13]. However, this mechanism can also damage non-dividing or slow-dividing cells, including neuronal and glial cells, resulting in neurotoxicity and cognitive decline [131]. Higher doses of Temozolomide are associated with greater neurotoxic effects [132].

Other chemotherapeutic agents, such as Nitrosoureas, have higher neurotoxicity profiles and are therefore less commonly used [65].

7.3. Radiotherapy

7.3.1. Radiotherapy Approaches

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Radiotherapy is an adjuvant therapeutic technique which is commonly used to target and destroy residual tumor cells after surgery. Radiotherapy techniques include external beam radiotherapy, intensity-modulated radiotherapy, and stereotactic radiosurgery [66,67].

7.3.2. Cognitive Side Effects

Radiation can cause both acute and delayed cognitive effects through white matter damage, especially periventricular white matter necrosis, vascular injury, and neuroinflammation [68,69,70]. Chronic cognitive effects of radiotherapy, including memory impairment and cognitive dysfunction, may present months to years following treatment [71]. There exist some strategies to minimize these effects, such as fractionation schedules and hippocampal-sparing techniques, but still there remain the adverse effects of radiotherapy on cognition [72,73].

7.4. Combination Therapies

Combining treatments can improve survival outcomes compared to single therapies alone but may also increase the risk and severity of cognitive decline [74,75]. Balancing treatment efficacy with quality-of-life considerations is essential [76] (Table 2).

Table 2. Treatment Modalities for Glioblastoma and Their Cognitive Effects.

TREATMENT MODALITY	POTENTIAL COGNITIVE BENEFITS	POTENTIAL COGNITIVE RISKS	STRATEGIES TO MITIGATE RISKS	REFERENCES
SURGICAL RESECTION	Reduces mass effect, alleviates symptoms	Risk of damage to eloquent brain areas	Awake craniotomy, intraoperative mapping	[51,52,56]
RADIOTHERAPY	Controls residual tumor growth	White matter damage, neuroinflammation	Fractionation schedules, hippocampal-sparing techniques	[66,68,70]
CHEMOTHERAPY (TEMOZOLOMIDE)	Crosses blood-brain barrier prolongs survival	Fatigue, concentration difficulties	Dose management, supportive care	[61,63,64]
COMBINED MODALITY THERAPY	Increased efficacy against tumor cells	Compounded neurotoxicity	Personalized treatment plans	[74,75,76]
EXPERIMENTAL THERAPIES	Potential for targeted treatment	Unknown long-term cognitive effects	Clinical trials, close monitoring	[104,106,108]
COGNITIVE REHABILITATION	Improves specific cognitive deficits	Requires sustained patient engagement	Personalized rehabilitation programs	[89,93,94]

8. Comparative Analysis of Cognitive Outcomes

Understanding the cognitive outcomes in patients with treated versus untreated GBM is crucial for informed decision-making and patient counseling. This comparison provides insights into how treatment modalities might affect cognitive function over time.

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8.1. Treated vs. Untreated Patients

Studies have shown that patients receiving treatment for GBM often experience initial stabilization or improvement in cognitive function, particularly in the early phases of treatment. This is due to tumor debulking and symptom management [77]. However, treatment-related neurotoxicity, including the effect of radiation and chemotherapy may contribute to cognitive decline over time, sometimes months or even years after treatment completion [78].

In contrast, in untreated patients, cognitive decline is typically much more rapid and progressive due to the tumor's aggressive nature that leads to significant tumor growth and quick invasion to the adjacent parenchyma [79]. Acevedo-Vergara et al. reported that high-grade gliomas cause significant alterations in cognitive domains, and patients require neuropsychological evaluation to determine the grade of cognitive dysfunction. Cognitive impairments are generally more severe in high-grade gliomas compared to low-grade gliomas, where brain plasticity processes are faster and more effective, potentially allowing for greater adaptation and less pronounced cognitive difficulties [25].

8.2. Factors Influencing Outcomes

- Several factors can predict cognitive outcomes in GBM patients. This includes age (older patients are more severely affected), baseline cognitive function (individuals with pre-existing cognitive declines may be more susceptible), tumor characteristics such as size, location within critical areas (the frontal lobe), and molecular profile.

Furthermore, the extent of surgical resection (while greater resection may improve survival, it can also increase the risk of cognitive decline). Finally, the type or intensity of treatment (more aggressive treatment options leading to more pronounced side effects) [80-84].

8.3. Importance of Neuropsychological Evaluation

Standard neuropsychological assessments are essential in the management of patients with brain tumors before and after surgery to monitor cognitive function, guide rehabilitation programs, and evaluate treatment outcomes [85]. Performing assessments help identify specific cognitive deficits and inform interventions aimed at improving quality of life [86].

9. Mitigation Strategies for Cognitive Decline

Addressing the cognitive decline in GBM patients involves a comprehensive approach, including advanced medical techniques and supportive therapies.

9.1. Advanced Surgical Techniques

- Awake Craniotomy: Reduces the risk of postoperative cognitive deficits by allowing for real-time monitoring [56,57].
- Functional Brain Mapping: Guides surgical planning to minimize cognitive risks [58].
- Intraoperative Technologies: Neuronavigation and intraoperative imaging enhance surgical precision [59,60].

9.2. Pharmacological Interventions

Research is exploring neuroprotective agents to prevent cognitive decline:

- Memantine: Shown to reduce cognitive decline during radiotherapy [87].
- Donepezil: May improve cognitive function in irradiated patients [88].

9.3. Rehabilitation Programs

9.3.1. Cognitive Rehabilitation

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Structured programs aim to improve specific cognitive deficits through targeted exercises and other strategies [89]. Interventions may focus on:

- Memory Training: Techniques to enhance recall and retention [90].
- Attention and Concentration: Exercises to improve focus [91].
- Executive Function: Problem-solving tasks and organizational skills [92].

Studies have demonstrated that cognitive rehabilitation can lead to significant improvements in cognitive performance and daily functioning [93].

9.3.2. Multidisciplinary Support

Comprehensive care includes the involvement of occupational therapists, speech-language pathologists, and neuropsychologists [94]. Support groups and counseling services address emotional and psychological needs [95].

10. Quality of Life Considerations

Quality of life (QoL) is a multifaceted construct encompassing physiological, psychological, social, and functional well-being. These domains exhibit intricate interdependencies and are integral to an individual's overall health status [96]. In the context of GBM, cognitive impairment is a critical factor that significantly affects the patient's ability to perform daily activities, maintain relationships, and engage in meaningful pursuits, ultimately diminishing their overall QoL [97].

10.1. Psychological Impact

Cognitive deficits can lead to depression and anxiety, social isolation, and emotional instability [98]. These issues contribute to social withdrawal and feelings of helplessness, increasing isolation and worsening emotional distress [99].

Providing psychological support, including cognitive-behavioral therapy (CBT) and counseling, is essential to help patients and families' cope [101].

10.2. Caregiver Burden

Caregivers of patients with GBM often experience significant stress, as they must adapt to the disease progression and patient's changing needs and behaviors. The burden includes constant monitoring, assistance with daily tasks, and navigating emotional complexities. [102]. Support services and respite care can help alleviate caregiver burden by offering practical assistance and providing emotional support, thereby improving the caregiver's well-being and ensuring long-term care for the patient [103].

11. Future Directions and Research Opportunities

Advancements in understanding GBM biology and cognitive neuroscience offer hope for improved outcomes.

11.1. Novel Therapies

11.1.1. Immunotherapy

Approaches such as immune checkpoint inhibitors, vaccines, and CAR T-cell therapy aim to harness the immune system against GBM [104]. Early trials show potential for enhanced efficacy with possibly fewer cognitive side effects [105].

11.1.2. Targeted Molecular Therapies

Drugs targeting specific genetic mutations and pathways in GBM cells may improve treatment specificity and reduce toxicity [106]. Examples include:

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- EGFR Inhibitors: Target overexpressed receptors in GBM [107].
- VEGF Inhibitors: Reduce angiogenesis, e.g., Bevacizumab [108].

11.1.3. Gene Therapy

Gene editing technologies like CRISPR/Cas9 offer avenues for correcting genetic abnormalities in tumor cells [109].

11.2. Personalized Medicine

Integrating genomic and molecular profiling into clinical practice enables tailored treatments based on individual tumor characteristics [110]. This approach aims to maximize efficacy and minimize adverse effects, including cognitive decline [111].

11.3. Neuroprotective Strategies

Ongoing research is focused on identifying agents and interventions that can protect neural tissue during treatment [112]. Investigations into the mechanisms of radiation-induced cognitive decline may lead to novel protective measures [113].

11.4. Rehabilitation Innovations

Advancements in neurorehabilitation, such as computerized cognitive training and virtual reality therapies, offer new modalities for cognitive improvement [114]. Research into neuroplasticity may uncover ways to promote brain recovery [115].

11.5. Clinical Trials and Collaborative Research

Participation in clinical trials provides access to innovative therapies and contributes to the collective understanding of GBM [116]. Collaborative efforts across institutions enhance research quality and accelerate progress [117].

12. Conclusion

Based on available studies and as a conclusion in this review, we can explain that GBM remains a disease that, either with or without treatment, can cause considerable damage to the brain, and then pose a serious threat to both survival and quality of life. On the other hand, cognitive decline in GBM patients is another critical concern that can impair patients' independence, relationships, and overall well-being. While current treatments can extend survival and preserve cognitive function in some cases, however, they also increase risks of neurological damage and then worsen the quality of life and function. Therefore, a personalized, multidisciplinary treatment approach is essential for these patients alongside their standard treatments.

Future research requires to introduce the treatment strategies with more effective and less neurotoxic therapies. In addition, to have better patient care, physicians require the integration of neuroprotective treatment techniques, cognitive rehabilitation programs, and a focus on assessing the quality of life. Furthermore, additional research will be required to systematically compare cognitive function in GBM patients with and without treatment.

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Abbreviations

The following abbreviations are used in this manuscript:

GBM	Glioblastoma multiform
WHO	World health organization
MSR	Maximal safe surgical resection
BBB	Blood-brain barrier
CSF	Cerebrospinal fluid
QoL	Quality of life

References

1. Grochans, S., Cybulska, A. M., Simińska, D., Korbecki, J., Kojder, K., Chlubek, D., & Baranowska-Bosiacka, I. (2022). Epidemiology of glioblastoma multiforme–literature review. Cancers, 14(10), 2412.
2. Thakkar, J. P., Peruzzi, P. P., & Prabhu, V. C. Glioblastoma multiforme. 2021.
3. Ostrom QT, Gittleman H, Truitt G, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011–2015. Neuro-Oncology. 2018;20(suppl_4)–iv86.
4. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A Summary. Acta Neuropathologica. 2016;131(6):803–820.
5. Omuro A, DeAngelis LM. Glioblastoma and Other Malignant Gliomas: A Clinical Review. JAMA. 2013;310(17):1842–1850.
6. Ostrom QT, Bauchet L, Davis FG, et al. The Epidemiology of Glioma in Adults: A "State of the Science" Review. Neuro-Oncology. 2014;16(7):896–913.
7. Thakkar JP, Dolecek TA, Horbinski C, et al. Epidemiologic and Molecular Prognostic Review of Glioblastoma. Cancer Epidemiology, Biomarkers & Prevention. 2014;23(10):1985–1996.
8. Brennan CW, Verhaak RGW, McKenna A, et al. The Somatic Genomic Landscape of Glioblastoma. Cell. 2013;155(2):462–477.
9. Ohgaki H, Kleihues P. The Definition of Primary and Secondary Glioblastoma. Clinical Cancer Research. 2013;19(4):764–772.
10. Furnari FB, Fenton T, Bachoo RM, et al. Malignant Astrocytic Glioma: Genetics, Biology, and Paths to Treatment. Genes & Development. 2007;21(21):2683–2710.
11. DeAngelis LM. Brain Tumors. New England Journal of Medicine. 2001;344(2):114–123.
12. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy Plus Concomitant and Adjuvant Temozolomide for Glioblastoma. New England Journal of Medicine. 2005;352(10):987–996.
13. Hegi ME, Diserens AC, Gorlia T, et al. MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma. New England Journal of Medicine. 2005;352(10):997–1003.
14. Johnson DR, O'Neill BP. Glioblastoma Survival in the United States Before and During the Temozolomide Era. Journal of Neuro-Oncology. 2012;107(2):359–364.
15. Weller M, van den Bent M, Hopkins K, et al. EANO Guideline for the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastoma. The Lancet Oncology. 2014;15(9) e403.
16. Reardon DA, Wen PY. Therapeutic Advances in the Treatment of Glioblastoma: Rationale and Potential Role of Targeted Agents. Oncologist. 2006;11(2):152–164.
17. Tucha O, Smely C, Preier M, Lange KW. Cognitive Deficits Before Treatment Among Patients with Brain Tumors. Neurosurgery. 2000;47(2):324–333.

18. Zucchella C, Bartolo M, Di Lorenzo C, Villani V, Pace A. Cognitive Impairment in Primary Brain Tumors Outpatients: A Prospective Cross-Sectional Survey. Journal of Neuro-Oncology. 2013;112(3):455–460.
19. Johnson DR, Wefel JS. Relationship Between Cognitive Function and Prognosis in Glioblastoma. CNS Oncology. 2013;2(2):195–201.
20. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Neurocognitive Functioning is Associated with Functional Independence in Newly Diagnosed Patients with Temporal Lobe Glioma. Neuro-Oncology Practice. 2018;5(3):184–193.
21. Guariglia L, Ieraci S, Villani V, Tanzilli A, Benincasa D, Sperati F, Terrenato I, Pace A. Coping style in glioma patients and their caregiver: evaluation during disease trajectory. Frontiers in Neurology. 2021 Sep 1; 12:709132.
22. Habets EJJ, Taphoorn MJB, Nederend S, et al. Cognitive Functioning in Patients with Low-Grade Glioma: Effects of Hemispheric Tumor Location and Surgical Procedure. Journal of Neurosurgery. 2019;131(6):1713–1721.
23. Barzilai O, Moshe SB, Sitt R, Sela G, Shofty B, Ram Z. Improvement in cognitive function after surgery for low-grade glioma. Journal of neurosurgery. 2018 Mar 23;130(2):426-34.
24. Tucha O, Smely C, Preier M, Lange KW. Cognitive Deficits Before Treatment Among Patients with Brain Tumors. Neurosurgery. 2000;47(2):324–333.
25. Acevedo-Vergara K, Perez-Florez M, Ramirez A, et al. Cognitive Deficits in Adult Patients with High-Grade Glioma: A Systematic Review. Clinical Neurology and Neurosurgery. 2022; 213:107296.
26. Aabedi AA, Lipkin B, Kaur J, Kakaizada S, Valdivia C, Reihl S, Young JS, Lee AT, Krishna S, Berger MS, Chang EF. Functional alterations in cortical processing of speech in glioma-infiltrated cortex. Proceedings of the National Academy of Sciences. 2021 Nov 16;118(46): e2108959118.
27. Rijnen SJM, Kaya G, Gehring K, et al. Cognitive Functioning in Patients with Low-Grade Glioma: Effects of Hemispheric Tumor Location and Surgical Procedure. Journal of Neurosurgery. 2019;131(6):1713–1721.
28. Duffau H. A New Concept of Diffuse (Low-Grade) Glioma Surgery. Advances and Technical Standards in Neurosurgery. 2003; 28:137–188.
29. O'Brien BJ, Villano JL. Glioblastoma Multiforme: Evidence-Based Approach to Therapy. Expert Review of Anticancer Therapy. 2006;6(11):1595–1606.
30. Hart MG, Romero-Garcia R, Price SJ, Suckling J. Global Effects of Focal Brain Tumors on Functional Complexity and Network Robustness: A Prospective Cohort Study. Neurosurgery. 2019;84(6):1201–1213.
31. Van Kessel E, Baumfalk AE, van Zandvoort MJ, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. Journal of neuro-oncology. 2017 Aug; 134:9-18.
32. Wang Q, Xiao F, Qi F, Song X, Yu Y. Risk factors for cognitive impairment in high-grade glioma patients treated with postoperative radiochemotherapy. Cancer research and treatment: official journal of Korean Cancer Association. 2020 Apr 1;52(2):586-93.
33. Coomans, M.B., Dirven, L. and Taphoorn, M.J., 2019. Quality of life and cognition. Oncology of CNS tumors, pp.769-786.
34. Rijnen SJM, Meskal I, Emons WHM, et al. Cognitive Functioning in Patients with Low-Grade Glioma: Effects of Hemispheric Tumor Location and Surgical Procedure. Journal of Neurosurgery. 2019;131(6):1713–1721.
35. Duffau H. Surgery of low-grade gliomas: towards a 'functional neurooncology'. Current opinion in oncology. 2009 Nov 1;21(6):543-9.
36. Johnson DR, Sawyer AM, Meyers CA, O'Neill BP, Wefel JS. Early Measures of Cognitive Function Predict Survival in Patients with Newly Diagnosed Glioblastoma. Neuro-Oncology. 2012;14(6):808–816.
37. Wefel JS, Noll KR, Scheurer ME. Neurocognitive Functioning and Genetic Variation in Patients with Primary Brain Tumours. The Lancet Oncology. 2016;17(4) e108.
38. Klein M, Engelberts NHJ, van der Ploeg HM, et al. Epilepsy in Low-Grade Gliomas: The Impact on Cognitive Function and Quality of Life. Annals of Neurology. 2003;54(4):514–520.
39. Olson RA, Chhanabhai T, McKenzie M. Feasibility Study of the Montreal Cognitive Assessment (MoCA) in Patients with Brain Metastases. Supportive Care in Cancer. 2008;16(11):1273–1278.

 doi:10.20944/preprints202501.2334.v1

40. Armstrong CL, Goldstein B, Shera D, et al. The Predictive Value of Longitudinal Neuropsychologic Assessment in the Early Detection of Brain Tumor Recurrence. Cancer. 2003;97(3):649–656.
41. Boele FW, Klein M, Reijneveld JC, Verdonck-de Leeuw IM, Heimans JJ. Symptom Management and Quality of Life in Glioma Patients. CNS Oncology. 2014;3(1):37–47.
42. Meyers CA, Hess KR, Yung WKA, Levin VA. Cognitive Function as a Predictor of Survival in Patients with Recurrent Malignant Glioma. Journal of Clinical Oncology. 2000;18(3):646–650.
43. 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. The Lancet Oncology. 2008;9(1):29–38.
44. Klein M, Postma TJ, Taphoorn MJB, et al. The Prognostic Value of Cognitive Functioning in the Survival of Patients with High-Grade Glioma. Neurology. 2003;61(12):1796–1798.
45. Li, J., Bentzen, S.M., Li, J., Renschler, M. and Mehta, M.P., 2008. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. International Journal of Radiation Oncology* Biology* Physics, 71(1), pp.64-70.
46. Meyers CA, Hess KR, Yung WKA, Levin VA. Cognitive Function as a Predictor of Survival in Patients with Recurrent Malignant Glioma. Journal of Clinical Oncology. 2000;18(3):646–650.
47. Johnson DR, Sawyer AM, Meyers CA, O'Neill BP, Wefel JS. Early Measures of Cognitive Function Predict Survival in Patients with Newly Diagnosed Glioblastoma. Neuro-Oncology. 2012;14(6):808–816.
48. Klein M, Postma TJ, Taphoorn MJB, et al. The Prognostic Value of Cognitive Functioning in the Survival of Patients with High-Grade Glioma. Neurology. 2003;61(12):1796–1798.
49. Weller M, van den Bent M, Hopkins K, et al. EANO Guideline for the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastoma. The Lancet Oncology. 2014;15(9) e403.
50. Douw L, Klein M, Fagel SS, et al. Cognitive and Radiological Effects of Radiotherapy in Patients with Low-Grade Glioma: Long-Term Follow-Up. The Lancet Neurology. 2009;8(9):810–818.
51. Sanai N, Berger MS. Glioma Extent of Resection and Its Impact on Patient Outcome. Neurosurgery. 2008;62(4):753–766.
52. Duffau H. Surgery of Low-Grade Gliomas: Towards a "Functional Neurooncology". Current Opinion in Oncology. 2009;21(6):543–549.
53. Meskal I, Gehring K, Rutten G-JM, Sitskoorn MM. Cognitive Functioning in Meningioma Patients: A Systematic Review. Journal of Neuro-Oncology. 2016;128(2):195–205.
54. Taphoorn MJB, Klein M. Cognitive Deficits in Adult Patients with Brain Tumours. The Lancet Neurology. 2004;3(3):159–168.
55. Gempt J, Ringel F, Ryang Y-M, et al. Postoperative Ischemic Changes Following Resection of Newly Diagnosed and Recurrent Gliomas and Their Clinical Relevance. Journal of Neurosurgery. 2013;118(4):866–872.
56. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of Intraoperative Stimulation Brain Mapping on Glioma Surgery Outcome: A Meta-Analysis. Journal of Clinical Oncology. 2012;30(20):2559–2565.
57. Duffau H. Awake Surgery for Nonlanguage Mapping. Neurosurgery. 2010;66(3):523–528.
58. Berger MS, Hadjipanayis CG. Surgery of Intrinsic Cerebral Tumors. Neurosurgery. 2007;61(1 Suppl):279–304.
59. Nimsky C, Ganslandt O, Buchfelder M, Fahlbusch R. Intraoperative Visualization for Resection of Gliomas: The Role of Functional Neuronavigation and Intraoperative 3D Ultrasonography. Child's Nervous System. 2002;18(3-4):445–451.
60. Sanai N, Berger MS. Surgical Oncology for Gliomas: The State of the Art. Nature Reviews Clinical Oncology. 2018;15(2):112–125.
61. 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. The Lancet Oncology. 2009;10(5):459–466.
62. Hegi ME, Diserens AC, Gorlia T, et al. MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma. New England Journal of Medicine. 2005;352(10):997–1003.

 doi:10.20944/preprints202501.2334.v1

63. Aygün C, Yıldırım Altınok A, Çakır A, Ağan AF, Balaban Y. Acute temozolomide induced liver injury: mixed type hepatocellular and cholestatic toxicity. Acta gastro-enterologica Belgica. 2016.
64. Batchelor TT, Betensky RA, Esposito JM, et al. Age-Dependent Prognostic Effects of Genetic Alterations in Glioblastoma. Clinical Cancer Research. 2004;10(1 Pt 1):228–233.
65. Walker MD, Green SB, Byar DP, et al. Randomized Comparisons of Radiotherapy and Nitrosoureas for the Treatment of Malignant Glioma After Surgery. New England Journal of Medicine. 1980;303(23):1323–1329.
66. Brown PD, Buckner JC, O'Fallon JR, et al. Effects of Radiotherapy on Cognitive Function in Patients with Low-Grade Glioma Measured by the Folstein Mini-Mental State Examination. Journal of Clinical Oncology. 2003;21(13):2519–2524.
67. Giordano FA, Brehmer S, Abo-Madyan Y, Welzel G, Sperk E, Keller A, Schneider F, Clausen S, Herskind C, Schmiedek P, Wenz F. INTRAGO: intraoperative radiotherapy in glioblastoma multiforme–a Phase I/II dose escalation study. BMC cancer. 2014 Dec; 14:1-9.
68. Monje ML, Palmer T. Radiation Injury and Neurogenesis. Current Opinion in Neurology. 2003;16(2):129–134.
69. Greene-Schloesser D, Robbins ME. Radiation-Induced Cognitive Impairment—From Bench to Bedside. Neuro-Oncology. 2012;14(Suppl 4) iv44.
70. Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of Radiotherapy-Associated Cognitive Disability in Patients with Brain Tumours. Nature Reviews Neurology. 2017;13(1):52–64.
71. Crossen JR, Garwood D, Glatstein E, Neuwelt EA. Neurobehavioral Sequelae of Cranial Irradiation in Adults: A Review of Radiation-Induced Encephalopathy. Journal of Clinical Oncology. 1994;12(3):627–642.
72. Gondi V, Pugh SL, Tome WA, et al. Preservation of Memory with Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial. Journal of Clinical Oncology. 2014;32(34):3810–3816.
73. Redmond KJ, Mehta M. Stereotactic Radiosurgery for Glioblastoma. Cureus. 2015;7(6).
74. Bae SH, Park MJ, Lee MM, et al. Toxicity Profile of Temozolomide in the Treatment of 300 Malignant Glioma Patients in Korea. Journal of Korean Medical Science. 2014;29(7):980–984.
75. Taphoorn MJB, Klein M. Cognitive Deficits in Adult Patients with Brain Tumours. The Lancet Neurology. 2004;3(3):159–168.
76. Armstrong TS, Lacour N, Gilbert MR, 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. Journal of Clinical Oncology. 2013;31(32):4076–4084.
77. Tucha O, Smely C, Preier M, Lange KW. Cognitive Deficits Before Treatment Among Patients with Brain Tumors. Neurosurgery. 2000;47(2):324–333.
78. Meyers CA, Brown PD. Role and Relevance of Neurocognitive Assessment in Clinical Trials of Patients with CNS Tumors. Journal of Clinical Oncology. 2006;24(8):1305–1309.
79. Deutsch, M.B. and DeAngelis, L.M., 2014. Neurologic complications of chemotherapy and radiation therapy. Aminoff's Neurology and General Medicine, pp.591-609.
80. Batchelor TT, Betensky RA, Esposito JM, et al. Age-Dependent Prognostic Effects of Genetic Alterations in Glioblastoma. Clinical Cancer Research. 2004;10(1 Pt 1):228–233.
81. Klein M, Engelberts NHJ, van der Ploeg HM, et al. Epilepsy in Low-Grade Gliomas: The Impact on Cognitive Function and Quality of Life. Annals of Neurology. 2003;54(4):514–520.
82. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Neurocognitive Functioning is Associated with Functional Independence in Newly Diagnosed Patients with Temporal Lobe Glioma. Neuro-Oncology Practice. 2018;5(3):184–193.
83. Sanai N, Berger MS. Glioma Extent of Resection and Its Impact on Patient Outcome. Neurosurgery. 2008;62(4):753–766.
84. Klein M, Heimans JJ, Aaronson NK, et al. Effect of Radiotherapy and Other Treatment-Related Factors on Mid-Term to Long-Term Cognitive Sequelae in Low-Grade Gliomas: A Comparative Study. The Lancet. 2002;360(9343):1361–1368.

85. Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. Journal of clinical oncology. 2006 Mar 10;24(8):1305-9.
86. Gehring K, Sitskoorn MM, Aaronson NK, Taphoorn MJB. Interventions for Cognitive Deficits in Adults with Brain Tumours. The Lancet Neurology. 2008;7(6):548–560.
87. Brown PD, Pugh S, Laack NN, et al. Memantine for the Prevention of Cognitive Dysfunction in Patients Receiving Whole-Brain Radiotherapy: A Randomized, Double-Blind, Placebo-Controlled Trial. Neuro-Oncology. 2013;15(10):1429–1437.
88. Shaw EG, Rosdhal R, D'Agostino RB Jr, et al. Phase II Study of Donepezil in Irradiated Brain Tumor Patients: Effect on Cognitive Function, Mood, and Quality of Life. Journal of Clinical Oncology. 2006;24(9):1415–1420.
89. Gehring K, Sitskoorn MM, Aaronson NK, Taphoorn MJB. Interventions for Cognitive Deficits in Adults with Brain Tumours. The Lancet Neurology. 2008;7(6):548–560.
90. Zucchella C, Capone L, Codella V, et al. Cognitive Rehabilitation for Early Post-Surgery Cognitive Decline in Patients with Brain Tumours: A Randomized, Controlled Trial. Journal of Neuro-Oncology. 2013;114(1):93–100.
91. Kesler SR, Lacayo NJ, Jo B. A Pilot Study of an Online Cognitive Rehabilitation Program for Executive Function Skills in Children with Cancer-Related Brain Injury. Brain Injury. 2011;25(1):101–112.
92. Locke DE, Cerhan JH, Wu W, et al. Cognitive Rehabilitation and Problem-Solving to Improve Quality of Life of Patients with Primary Brain Tumors: A Pilot Study. Journal of Supportive Oncology. 2008;6(8):383–391.
93. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive Rehabilitation in Patients with Gliomas: A Randomized, Controlled Trial. Journal of Clinical Oncology. 2009;27(22):3712–3722.
94. Bartolo M, Zucchella C, Pace A, et al. Early Rehabilitation After Surgery Improves Functional Outcome in Inpatients with Brain Tumours. Journal of Neuro-Oncology. 2012;107(3):537–544.
95. Moore G, Collins A, Brand C, Gold M, Lethborg C, Murphy M, Sundararajan V, Philip J. Palliative and supportive care needs of patients with high-grade glioma and their carers: a systematic review of qualitative literature. Patient Education and Counseling. 2013 May 1;91(2):141-53.
96. Aaronson NK, Taphoorn MJB, Heimans JJ, et al. Compromised Health-Related Quality of Life in Patients with Low-Grade Glioma. Journal of Clinical Oncology. 2011;29(33):4430–4435.
97. Armstrong TS, Mendoza T, Gning I, et al. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). Journal of Neuro-Oncology. 2006;80(1):27–35.
98. Rooney AG, Carson A, Grant R. Depression in Cerebral Glioma Patients: A Systematic Review of Observational Studies. Journal of the National Cancer Institute. 2011;103(1):61–76.
99. Cavers D, Hacking B, Erridge SC, et al. Social, Psychological and Existential Well-Being in Patients with Glioma and Their Caregivers: A Qualitative Study. CMAJ. 2012;184(7) E382.
100. Ownsworth T, Hawkes A, Steginga S, et al. A Biopsychosocial Perspective on Adjustment and Quality of Life Following Brain Tumor: A Systematic Evaluation of the Literature. Disability and Rehabilitation. 2009;31(13):1038–1055.
101. Sherwood PR, Given BA, Given CW, et al. Predictors of Distress in Caregivers of Persons with a Primary Malignant Brain Tumor. Research in Nursing & Health. 2006;29(2):105–120.
102. Peeters M, Ottenheijm G, Bienfait P, Eekers D, Gijtenbeek A, Hanse M, Koekkoek J, van Leeuwen L, Tijssen C, Dirven L, Taphoorn M. Glioma patient-reported outcomes: patients and clinicians. BMJ Supportive & Palliative Care. 2023 Oct 1;13(e1): e205-12.
103. Sherwood PR, Given BA, Given CW, et al. Predictors of Distress in Caregivers of Persons with a Primary Malignant Brain Tumor. Research in Nursing & Health. 2006;29(2):105–120.
104. 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 Oncology. 2020;6(7):1003–1010.
105. Jackson CM, Lim M, Drake CG. Immunotherapy for Brain Cancer: Recent Progress and Future Promise. Clinical Cancer Research. 2014;20(14):3651–3659.

106. Cloughesy, T., Finocchiaro, G., Belda-Iniesta, C., Recht, L., Brandes, A.A., Pineda, E., Mikkelsen, T., Chinot, O.L., Balana, C., Macdonald, D.R. and Westphal, M., 2017. Randomized, double-blind, placebo-controlled, multicenter phase ii study of onartuzumab plus bevacizumab versus placebo plus bevacizumab in patients with recurrent glioblastoma: efficacy, safety, and hepatocyte growth factor and O6-methylguanine–DNA methyltransferase biomarker analyses. Journal of clinical oncology, 35(3), pp.343-351.
107. Touat M, Idbaih A, Sanson M, Ligon KL. Glioblastoma Targeted Therapy: Updated Approaches from Recent Biological Insights. Annals of Oncology. 2017;28(7):1457–1472.
108. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab Alone and in Combination with Irinotecan in Recurrent Glioblastoma. Journal of Clinical Oncology. 2009;27(28):4733–4740.
109. Han J, Alvarez-Breckenridge CA, Wang QE, Yu J. TGF-β Signaling and Its Targeting for Glioma Treatment. American Journal of Cancer Research. 2015;5(3):945–955.
110. Verhaak RGW, Hoadley KA, Purdom E, et al. Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010;17(1):98–110.
111. Beroukhim R, Mermel CH, Porter D, et al. The Landscape of Somatic Copy-Number Alteration Across Human Cancers. Nature. 2010;463(7283):899–905.
112. Dietrich J, Rao K, Pastorino S, Kesari S. Corticosteroids in Brain Cancer Patients: Benefits and Pitfalls. Expert Review of Clinical Pharmacology. 2011;4(2):233–242.
113. Greene-Schloesser D, Moore E, Robbins ME. Molecular Pathways: Radiation-Induced Cognitive Impairment. Clinical Cancer Research. 2013;19(9):2294–2300.
114. Willard VW, Cox LE, Russell KM, Kenney A, Jurbergs N, Molnar Jr AE, Harman JL. Cognitive and psychosocial functioning of preschool-aged children with cancer. Journal of Developmental & Behavioral Pediatrics. 2017 Oct 1;38(8):638-45.
115. Kannan S, Murugan AK, Balasubramanian S, Munirajan AK, Alzahrani AS. Gliomas: Genetic alterations, mechanisms of metastasis, recurrence, drug resistance, and recent trends in molecular therapeutic options. Biochemical pharmacology. 2022 Jul 1; 201:115090.
116. O'Connor JPB, Rose CJ, Jackson A, et al. DCE-MRI Biomarkers of Tumor Heterogeneity Predict CRC Liver Metastasis Shrinkage Following Combination Chemotherapy. Cancer Research. 2011;71(3):666–675.
117. Stupp R, Taillibert S, Kanner AA, 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. 2015;314(23):2535–2543.
118. Duffau H. Brain plasticity: from pathophysiological mechanisms to therapeutic applications. J Clin Neurosci. 2006 Nov;13(9):885-97. doi: 10.1016/j.jocn.2005.11.045. Epub 2006 Oct 17. PMID: 17049865.
119. Noll KR, Ziu M, Weinberg JS, Wefel JS. Neurocognitive functioning in patients with glioma of the left and right temporal lobes. J Neurooncol. 2016 Jun;128(2):323-31. doi: 10.1007/s11060-016-2114-0. Epub 2016 Mar 29. PMID: 27022915; PMCID: PMC4884162.
120. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. Neurosurgery. 2000 Aug;47(2):324-33; discussion 333-4. doi: 10.1097/00006123-200008000-00011. PMID: 10942005.
121. Weller M, Wick W, Aldape K, Brada M, Berger M, Pfister SM, Nishikawa R, Rosenthal M, Wen PY, Stupp R, Reifenberger G. Glioma. Nat Rev Dis Primers. 2015 Jul 16; 1:15017. doi: 10.1038/nrdp.2015.17. PMID: 27188790.
122. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. Lancet Neurol. 2004 Mar;3(3):159-68. doi: 10.1016/S1474-4422(04)00680-5. PMID: 14980531.
123. Bootsma HP, Aldenkamp AP, Diepman L, Hulsman J, Lambrechts D, Leenen L, Majoie M, Schellekens A, de Krom M. The Effect of Antiepileptic Drugs on Cognition: Patient Perceived Cognitive Problems of Topiramate versus Levetiracetam in Clinical Practice. Epilepsia. 2006;47 Suppl 2:24-7. doi: 10.1111/j.1528-1167.2006.00683. x. PMID: 17105455.
124. Weller M, Cloughesy T, Perry JR, Wick W. Standards of care for treatment of recurrent glioblastoma--are we there yet? Neuro Oncol. 2013 Jan;15(1):4-27. doi: 10.1093/neuonc/nos273. Epub 2012 Nov 7. PMID: 23136223; PMCID: PMC3534423.

125. Renovanz M, Maurer D, Lahr H, Weimann E, Deininger M, Wirtz CR, Ringel F, Singer S, Coburger J. Supportive Care Needs in Glioma Patients and Their Caregivers in Clinical Practice: Results of a Multicenter Cross-Sectional Study. Front Neurol. 2018 Sep 11; 9:763. doi: 10.3389/fneur.2018.00763. PMID: 30254605; PMCID: PMC6141995.
126. Noll KR, Bradshaw ME, Parsons MW, Dawson EL, Rexer J, Wefel JS. Monitoring of Neurocognitive Function in the Care of Patients with Brain Tumors. Curr Treat Options Neurol. 2019 Jun 28;21(7):33. doi: 10.1007/s11940-019-0573-2. PMID: 31250277.
127. Sanai N, Berger MS. Surgical oncology for gliomas: the state of the art. Nat Rev Clin Oncol. 2018 Feb;15(2):112-125. doi: 10.1038/nrclinonc.2017.171. Epub 2017 Nov 21. PMID: 29158591.
128. Hardesty DA, Sanai N. The value of glioma extent of resection in the modern neurosurgical era. Front Neurol. 2012 Oct 18; 3:140. doi: 10.3389/fneur.2012.00140. PMID: 23087667; PMCID: PMC3474933.
129. Brown PD, Gondi V, Pugh S, Tome WA, Wefel JS, Armstrong TS, Bovi JA, Robinson C, Konski A, Khuntia D, Grosshans D, Benzinger TLS, Bruner D, Gilbert MR, Roberge D, Kundapur V, Devisetty K, Shah S, Usuki K, Anderson BM, Stea B, Yoon H, Li J, Laack NN, Kruser TJ, Chmura SJ, Shi W, Deshmukh S, Mehta MP, Kachnic LA; for NRG Oncology. Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients with Brain Metastases: Phase III Trial NRG Oncology CC001. J Clin Oncol. 2020 Apr 1;38(10):1019-1029. doi: 10.1200/JCO.19.02767. Epub 2020 Feb 14. PMID: 32058845; PMCID: PMC7106984.
130. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10;352(10):987-96. doi: 10.1056/NEJMoa043330. PMID: 15758009.
131. Johnson DR, Wefel JS. Relationship between cognitive function and prognosis in glioblastoma. CNS Oncol. 2013 Mar;2(2):195-201. doi: 10.2217/cns.13.5. PMID: 25057978; PMCID: PMC6169490.
132. Chamberlain MC, Kormanik PA. Practical guidelines for the treatment of malignant gliomas. West J Med. 1998 Feb;168(2):114-20. PMID: 9499745; PMCID: PMC1304839.
133. Butterbrod E, Synhaeve N, Rutten GJ, Schwabe I, Gehring K, Sitskoorn M. Cognitive impairment three months after surgery is an independent predictor of survival time in glioblastoma patients. Journal of Neuro-oncology. 2020 Aug;149:103-11.
134. Sharma, Prashasti, Partha Pratim Medhi, Apurba Kumar Kalita, Mouchumee Bhattacharyya, Jyotiman Nath, Gautam Sarma, and Yanpothung Yanthan. "Factors associated with neurocognitive impairment following chemoradiotherapy in patients with high-grade glioma: results of a prospective trial." *Brain Tumor Research and Treatment* 11, no. 3 (2023): 183-190.
135. Schagen SB, Wefel JS. Chemotherapy-related changes in cognitive functioning. European Journal of Cancer Supplements. 2013 Sep 1;11(2):225-32.