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REVIEW ARTICLE

Neuro-oncology and supportive care: the role of the neurologist

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Abstract
The diagnosis of a brain tumor is a life-changing event for patients and their families. Despite numerous treatment advances, malignant brain tumors are universally incurable and long-term survival is limited. Treatment response, prognosis, and survival depend on underlying histopathology and recently defined molecular features. Patients suffer from a disproportionately high symptom burden throughout the disease trajectory and at the end of life. Pronounced neurologic decline and psychological distress significantly impair quality of life (QoL) and impose high supportive care needs relative to other systemic cancers. Palliative interventions addressing brain tumor-specific symptoms, such as seizures, cognitive dysfunction, and headaches, are paramount to maintaining QoL. In the terminal phase of illness, most brain tumor patients lose the ability to communicate and participate in end-of-life decision-making. The benefits of advance care planning and early integration of specialized palliative care are well-established in other systemic cancers and have received wider recognition in neuro-oncology. We review how to approach neurological symptoms in brain tumor patients, as well as address prognosis and advance care planning with the goal of improving QoL for patients and caregivers.

Keywords Brain tumor · Supportive care · End of life · Glioblastoma · Palliative care · Quality of life

Brain tumors: an overview

Brain tumors are a diverse group of low-grade and malignant neoplasms arising directly from brain tissue. Primary malignant brain neoplasms comprise 2% of adult cancers and are characterized by high morbidity and mortality [1]. The majority (80–85%) of malignant brain tumors are high-grade gliomas (HGGs), including glioblastoma (GBM), anaplastic astrocytomas, and anaplastic oligodendrogliomas. GBM, a WHO grade IV astrocytoma, is the most common malignant brain tumor in adults and portends an extremely poor prognosis with a median survival of 12–15 months despite aggressive multimodal therapy [2].

Standard oncologic staging paradigms are inapplicable to primary brain tumors as they rarely disseminate beyond the neuroaxis. Instead, brain tumors are graded based on biologic and genetic features per the WHO Classification of Tumors of the Central Nervous System [3]. This grading system provides a framework for prognostication and treatment decision-making. The last several decades have seen a radical shift from histology-based diagnosis towards molecular and genetic categorization of gliomas. These insights represent important progress in our understanding of glioma pathogenesis and are the basis for the future development of targeted therapies. Key prognostic and predictive molecular alterations per the WHO 2021 Classification are delineated in Table 1 [3].

Treatment of gliomas

The current standard of care for HGG includes maximal safe resection and external beam radiotherapy (EBRT) with concurrent temozolomide (TMZ), followed by adjuvant TMZ for 6–12 cycles. Tumor treating field (TTF) is a novel device that is thought to induce tumor cell death by delivering alternating electrical fields through superficial scalp electrodes. TTF is Food & Drug Administration (FDA) approved in the treatment of supratentorial GBM after a statistically significant survival benefit (20.9 vs 16.0 months)

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Table 1 Important molecular markers define glioma and predict outcomes

Isocitrate dehydrogenase (IDH) mutation: IDH is an enzyme in the citric acid cycle that converts isocitrate to alpha-ketoglutarate. In GBM, IDH wild type indicates a spontaneous or de novo lesion. The vast majority of grade IV gliomas are IDH wild type, which portends a poorer prognosis regardless of histology. IDH mutations are strongly associated with younger age and longer survival, independent of tumor grade [3]. Histologically low-grade gliomas with IDH wild type are generally associated with a prognosis that is similar to GBM and require aggressive treatment
1p/19q codeletion: In IDH mutant tumors, the presence of a balanced 1p19q translocation defines the diagnosis of oligodendroglioma. Patients with this codeletion have improved survival and its presence predicts response to both chemotherapy and radiotherapy. Intact 1p19q, or the loss of one chromosomal arm in the presence of a TP53 or ATRX mutation, is diagnostic of astrocytoma. 1p19q codeletion status has eliminated mixed oligoastrocytoma, a problematic diagnosis with frequent inter-observer disagreement, from the revised 2016 WHO classification of gliomas [3]
H3K27M mutation: This mutation defines a new glioma subclass in the 2016 WHO criteria referred to as "diffuse midline glioma." These tumors are considered WHO grade IV and classically occur in midline structures including the brainstem, thalamus, and basal ganglia [3]. Diffuse midline gliomas are rare in adults and are associated with younger age, aggressive growth, no proven response to chemotherapy, and overall poor prognosis
O6-Methylguanine-DNA methyltransferase (MGMT) promotor methylation: MGMT is a DNA repair enzyme that predicts the response to chemotherapy with alkylating agents such as temozolomide. During tumor development, the *MGMT* gene may be silenced by epigenetic modification. Methylated MGMT is inactive, allowing alkylating agents such as temozolomide to exert their mechanistic effects against glioma cells, resulting in improved survival. In contrast, un-methylated and therefore active MGMT confers to chemoresistance by driving cellular repair and counteracting temozolomide-induced DNA alkylation. Accordingly, an un-methylated MGMT promotor is resistant to temozolomide treatment and is associated with a poorer prognosis

was demonstrated in a randomized, un-blinded clinical trial [4]. TMZ is a generally well-tolerated alkylating agent that is orally administered during EBRT and in the adjuvant setting for five sequential days in a 28-day cycle. It induces double-stranded DNA breaks and subsequent tumor cell apoptosis. Commonly encountered adverse effects include dose-dependent myelosuppression (especially thrombocytopenia), fatigue (which may be severe and prolonged after radiation), and GI distress (nausea, vomiting, constipation). Tumor progression is unfortunately inevitable for most patients, but clinical trial enrollment, re-irradiation, second-line chemotherapy, and repeated surgical interventions may improve survival and quality of life (QoL) in an overall fatal disease. Management of low-grade gliomas uses a similar treatment approach; however, decision-making is more complex and depends on molecular profiling. In the case of metastatic brain disease, both primary and secondary tumor characteristics influence treatment course, including surgical resection, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and systemic and intrathecal chemotherapy.

Palliative care and symptom management in neuro-oncology

Persons with brain tumors experience progressive neurologic decline resulting in disproportionately high symptom burden throughout the disease trajectory, particularly at the end of life [5]. Caregivers report significant physical burden and high levels of psychological distress [6]. Although many symptoms in central nervous system (CNS) and non-CNS cancers overlap, others are more prevalent in patients experiencing brain tumors, such as seizures, cognitive dysfunction, confusion, headaches, mood disturbances, and fatigue.

The World Health Organization describes palliative care (PC) as a clinical approach that improves the QoL of patients and their families when facing a life-threatening illness, regardless of life expectancy. PC emphasizes the prevention and proactive assessment and treatment of pain and other physical, psychosocial, or spiritual needs. This multidimensional approach has been recommended for chronic and progressive neurological diseases and specifically for patients with brain tumors [7, 8].

Brain tumors produce localization-related focal deficits that may be exacerbated by intrinsic and treatment-induced peritumoral edema. Headaches, seizures, altered mental status, and cognitive dysfunction are prevalent tumor-centric symptoms that are often multifactorial. While radiation plays an integral role in the treatment and palliation of malignant brain neoplasms, its neurotoxic effects, including tumor pseudoprogression and radiation necrosis, often produce significant morbidity. One study involving more than 600 primary brain tumor patients found that 50% of patients reported at least 10 concurrent symptoms, and 40% had at least three symptoms rated as moderate to severe [9]. Symptoms interfered with general activity, ability to work, or enjoyment of life in at least 25% of patients [9].

Prospective literature pertaining to symptomatic management, specifically at the end of life, is sparse. Many neuro-oncologists do not feel adequately equipped to manage the unique and challenging needs of this patient population beyond the scope of commonly encountered neurological symptoms [10]. Early specialized palliative care referral to

address more complex symptomatology and decision-making has been recommended [11]. However, the majority of neuro-oncologists in a recent survey reported utilizing PC and hospice late in the disease trajectory, after curative and investigative options have been exhausted [12]. This pattern results in decreased exposure to specialized PC in comparison to other solid tumor populations. Patients with brain cancer require a comprehensive approach with a focus on maintaining QOL beyond prolonging survival.

The goal of this chapter is to provide insight on the unique palliative needs of this patient population, as well as optimization of end-of-life symptom management. It will also delineate the role of PC in the context of a multidisciplinary approach to brain cancer and describe the benefits of earlier involvement of PC and advance care planning. Areas of opportunity for continued research and inquiry will be explored.

Direct tumor effects and treatment-induced neurotoxicity

Mass effect caused by the brain tumor or edema contributes substantially to brain tumor morbidity and mortality. Peritumoral edema can exacerbate focal deficits, headaches, seizures, encephalopathy, and sequelae of increased intracranial pressure. Radiation-induced neurotoxicity is a highly relevant iatrogenic trigger of peritumoral edema and mass effect. "Pseudoprogression" is a common subacute radiotoxic effect that most often presents within the first 90 days of adjuvant radiotherapy and occurs in up to 25% of patients with GBM [13, 14]. Spontaneous recovery over weeks to months is expected, and several studies suggest an improved overall survival of brain tumor patients with pseudoprogression when compared to tumor progression [14].

Radionecrosis refers to the development of a radiation-induced space-occupying necrotic mass lesion. Distinguishing between radionecrosis and disease progression is challenging due to significant clinical and radiographic overlap [15]. Both necrotic tissue and tumor recurrence produce focal symptoms secondary to edema and mass effect. Core MRI features, including intravenous contrast enhancement, mass effect, central necrosis, and vasogenic edema, are shared between the two conditions [15]. Treatment with dexamethasone or bevacizumab (as delineated below) provides short-term symptomatic improvement; however, long-term benefits are uncertain [16].

Corticosteroids are the mainstay of treatment for symptomatic edema in brain tumor patients. Dexamethasone is often preferred due to its low mineralocorticoid activity, long half-life (more than 36 h), ease of administration, and dampened psychiatric effects [17]. Steroids can result in rapid clinical improvement in patients with acute neurologic symptoms and can be given in large intravenous doses in this setting. Despite widespread use, high-quality studies addressing various steroid dosing regimens are lacking, and some data favor a more conservative approach as compared with current practice [17]. While elevated doses are often reflexively prescribed with good intention (i.e., dexamethasone 16 mg daily), resultant side effects can paradoxically lead to negative impacts on QoL. Prolonged high-dose corticosteroid use (weeks to months) is associated with adrenal insufficiency (which may exacerbate fatigue and cognitive changes), diabetes requiring insulin therapy, immune suppression and resultant opportunistic infections (oral thrush), gastritis, peptic ulcers and gastrointestinal bleeding, weakness, and myopathy, as well as neuropsychiatric effects [9]. In addition to deleterious side effects impacting QoL, corticosteroids may negatively influence overall survival and outcomes [18]. Generally, minimum corticosteroid dosing with shortest durations required for symptom control is preferred. Alongside appropriate titration based on symptom control and neuroimaging, 4–8 mg of dexamethasone daily usually provides effective symptom management in clinical practice [16].

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF) that exhibits potent anti-angiogenic properties. It is approved as a second-line treatment for HGG in several countries. Bevacizumab is particularly effective in treating refractory peritumoral edema, especially in patients for whom tapering or discontinuing steroids is unfeasible. Notable clinical benefits include improvement of tumor-related neurologic symptoms, decreased steroid requirements, and maintenance of performance status [16]. Radiographic response is often remarkable, with significant "pseudo-resolution" of tumor enhancement. Unfortunately, the anti-tumor effects of bevacizumab treatment are short-lived in most patients, and disease progression ensues after several months of use. Although generally well tolerated, side effects including hypertension, intracranial hemorrhage, thromboembolism, posterior reversible encephalopathy syndrome, and impaired wound healing preclude the routine use of bevacizumab in asymptomatic patients [19].

Seizures

Epileptic seizures are common in patients with brain tumors. Although the exact frequency is unknown, it is suggested that up to 50% of patients experience seizures at some point of their disease [20]. In 30–50% of patients with brain tumors, seizures may be the first clinical sign of an underlying mass [21]. Focal seizures with impaired awareness are the most common semiology and usually localize to the temporal lobes, whereas intact-awareness focal seizures predominate in frontal, parietal, and occipital

lesions [22]. Secondary generalization is common, and brain tumor patients are at elevated risk of both convulsive and nonconvulsive status epilepticus (NCSE) [22]. NSCE may masquerade as altered mental status from other causes, such as cognitive dysfunction, fatigue, increased intracranial pressure, hemorrhage, and direct tumor-related effects. Clinical examination alone cannot reliably identify NCSE, and its incidence may therefore be underreported [23]. One study postulates a strongly negative impact of NCSE on survival, making NCSE a potentially critical cause of depressed mental status in brain tumor patients [23]. Currently, it remains unclear how identification and treatment of NCSE may affect outcomes.

Low-grade, IDH1 mutant, WHO grade II, and cortically located tumors (especially in the temporal and parietal lobes) are the most epileptogenic, and up to 100% of patients with low-grade brain tumors develop epilepsy, as compared with GBM (29–49%) and metastatic brain lesions (20–35%) [21]. Perhaps counterintuitively, early-onset seizures are associated with low-grade pathology and might represent more chronic and indolent underlying structural changes. Well-differentiated glioma cells and IDH-1 mutant cells are thought to produce epileptogenic neurotransmitters or modulators that increase seizure propensity [24]. Overall, early-onset seizures are associated with low-grade pathology and may therefore imply favorable survival outcomes [25]. Seizures that are new, reappear, or increase in frequency often signal disease progression and require thorough evaluation.

Seizures are a significant source of direct and indirect morbidity. Patients with brain tumors generally experience more frequent and severe side effects from anti-seizure medications, possibly related to polypharmacy, tumor burden, deficits from prior treatment, and radiation therapy [26]. However, reported adverse effects from anti-seizure medications often pertain to older agents (such as phenytoin, phenobarbital, oxcarbazepine, and carbamazepine), and it is unclear whether a similar degree of morbidity occurs with newer-generation drugs. Seizures are often distressing and impair QoL by evoking fears of tumor recurrence, increasing caregiver burden and anxiety, limiting patient independence, and increasing the frequency of emergency department visits and hospitalizations. Seizure prevalence and refractoriness increase towards death, and a minority (10–15%) of patients with HGG may not develop epilepsy until the terminal phase of illness [27]. One study suggests that seizures may occur in approximately 30% of brain tumor patients at the end of life and have been strongly associated with non-peaceful death [28].

The utility of primary seizure prophylaxis in brain tumor patients, both peri-operatively and otherwise, has been a topic of uncertainty in recent decades. Methodological issues have prevented most studies from rendering conclusive high-level evidence, and it remains unclear whether primary seizure prophylaxis is beneficial [29]. Despite these findings, a recent survey including 144 practicing neurosurgeons found that 63% of respondents reported regularly prescribing empiric postoperative anti-seizure medications in seizure-naïve patients with supratentorial brain tumors [30]. The American Academy of Neurology seizure guidelines were recently updated by the Society of Neuro-Oncology and the European Association of Neuro-Oncology and explicitly do not support the prophylactic use of anti-seizure medications in these settings [29]. This systemic literature review conducted in 2021 identified level A evidence against the use of anti-seizure medications to reduce the risk of seizures in brain tumor patients and concluded that there is overall insufficient evidence to recommend prophylactic peri- or postoperative anti-epileptic drug (AED) treatment [29].

In the event of a single seizure, long-term AED treatment is generally justified and should be considered. No randomized trials have established specific AED superiority. Patient characteristics, seizure type, tolerability, and drug interaction potential should guide AED selection. Generally, lowest effective doses should be given in an effort to minimize toxicity. Cytochrome P450 (CYP450) inducers including phenobarbital, phenytoin, primidone, carbamazepine, and oxcarbazepine may alter the metabolism and efficacy of commonly used chemotherapeutics as well as dexamethasone. Therefore, these older agents are usually avoided unless absolutely necessary. Valproic acid is a known histone deacetylase inhibitor with purported intrinsic antineoplastic properties [26]. Based on the most recent updated seizure guidelines, the use of valproic acid as an antineoplastic agent is not recommended [29].

Newer-generation anti-seizure medications including levetiracetam, zonisamide, and lacosamide are renally excreted and do not affect CYP450 metabolism. Their superior side effect profiles make them top choices for seizure management in brain tumors. Levetiracetam is frequently used due to its established effectiveness, tolerability, low pricing, and relative ease of dosing [31]. Neuropsychiatric disturbance is an important side effect that may be exacerbated by concomitant steroid use. Brivaracetam is an analogue of levetiracetam that is FDA approved for adjunctive use in focal seizures. In a retrospective study involving 33 patients with brain tumors, brivaracetam induced seizure freedom in 60.6% of patients, with greater than 50% reduction in seizure frequency in 18% [32]. Adverse effects including agitation, anxiety, fatigue, and vertigo occurred in approximately 20% of patients [32]. Brivaracetam is a potentially safe and effective option in brain tumor-related epilepsy pending further trials; however, cost and regional availability may limit widespread use [32]. Perampanel is a non-competitive ionotropic glutamate receptor antagonist that has demonstrated good tolerability and clinically significant seizure reduction

in patients with brain tumor-related epilepsy and may also be a viable treatment option in this setting [33].

Brain tumor-related epilepsy is pharmaco-resistant in up to 30% of patients but can improve with tumor-directed therapies including surgical resection, radiotherapy, and chemotherapy [25]. Although high-quality studies are lacking, the prevalence of refractory seizures at the end of life may approach 30% [7]. Patients with a history of tumor-induced epilepsy have the highest risk of developing seizures in the end-of-life stage, which may cause significant distress for caregivers. Dysphagia and altered mental status in this setting may make AED optimization challenging; however, anti-seizure medications should be continued if possible. Other routes, including intranasal, sublingual, buccal, rectal, subcutaneous, or intravenous, can be incorporated. Agents with comparable efficacy include intranasal midazolam, buccal lorazepam, rectal diazepam, and lorazepam oral concentrates [34]. In a small prospective study with 25 glioma patients, prophylactic buccal clonazepam and abortive treatment with intranasal midazolam were found to be feasible, effective, and well received by caregivers in the treatment of brain tumor-related seizures in the home setting [35].

Headaches and pain

Headaches are experienced by 30–70% of patients with brain tumors and are the most common source of pain in this patient group [36]. Only a small minority (2–8%) of patients experience isolated headaches as a first clinical manifestation of a brain tumor, while most headaches occur in conjunction with other neurologic symptoms [37, 38]. Patients with a history of headaches are more likely to experience headaches in the context of brain cancer. In these cases, brain tumor-related headaches are comparable in character but are often more severe than prior headaches [36]. Brain tumor-related headaches are generally described as tension-type and nonspecifically localized, while migrainous headaches are less common [39–41]. "Classic" brain tumor-type headaches, described as "worse in the morning," aggravated by Valsalva-like maneuvers, and associated with nausea or vomiting, occur in a minority (17%) of patients [40]. Ophthalmoscopic evaluation may be of benefit to evaluate for papilledema in this context. The site of pain correlates with tumor location in only 30% of all patients and is therefore of limited diagnostic utility [42]. Generally, supratentorial tumors are associated with vertex and bifrontal pain, whereas occipital pain more reliably accompanies infratentorial tumors [39, 40].

The brain parenchyma itself is devoid of pain receptors. Expanding tumor tissue and peritumoral edema produce pain via traction on richly innervated surrounding structures such as dura, dural, and meningeal vessels, venous sinuses, and cranial periosteum [43]. Direct compression of exiting cranial nerves, such as occipital nerve compression in craniomedullary junction tumors, has also resulted in similar headaches [38, 43]. In patients with preoperative headaches, neurogenic inflammation and central sensitization may result in headache persistence following surgical debulking [43].

Post-craniotomy headaches (PCHs) occur in over two-thirds of patients and are among the most frequently encountered adverse events after craniotomy [44]. The International Headache Society diagnostic criteria for acute and chronic post-craniotomy headache are delineated in Table 2 [45]. Direct soft tissue trauma, nerve injury, meningeal irritation, neuroma formation, dural muscle adherence, and aberrant nerve regeneration are the leading hypotheses [44]. Longer neurosurgical duration (> 4 h) and suboccipital approach have been reported to increase the risk of post-craniotomy pain [46]. PCHs are typically described to have tension-type character combined with localized surgical site pain [47]. Other manifestations include focal lancinating pain or dysesthesias as well as occipital neuralgiform features [36]. Acute PCH is moderate to severe in up to 80% of patients, and approximately 50% will develop chronic PCH as defined by pain persisting beyond 3 months [48]. Incapacitating pain (22%), negative impact on mood (15%), and interference with daily activities (29–60%) are also reported among post-craniotomy patients [44]. Unfortunately, post-craniotomy pain is often undertreated, and optimal management has not been established. Preoperative diclofenac was associated

Table 2 Diagnostic criteria for post-craniotomy headache according to the International Headache Society*

Description:	Headache directly caused by surgical craniotomy
A	Surgical craniotomy has been performed, not in the context of traumatic head injury
B	Headache starts within 7 days of craniotomy, regaining consciousness following craniotomy, or discontinuation of medication(s) impairing the ability to sense or report headache following craniotomy
C	Acute: Headache resolves within 3 months after its onset, or less than 3 months have passed since headache onset
	Chronic: Headache for more than 3 months' duration
D	Other secondary headache disorders (e.g., cervicogenic headache, CSF leak, hydrocephalus, intracranial hemorrhage) have been excluded

*Adapted from the International Headache Society Diagnostic Criteria for post-craniotomy headache[56]

with decreased headache intensity following infratentorial surgery in one randomized, blinded, single-center trial [49]. Other interventions, including occipital nerve blocks, duloxetine, gabapentin, and tizanidine, are often helpful. Physical therapy, locally applied heat or ice, massage, biobehavioral interventions, and botulinum toxin are potentially viable non-pharmacologic adjuncts [50]. Secondary causes of PCH, such as cerebrospinal fluid leak, hydrocephalus, hemorrhage, and meningoencephalitis, also need to be considered.

Headache management in patients with brain tumors depends on severity, underlying mechanism, and overall performance status. Tumor- and treatment-induced edema, not tumor size, has been correlated with headache severity and demonstrates excellent steroid responsiveness [36, 51]. If feasible, corticosteroids should be avoided in the late afternoon as they may cause insomnia. Sleep disturbance is common and may exacerbate other QoL-defining symptoms such as fatigue, and mood disorders. Adjunctive bevacizumab can be considered in patients with extensive cerebral edema refractory to corticosteroids [36].

In the absence of increased intracranial pressure, treatment of corticosteroid-refractory headaches follows conventional guidelines, with a few exceptions. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are first-line agents for mild headaches. Opioid combinations such as hydrocodone or oxycodone with nonopioid analgesics are often needed to treat moderate headaches, while more severe headaches may warrant higher potency opiates such as morphine or hydromorphone. Tramadol is a weak opioid that is contraindicated in patients with brain tumor-related epilepsy due to its propensity to lower the seizure threshold. Post-marketing surveillance has shown that most seizure events occur with tramadol doses above 200 mg (dosage in clinical practice usually ranges from 50 to 100 mg) and in younger patients (occurring rarely in patients above the age of 59) [52, 53]. Therefore, tramadol may be used with caution in brain tumor patients in the appropriate clinical context. Meperidine also lowers seizure threshold and is strictly contraindicated. Opiate use may decrease QoL due to their addictive potential and adverse effects. Common side effects include constipation, nausea and vomiting, sedation, delirium, and withdrawal symptoms in the event of dependency. In the setting of chronic opioid use, combined long-acting and short-acting opioids exhibit incomplete cross-tolerance resulting in a reduction of total opiate dosage, increased opiate efficacy, and decreased adverse opiate effects [53]. Consultation with a PC team or pain service is encouraged.

Patients requiring frequent use of abortive medications (more than four times weekly) may benefit from preventive therapy. Commonly used agents include topiramate and tricyclic antidepressants such as nortriptyline and amitriptyline. One study observed that patients on beta-blockers for other indications had lower frequency and intensity of brain tumor-related headaches [39]. It is important to consider potential known side effects of prophylactic headache medications such as neurocognitive impairment and weight loss with topiramate. Treatment with gabapentin or tricyclic antidepressants may result in lethargy, weight gain, and delirium. No studies have concluded superiority of any abortive or preventive agent specifically for this indication, and more research on this topic is needed.

Headaches have both physical and emotional implications on brain tumor patients. One study found that recurrent headaches served as a frequent reminder of life-threatening illness, resulting in anxiety and difficulty maintaining a positive outlook [54]. This demonstrates the complex interplay of commonly experienced symptoms in brain tumor patients, including headaches, mood disorders, sleep disturbances, and fatigue.

Cognitive dysfunction

Most patients with brain tumors exhibit some degree of cognitive impairment throughout their disease course [55]. Due to advanced age or tumor-induced changes, the majority (> 90%) of patients show cognitive deficits prior to treatment [56]. HGG has been associated with a greater degree of impairment regardless of implemented treatments [57]. Frequently affected domains include memory, attention, and executive functioning; however, the severity and pattern of symptoms vary considerably [58]. Given its multifactorial nature, brain tumor-related neurocognitive impairment is often impractical to approach as an isolated clinical syndrome. Mass effect, tumor location, seizures, comorbid psychiatric conditions, fatigue, insomnia, and pharmacologic effects are plausible contributors. The negative impacts caused by neurotoxic effects of local and systemic anti-cancer therapies are gaining more attention in the field of oncology and are important considerations in the brain tumor population.

Radiation-induced neurotoxicity occurs in 50–90% of brain tumor patients and is a frequent source of apprehension and distress [56, 59]. Effects are often debilitating and occur in the acute (during radiation), early-delayed (4–8 weeks), and chronic phase (months to years) of radiation treatment. Acute toxicity is transient and might present with headaches, nausea and vomiting, seizures, fever, somnolence, encephalopathy, and worsening of pre-existing focal deficits [60]. Symptoms are usually briskly responsive to corticosteroids and a full recovery is expected in most patients. Somnolence syndrome is a debilitating subacute toxic encephalopathy characterized by pervasive lethargy and mental clouding. Steroids may hasten recovery or prevent severe

presentations. Diffuse cerebral injury is a late radiation-induced neurotoxic sequelae that can occur months to years following brain irradiation. It usually manifests in patients following radiation to low-grade neoplasms due to longer overall survival. Possible clinical features include progressive dementia, gait disturbance, apraxia, and urinary incontinence [13]. While the precise mechanisms causing these symptoms are unknown, direct injury to the hippocampus and to pluripotent neural stem cells (NSCs) have been implicated [61]. Radiation techniques aimed at improving neurocognitive outcomes, such as WBRT with hippocampal sparing, are more relevant in metastatic brain disease and have resulted in better preserved neurocognitive function [62, 63].

There is limited high-quality evidence to guide treatment of cognitive complaints in brain tumor patients [56]. Memantine has been shown to delay and reduce the degree of cognitive dysfunction over time when used preventatively with WBRT or hippocampal-sparing WBRT in brain metastases [62]. Donepezil, a reversible acetylcholinesterase inhibitor, may provide modest improvement in several cognitive domains [64]. Occupational interventions such as cognitive rehabilitation have been used to improve daily functioning by developing compensatory strategies and skills [56]. Although optimal timing has not been established, proactive cognitive training soon after craniotomy is thought to be most effective at preventing adverse treatment-induced cognitive outcomes [56]. Cognitive dysfunction may be irreversible, and even minor deficits can affect health-related QoL and functional independence. In one survey involving 226 patients with terminal illness, 88% of respondents stated that they would rather decline some aspects of treatment if the outcome was prolonged survival but associated with significant cognitive impairment [65]. Impaired cognition threatens individual autonomy by affecting decision-making capacity. Furthermore, rapid cognitive deterioration in the final weeks of life precludes participation in end-of-life decision-making, thus emphasizing the importance of early advance care planning.

The role of palliative care in brain tumor patients

Specialized PC in patients with advanced systemic cancer, particularly early in the disease course during active oncology treatment, has demonstrated positive impacts on QoL and survival. In a single-center, non-blinded randomized trial involving patients with metastatic lung cancer, early and structured PC, parallel to ongoing oncological treatment, resulted in significantly improved QoL and symptom burden of cancer patients [66]. The early involvement of specialized PC during active cancer treatment is now part of the American Society of Clinical Oncology guidelines [67]. Introducing PC early in the disease course serves to build therapeutic relationships and trust between patients, caregivers, and the PC team. Effective PC is navigated by the unique and personal treatment goals of each patient and should involve the development of an early advance care plan that is congruent with the patient's wishes. These discussions should take place while the patient is able to actively engage in treatment decision-making. Neuropalliative care addresses specific neurological issues in diseases with high symptom burdens, such as ALS, movement disorders, and brain tumors [7, 68]. In an online survey of PC and neurology providers throughout Europe, collaboration between brain tumor services and PC in the form of joint meetings, clinic visits, and telephone encounters were found to positively impact QoL, functional status, complex decision-making, and end-of-life care as compared with other neurology subspecialty services that were lacking such collaboration [69]. Unfortunately, when and how to introduce neuropalliative care is currently not as clear, and this uncertainty likely contributes to the current state of PC underutilization in neuro-oncology [70].

A 2016 survey of neuro-oncology providers in the USA showed that early PC referrals remain rare. In this study, only 14% of patients with HGG were referred to PC at the time of diagnosis, while almost two-thirds of providers referred patients only at the onset of symptoms requiring palliation [10]. In the same survey, only one-third of providers felt comfortable addressing end-of-life issues [10]. Another study demonstrated hospice underutilization in the brain tumor population, with only 63% of patients enrolled in hospice, 20% of whom were enrolled in their last week of life [71]. Delayed hospice enrolment is a disservice to patients and their families as it results in suboptimal utilization of specialized end-of-life care. These findings indicate a need for more specific training in end-of-life management and resources on the value of specialized neuropalliative care for patients and their families.

Advance care planning

Patients with HGG have a high symptom burden throughout their disease trajectory, especially during the terminal phase of illness [5]. Numerous multifactorial and interrelated symptoms define QoL, including focal weakness, cognitive disturbances, drowsiness, seizures, and the inability to communicate. In contrast with other systemic cancers, brain tumor patients are often referred to PC and hospice later in their disease course, resulting in suboptimal symptom control and prolonged suffering [12, 71].

Rapid cognitive deterioration several weeks prior to death often precludes effective participation in end-of-life decision-making [72]. Therefore, the concept of advance

care planning and hospice should be approached early in the disease trajectory [11]. While the timing of advance care planning in HGG patients has been understudied, it is generally recognized that earlier conversations, while the patient has a higher likelihood of active participation and decision-making, are beneficial [73]. Ideally, the patient should have an opportunity to convey their personal wishes while legal capacity remains intact. Advance care planning should be approached as an ongoing process rather than a one-time conversation. When approaching end-of-life discussions, important topics include the assignment of a healthcare power of attorney and open-ended exploration of values, treatment goals, and end-of-life care [73]. Effective conversations strike a balance between emphasizing the futility of brain cancer while maintaining the hope of healing, comfort, and peace. The focus should be on finding joy in the remaining time rather than focusing on survival.

In addition to preserving patient autonomy and dignity, advance directives alleviate caregiver burden by diminishing sentiments of uncertainty, guilt, or overwhelming responsibility regarding a patient's end-of-life care. Documented benefits of advance care planning include reduced unwanted and unnecessary treatments, reduced length of stay, reduced number of hospitalizations, and decreased decisional conflict among caregivers in critically ill patients [74]. For many patients, preserving dignity is a crucial goal when considering the end-of-life phase, and families often benefit from hearing explicitly expressed wishes and considerations [75, 76]. During the transition to end-of-life and hospice care, an important motivator for involved caregivers includes the hope that their loved one can experience a dignified death according to his or her wishes [77]. In the case of preserved cognitive and communicative capacity at the end of life, patients who had detailed discussions regarding end-of-life wishes with designated caregivers were perceived to die with dignity more often than those without this opportunity [75]. Advance care planning should therefore include specific conversations about end-of-life care. In a meta-analysis examining the components of effective advance care planning conversations in multiple sclerosis, several factors were found to impact patient perception, participation, and discussion outcomes [78]. Cumulative losses in cognition or functional status throughout the disease resulted in patients redefining themselves as individuals with a terminal illness [78]. Patients thus became more likely to achieve self-acceptance and recognize the value of advance care planning. One other study found that inconsistencies in information, attitudes, and skills among healthcare providers resulted in mistrust, uncertainty regarding prognosis, and impaired PC delivery among patients with chronic neurologic diseases [79]. Further research exploring the applicability and limitations of these findings in brain tumor patients is indicated.

The problem of late referral to PC and hospice is further potentiated by provider discomfort and perceived unpreparedness to lead effective goals-of-care discussions. In a survey involving 552 practicing neuro-oncologists, one-third of respondents were concerned that end-of-life discussions may have negative consequences on their patients' emotional well-being [10, 80]. However, patient-centered studies show that most patients prefer detailed information about their disease, especially pertaining to anticipated end-of-life symptoms and realistic survival [80, 81]. As such, there remains a significant discrepancy between optimal and current end-of-life transitions for patients with brain tumors.

Psychosocial support

Psychosocial support has been shown to be important for brain tumor patients and their caregivers alike. Providing care to patients with HGG is challenging. Patients and their families face issues beyond those directly related to neurological symptoms. Additional stressors include significant financial burden resulting from the cost of care and an inability to work [82]. Generally, a high level of distress and burnout among brain tumor caregivers is common and often rated higher when compared to other systemic cancers [83]. Neurologic declines, especially in the form of cognitive dysfunction, communication difficulty, mood disturbances, and personality changes, are highly distressing and decrease caregiver well-being [84]. These changes are often present prior to formal diagnosis and have a lasting impact on interpersonal relationships with family and caregivers. The loss of decision-making capacity and ability to participate in care place increasing responsibility on caregivers as the disease progresses [85]. Taking care of the caregiver and providing them with structured support and guidance in clinical practice not only have the potential to improve caregivers' feelings of mastery and control but also have been shown to be predictive of brain tumor patient survival [86]. Therefore, it is important to provide patients and caregivers with a concrete plan of care [83]. Patients and caregivers often seek detailed information, which should be provided in a stepwise fashion starting at diagnosis, followed by preparing patients and caregivers for future transitions of care as well as end-of-life planning [11]. Hospice enrollment has been shown to increase caregiver satisfaction in the end-of-life phase of brain tumor patients [87]. Several studies show that patients and their caregivers experience reduced anxiety when receiving tailored information about diagnosis, prognosis, treatment options, recurrence, and end-of-life care, all of which collectively diminish the psychosocial impact of the disease [11, 85, 87]. A recently developed framework to address patient and caregiver supportive care needs includes coordination of care, repeated needs assessment, staged

information based on symptom and tumor progression, and referrals to behavioral health and PC as needed [11]. Regularly scheduled assessments of patient and family caregiver needs should not only focus on physical symptoms but also include assessments of psychosocial status.

Conclusion

Brain tumor patients face an almost invariably futile disease with a limited prognosis and high symptom burden, particularly at the end of life. Identifying and controlling symptoms early in the disease course is paramount to maintaining QoL of patients and their families. Symptoms require frequent assessment and proactive management throughout all stages of illness. Distressing symptoms such as seizures and headaches are common and often multifactorial. Studies pertaining to symptom control in brain tumors are scarce and therapeutic approaches are often based on other cancer types or general neurologic treatment paradigms. Future studies are indicated to address brain tumor-specific issues. Brain tumor patients are at elevated risk of impaired medical decision-making early in the disease course, and they often lose their ability to communicate at the end of life. Advance care planning conversations should be initiated early in the disease process by the treating physician. The benefit of early PC has been clearly established in systemic cancers; however, its role in brain cancer patients remains less defined and continues to be understudied. Physician training, patient factors, and the lack of empiric PC frameworks may contribute to the continued underutilization of specialized PC and hospice services. A holistic and multidisciplinary approach with early involvement of specialized PC may aid in optimizing QoL in this population.

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Declarations

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