



# Easing the Journey—an Updated Review of Palliative Care for the Patient with High-Grade Glioma

Rita C. Crooms<sup>1,2</sup> · Margaret O. Johnson<sup>3,4</sup> · Heather Leeper<sup>5</sup> · Ambereen Mehta<sup>6,7</sup> · Michelle McWhirter<sup>6,8</sup> · Akanksha Sharma<sup>9</sup> 

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## Abstract

**Purpose of Review** High-grade gliomas (HGG) are rare brain tumors that cause disproportionate suffering and mortality. Palliative care, whose aim is to relieve the symptoms and stressors of serious illness, may benefit patients with HGG and their families. In this review, we summarize the extant literature and provide recommendations for addressing the symptom management and communication needs of brain tumor patients and their caregivers at key points in the illness trajectory: initial diagnosis; during upfront treatment; disease recurrence; end-of-life period; and after death during bereavement.

**Recent Findings** Patients with HGG experience highly intrusive symptoms, cognitive and functional decline, and emotional and existential distress throughout the disease course. The caregiver burden is also substantial during the patient's illness and after death. There is limited evidence to guide the palliative management of these issues.

**Summary** Palliative care is likely to benefit patients with HGG, yet further research is needed to optimize the delivery of palliative care in neuro-oncology.

**Keywords** Neuro-oncology · Glioma · Brain tumor · Palliative care · Supportive care · End of life · Metastatic disease · Glioblastoma · Advance care planning · Advance directive · Goals of care · High-grade glioma

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✉ Akanksha Sharma  
asharma@pacificneuro.org

Rita C. Crooms  
caroline.crooms@mssm.edu

Margaret O. Johnson  
Margaret.o.johnson@duke.edu

Heather Leeper  
heather.leeper@nih.gov

Ambereen Mehta  
amehta23@jhmi.edu

Michelle McWhirter  
mmcwhir1@jh.edu

<sup>1</sup> Department of Neurology, Icahn School of Medicine at Mount Sinai, 1468 Madison Ave, 1052, NY 10029 New York, USA

<sup>2</sup> Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

<sup>3</sup> Department of Neurosurgery, Duke University Medical Center, Trent Drive 047 Baker House, Durham, NC 27710, USA

<sup>4</sup> The Preston Robert Tirsch Brain Tumor Center, Duke University Medical Center, Trent Drive 047 Baker House, NC 27710 Durham, USA

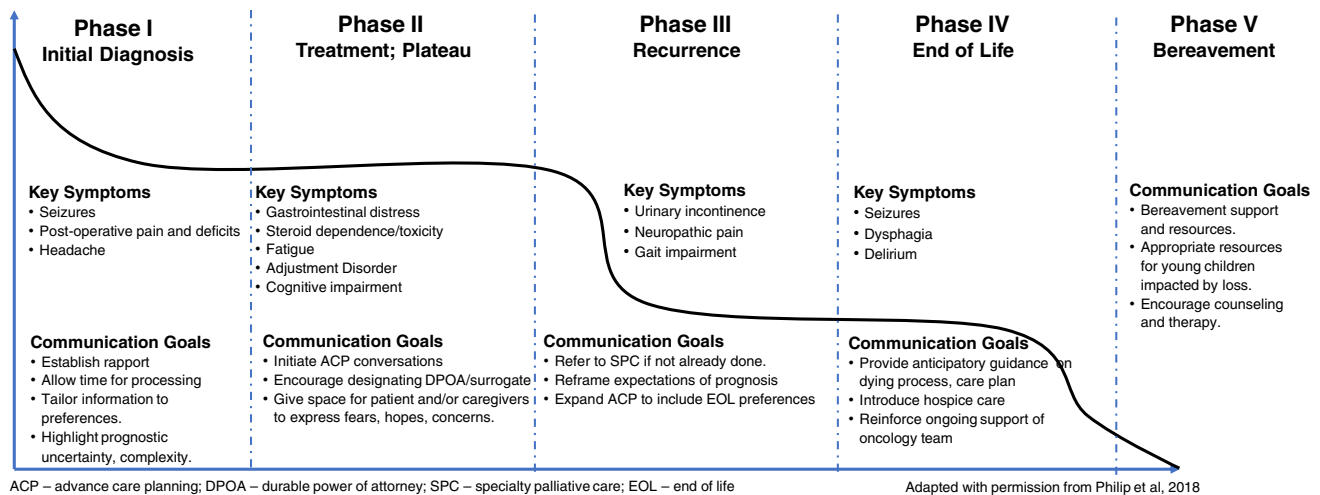
<sup>5</sup> Neuro-Oncology Branch, National Institutes of Health, National Cancer Institute, 9030 Old Georgetown Rd, Bloch Bldg 82, Bethesda, MD 20892, USA

<sup>6</sup> Palliative Care Program, Division of Medicine, Johns Hopkins School of Medicine, Johns Hopkins Bayview Medical Center, Baltimore 21224, MD, USA

<sup>7</sup> Division of Medicine, Johns Hopkins School of Medicine, Johns Hopkins Bayview Medical Center, Baltimore 21224, MD, USA

<sup>8</sup> Department of Social Work, Johns Hopkins Bayview Medical Center, Baltimore 21224, MD, USA

<sup>9</sup> Department of Translational Neurosciences, Pacific Neuroscience Institute/Saint John's Cancer Institute, 2200 Santa Monica Blvd, Santa Monica, CA 90404, USA



**Fig. 1** Disease trajectory for the high grade glioma patient

## Introduction

High-grade gliomas (World Health Organization (WHO) Grade 3 and 4 gliomas) account for the majority of primary malignant brain tumors (PMBT) and are extremely aggressive, with high mortality despite advances in treatment [1]. Quality of life (QOL) in HGG may be adversely affected by physical symptoms [2•], neuropsychiatric symptoms [3•], functional decline related to focal neurologic deficits [4], and existential distress [5]. These symptoms and stressors may be alleviated through palliative care (PC), an interdisciplinary medical specialty whose aim is to improve QOL for patients and their caregivers by addressing physical, emotional, and spiritual distress, and providing an extra layer of support at any point in the disease trajectory [6]. PC addresses the holistic needs of patients and caregivers through communication/shared decision-making (including goals of care (GOC) discussion), coordination and continuity of care; physical and psychological symptom management; psychosocial and spiritual support for patients and caregivers; and advance care planning (ACP), in addition to end-of-life (EOL) care [7]. Early referral to specialty palliative care (SPC) yields improvements in QOL, patient and caregiver satisfaction with care, and greater alignment of treatment with patient preferences and goals [8, 9]. Given these benefits, demonstrated in clinical trials of PC interventions, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommends patients with advanced cancer be referred to specialty palliative care (SPC) early (within 3 months of diagnosis) in conjunction with cancer treatment by an oncologist [10, 11]. The European Association for Neuro-Oncology also recommends early SPC for patients with HGG, yet it is not clear

how often this guideline is met and there is limited evidence to guide practice [12]. Proficiency in basic PC skills (e.g., symptom management and communication) is critical for all clinicians, including neuro-oncology specialists [13]. The purpose of this narrative review is to summarize the PC needs of patients with HGG and their caregivers and to recommend symptom management and communication techniques aiming to guide clinicians as they traverse the key phases of the disease trajectory: initial diagnosis; first course of treatment; disease recurrence; EOL period; and bereavement (postmortem) (Fig. 1). We present evidence and professional society guidelines where available and expert opinion when none exists.

## Phase I: Initial Diagnosis

### Symptoms

The diagnostic phase (defined as the period from symptom onset through biopsy/resection confirming diagnosis) is often overwhelming for patients with HGG and their caregivers [14–16]. Presenting symptoms depend on several factors, including age and pre-morbid functional status of the patient, comorbidities, and tumor size, grade, and location. Tumors in eloquent locations may lead to severe, permanent disability despite treatment. High symptom burden and low functional status at diagnosis are associated with poor overall prognosis, as well as with reduced QOL [17, 18]. Among the most common symptoms in the diagnostic phase are seizures, headaches, and focal neurologic deficits [2•].

The prevalence of seizures at presentation or early in the disease course is estimated to be 20–40% [19]. Both seizures and side effects from anticonvulsants can significantly

affect QOL. Prophylactic use of anticonvulsants in patients with brain tumors who have never had a seizure remains controversial, is not supported by extant literature, and may result in harmful side effects. In the 2021 guideline from the Society for Neuro-Oncology (SNO) and the European Association of Neuro-Oncology (EANO), prophylaxis was not recommended for patients with any type of PMBT with no known history of seizure, consistent with the previous AAN guidelines [20, 21••]. However, even a single seizure warrants treatment with an anticonvulsant. Choice of anticonvulsant is crucial, based on drug interaction profile, pharmacokinetics, and side effects. The most widely used agents in neuro-oncology are levetiracetam, valproic acid, and lacosamide, due to the lower risk of drug-drug interactions (a key consideration in this patient population receiving concurrent chemotherapy) and overall tolerability [22]. Almost all anticonvulsants may contribute to fatigue and are variably psychoactive [23]. Levetiracetam may worsen irritability and depression in PMBT patients, while lacosamide appears to have the lowest impact on mood and cognition [23].

Post-operatively, common symptoms include headaches, incisional pain at the craniotomy site, and neurological deficits from surgery or edema. Common recommendations for management are outlined in Table 1. Physical and cognitive impairment may impact independence, functionality, and QOL [24, 25]. Early rehabilitation and exercise may improve and maintain functional status and decrease symptoms through radiation and adjuvant chemotherapy, thereby preserving eligibility for clinical trials or other cancer-directed therapies [26]. In systemic cancer patients, higher functional status has been associated with better QOL and mental health, decreased fatigue, improved sleep, and greater tolerance of cancer treatment [27, 28]. Preliminary data suggests that regular exercise training and comprehensive rehabilitation (with physical, occupational, and speech therapy or physical medicine expertise) may result in the same benefits in PMBT patients [29–31]. Individualized acupuncture is associated with improvements in motor function and fatigue in patients with post-operative hemiparesis [32]. Overall, engaging the services of a multidisciplinary rehabilitation and/or integrative medicine program may help the patient recover from symptoms and complications of the post-operative period.

## Communication

A new diagnosis of HGG is overwhelming, anxiety-inducing, and stressful, for both the patient and the caregiver. Immediately after diagnosis and surgery, while still in the inpatient setting, they may struggle to process information, especially around prognosis [15]. Patients and caregivers value compassionate, honest communication that allows for

hope but they may also need time to understand treatment options and prognosis [15, 33]. Patient-centered communication starts with understanding information preferences: some patients and caregivers may want to know “everything,” some might prefer only “critical” details, and some may not be ready for any information at all or may be ambivalent [34]. For patients, cognitive impairment may affect information processing and memory retention [35]. A brief in-clinic cognitive assessment may be helpful in establishing a baseline and guide how counseling around treatment and prognostic information should be provided and reinforced. Caregivers have different information needs and awareness of prognosis compared to patients, which should be taken into consideration while respecting patient autonomy and independence [36•].

When patients and caregivers do wish to discuss prognosis in the post-operative period, it can be challenging for clinicians to provide detailed predictions. Certain positive and negative prognostic factors have been identified in the literature and can be helpful in providing some guidance: age, functional status, lesion location, number and size, amenability to gross total resection, involvement of mid-line structures, symptoms and cognitive status at presentation, comorbidities, and steroid dependence can all affect overall prognosis [37]. A nomogram integrating seven such prognostic factors to predict survival in newly diagnosed glioblastoma patients was developed and validated by the European Organization for Research and Treatment of Cancer (EORTC), and is available online [38]. In counseling patients and caregivers, providing exact numbers should be avoided—average survival numbers are generally applied to the larger population and may not reflect the individual experience. Instead, ranges in months or years may be more appropriate [37].

These early conversations should be undertaken carefully and patiently, allowing for time and space, balancing honesty and hope, respecting the participants’ individual needs, and appropriately responding to emotions [15]. In our experience, extremes—demonstrating overt optimism or overt pessimism—in early conversations can negatively impact rapport, to the detriment of future GOC discussions as the disease progresses. For breaking bad news in the diagnostic phase, we recommend the use of the “SPIKES” tool (Setting up discussions; assessing patient/caregiver Perceptions; eliciting an Invitation to share new information; providing Knowledge; expecting Emotion, and Summarizing a plan of action with the patient and their loved one; Table 2) [39]. Jacobsen et al. have also developed a framework for emphasizing clinician support for living well while also discussing the possibility of death, which may be useful in introducing these conversations early in the clinician-patient-caregiver relationship as they start the treatment phase [40].

**Table 1** Common symptoms and their management at each phase

Phase	Symptom	Management	Comments	
I – Initial diagnosis	Seizures	<ul style="list-style-type: none"> <li>• Prophylaxis without seizure not recommended.</li> <li>• When started, non-enzyme inducing drug preferred.</li> <li>• Most commonly used are levetiracetam (level I), valproic acid (level II) or lacosamide.</li> </ul>	<ul style="list-style-type: none"> <li>• Evaluate for mood changes with levetiracetam (irritability, depression, suicidality, lability).</li> <li>• Valproic acid can contribute to fatigue, tremors, and not ideal in women of childbearing age. This may also contribute to thrombocytopenia, especially when combined with temozolomide.</li> <li>• Oxcarbazepine, topiramate have more interactions, but do not interact with temozolomide and have been studied in PMBT.</li> </ul>	
		<ul style="list-style-type: none"> <li>• Scant trial data.</li> <li>• Gabapentin can help with acute post-operative pain and decrease analgesic consumption, but may have sedative side effects (Ture 2009).</li> <li>• NSAIDs generally avoided, but no clear evidence suggesting harm.</li> </ul>		<ul style="list-style-type: none"> <li>• Acetaminophen often dosed around the clock in the post-operative setting, increasing risk of overuse headache, risk of overuse headache.</li> <li>• Steroids may be slowly weaned to help with pain.</li> <li>• Short course of opioids may be needed.</li> <li>• Local pain may respond to topical gels such as lidocaine and diclofenac, etc.</li> </ul>
		<ul style="list-style-type: none"> <li>• Scant data but frequent symptom.</li> <li>• Management usually extrapolated from general population – gabapentin, tricyclic antidepressants, beta-blockers.</li> <li>• Opioids generally avoided due to neurological side effects.</li> <li>• Steroid burst or taper may be appropriate if severe.</li> </ul>		<ul style="list-style-type: none"> <li>• Resources may be limited depending on location, insurance coverage, financial resources.</li> </ul>
	Post-incisional pain	<ul style="list-style-type: none"> <li>• Limited data.</li> <li>• Early rehabilitation and routine exercise program helpful in long run.</li> <li>• Acupuncture may play a role in motor rehabilitation post-operatively.</li> </ul>		
	Headaches	<ul style="list-style-type: none"> <li>• Olanzapine for breakthrough symptoms.</li> </ul>		
		Weakness and deconditioning	<ul style="list-style-type: none"> <li>• Pre-medication with 5-HT<sub>3</sub> receptor antagonist (e.g., ondansetron) prior to temozolomide and PRN.</li> </ul>	
II – Initial treatment	CINV	<ul style="list-style-type: none"> <li>• Ondansetron for breakthrough symptoms.</li> </ul>	<ul style="list-style-type: none"> <li>• If concern for QTc prolongation, consider prochlorperazine or neurokinin receptor antagonists.</li> <li>• If gastroparesis or constipation is an issue, consider metoclopramide.</li> <li>• If temozolomide is well tolerated, antiemetics can be stopped/avoided entirely.</li> <li>• Consider substituting ondansetron with another anti-emetic.</li> <li>• Encourage high fiber food, exercise and hydration.</li> </ul>	
	Constipation	<ul style="list-style-type: none"> <li>• Titrate sennosides or polyethylene glycol.</li> <li>• Magnesium citrate effective for severe cases.</li> </ul>	<ul style="list-style-type: none"> <li>• Consider proton pump inhibitor, especially with concurrent use of NSAIDs or bevacizumab.</li> </ul>	
	Steroid related side effects	<ul style="list-style-type: none"> <li>• Assess need for steroids and dosing at each visit, decrease as tolerated.</li> <li>• Physical therapy referral and encourage regular exercise for myopathy.</li> <li>• Check for insulin resistance and steroid-related diabetes.</li> <li>• Evaluate for skin breakdown or healing issues.</li> <li>• Address edema, fat deposition, and physical effects (moon faces, etc.).</li> <li>• Vitamin D supplementation for bone protection.</li> <li>• Assess hormonal status when indicated.</li> </ul>	<ul style="list-style-type: none"> <li>• Especially important if the patient has comorbidities or is hospitalized.</li> <li>• PCP prophylaxis when “steroids are” combined with radiation and chemotherapy, or with lymphopenia.</li> </ul>	
	Fatigue	<ul style="list-style-type: none"> <li>• Evaluate and treat reversible causes – depression, thyroid dysfunction, sleep apnea, low vitamin B12, low vitamin D.</li> <li>• Sleep hygiene counseling.</li> <li>• Ensure steroids are earlier in day (ideally before 3 pm).</li> <li>• Encourage physical activity.</li> <li>• Stimulants: consider methylphenidate BID in patients with well-controlled seizures.</li> </ul>	<ul style="list-style-type: none"> <li>• For sleep quality – magnesium supplementation and melatonin may be helpful, though no strong evidence exists.</li> <li>• Mindfulness and meditation may be helpful in battling anxiety, sleep disturbance, and fatigue.</li> </ul>	
	Adjustment disorder	<ul style="list-style-type: none"> <li>• Regularly screen patients for symptoms, obtain caregiver opinion, consider referral to cancer center or community based therapy, psychiatrist, and/or survivorship specialists.</li> <li>• Consider pharmacological intervention with SSRI (escitalopram) or SNRI (venlafaxine).</li> <li>• Address sleep disturbance if present.</li> <li>• Quetiapine or olanzapine may be needed if there is severe agitation contributing to caregiver burden or danger to patient/others.</li> </ul>	<ul style="list-style-type: none"> <li>• Avoid bupropion given increased seizure risk.</li> <li>• Avoid benzodiazepines unless used for panic attacks/episodic use.</li> <li>• Monitor QTc if antipsychotics are used and consider risk for serotonin syndrome with other medications.</li> </ul>	

**Table 1** (continued)

Phase	Symptom	Management	Comments
III – Recurrence	Urinary incontinence	<ul style="list-style-type: none"> <li>• Evaluate for urinary tract infection.</li> <li>• Consider bladder scan to assess for retention.</li> <li>• Spinal MRI if clinical history and exam is concerning for drop metastases.</li> </ul>	<ul style="list-style-type: none"> <li>• Urological consult may be helpful for teaching, education, pharmacological suggestions.</li> </ul>
	Neuropathic Pain	<ul style="list-style-type: none"> <li>• Scant data specifically in PMBT population.</li> <li>• First-line neuropathic pain agents: nortriptyline/amitriptyline, gabapentin, pregabalin, duloxetine, venlafaxine.</li> <li>• Interventional pain options: peripheral nerve block, nerve injections, neuromodulation.</li> <li>• Non-pharmacological interventions: acupuncture, massage, ultrasound, CBT</li> </ul>	
	Gait impairment	<ul style="list-style-type: none"> <li>• Evaluate for cause – sensory exam, consider EMG/NCS, consider LP for evaluation for hydrocephalus, visual assessment, frontal anhedonia, B12 deficiency.</li> <li>• Physical and occupational therapy referral.</li> <li>• Evaluation for assistive devices.</li> </ul>	
IV – End-of-life	Seizures	<ul style="list-style-type: none"> <li>• Evaluate of factors lowering seizure threshold (infection, medications, sleep disturbance, etc.)</li> <li>• Consider antiepileptic drugs available in non-oral formulations (e.g., levetiracetam) or standing benzodiazepines</li> <li>• Develop rescue plan (e.g., benzodiazepines)</li> <li>• Counsel caregivers about seizure management at home</li> </ul>	Discuss balance of seizure control and sedation with patient and/or caregivers.
	Dysphagia	<ul style="list-style-type: none"> <li>• Address nutrition/hydration with family during goals of care discussions</li> <li>• Consider non-oral medications for comfort</li> </ul>	Artificial nutrition and hydration may prolong the dying process without adding to comfort.
	Delirium	<ul style="list-style-type: none"> <li>• Neuroleptics (haloperidol, chlorpromazine) can relieve symptoms within 24 h</li> </ul>	
V - Bereavement	Bereavement risk	<ul style="list-style-type: none"> <li>• Tools such as the Bereavement Risk-Screening Tool (BRST) and PG-13 can help identify bereaved caregivers at risk of prolonged and complicated grief disorder.</li> <li>• Clinical social workers are skilled in assessing for bereavement in scope of family systems theory, evaluating psychosocial stressors, and providing bereavement counseling support.</li> </ul>	

NSAIDS, non-steroidal anti-inflammatory drugs; *CINV*, chemotherapy-induced nausea and vomiting; *CBT*, cognitive behavioral therapy

**Table 2** Recommendations for communication strategies for each phase

Phase; communication goal	Communication skill	Examples
<b>Diagnosis;</b> Break bad news	<b>SPIKES</b> Set up interview Perception (of patient/caregivers) Obtain Invitation Give Knowledge Address Emotions Strategy/Summarize <b>Dual Framework to Focus on Living Well and Tolerate the Possibility of Dying</b> Discuss the logistics Consider the advantages and disadvantages Explore what the patient wants to know	<b>S:</b> Arrange private meeting room with adequate seating. <b>P:</b> “What have the doctors told you about your illness so far?” <b>I:</b> “May I share the diagnosis with you?” <b>K:</b> “Unfortunately, the news is not good. The biopsy showed that you have an aggressive brain tumor called a glioblastoma.” <b>E:</b> “I can’t imagine what a shock this must be.” <b>S:</b> “When you’re ready, let’s talk about the plan for treatment and answer any questions you have about the future.” “If we were to have a conversation about the big picture, what topics would you like to cover? What would tell you it was the right time to talk about these issues?” “Can you think of some advantages to talking about the future? What disadvantages are you concerned about?” “Some people like to know all the details about their condition and some people prefer to discuss broad strokes. What kind of person are you?”
<b>Treatment;</b> Open goals of care discussion	<b>PAUSE</b> Pause and make time Ask permission <sup>‡</sup> Understand big picture Suggest choosing surrogate Expect emotion <sup>‡</sup> Patients and caregivers might have different needs and willingness; offer opportunity for separate discussions. <b>What if?</b>	<b>P:</b> “In my practice, I like to routinely check in with all my patients and ask how they’re prepared for the future. I would like to make some time to talk about that today.” <b>A:</b> Would that be okay with you? <b>U:</b> What is your understanding of your overall condition and treatment plan? <b>S:</b> “I would like to be sure that in the rare chance you are unable to speak for yourself, we are turning to the right people to make medical decisions for you. Have you considered who that person would be for you?” “While we all remain very hopeful that this treatment will give you time with your loved ones, do you ever worry about what if it doesn’t work? Can you share some of your concerns or worries with me?”
<b>Recurrence and EoL;</b> Discuss EoL preferences	Reframe Expect emotion Map out goals/values Align with preferences Plan	<b>R:</b> “Unfortunately, now that the tumor has come back, treatment options are limited.” <b>E:</b> “I know this is devastating. We will continue to support you as a team.” <b>M:</b> “Given this new information that time is short, what feels most important to you?” <b>A:</b> “I’m hearing that we should prioritize treatments that give you the most time awake to be with family, is that right?” <b>P:</b> “I’d like to make some suggestions that will help you reach those goals.”
<b>Bereavement</b>	<b>Bereavement support</b>	<ul style="list-style-type: none"> <li>• Supportive psycho-education</li> <li>• Normalization of symptoms when possible</li> <li>• Ongoing assessment to recognize complications of grief and bereavement</li> </ul>

## Phase II: Initial Treatment

### Symptoms

Following surgery, initial treatment for HGG most commonly includes a 6-week course of radiotherapy combined with temozolomide [41]. During this treatment-intensive

phase, the most common symptoms include nausea, vomiting, constipation, adverse effects of steroids, fatigue, sleep disruption, and mood disturbance [2•]. Refer to Table 1

Temozolomide is a moderately emetogenic oral chemotherapy taken daily during radiation. In most patients, nausea is effectively managed by pre-medication with serotonin receptor antagonists, most commonly ondansetron, as

recommended per ASCO's 2020 guideline [42]. A randomized phase II trial of rolapitant (a neurokinin-1 receptor antagonist) plus ondansetron versus ondansetron alone for the prevention of chemoradiation-induced nausea and vomiting (CINV) in malignant glioma patients is ongoing (NCT02991456). Although there are no prospective studies in HGG of the antipsychotic olanzapine, we support its use in patients with breakthrough CINV given favorable data in other cancers [42, 43, 44]. Constipation is a common and well-known side effect of both temozolomide and 5-HT3 receptor antagonists, which can be effectively managed with most over-the-counter oral laxatives and senna preparations [45].

Dexamethasone is the steroid most used for cerebral edema given its long half-life and CNS penetration. Its adverse effects may emerge during initial treatment, including weight gain, lower extremity edema, insulin resistance, changes in appearance, and myopathy, which can worsen immobility in patients who may already be neurologically compromised. Pneumocystis jiroveci pneumonia (PJP) prophylaxis should be considered for steroid-induced immunosuppression, especially when the patient is lymphopenic from temozolomide and radiation [46]. Other adverse effects of glucocorticoids include insomnia, hyperglycemia, irritability, gastroesophageal reflux, and adrenal insufficiency. Dexamethasone use during concurrent radiation and temozolomide has been associated with poorer outcomes for patients with HGG, though the relationship is not entirely understood [47, 48] and may be related to the timing (pre- versus post-operative period) [49]. Thus, although steroids reduce acute neurological symptoms associated with cerebral edema, they should be tapered to the lowest possible efficacious dose and discontinued when possible [50].

Fatigue affects roughly half of all glioblastoma patients starting at diagnosis and is an anticipated side effect of radiation [51]. Trials of psychostimulants (methylphenidate and armodafinil) for brain tumor patients undergoing radiotherapy showed no benefit for fatigue [52, 53, 54]. In certain cases, armodafinil may aid concentration [54]. Of note, there is no specific data on stimulant use and the risk of breakthrough seizures in adult patients with brain tumors. However, increased seizure risk has not been clearly demonstrated in children or adults with other types of epilepsy who receive psychostimulants [55]. Current NCCN guidelines recommend brain tumor patients be screened for fatigue regularly and non-pharmacological interventions (e.g., physical activity and personal health coaching) be prioritized [31, 56–58]. Evaluation for alternate causes of fatigue and management of sleep disturbance is recommended.

Sleep disturbance may be due to treatment side effects (especially steroids), pain or anxiety [59]. We recommend dosing steroids earlier in the day (before 2 pm). Mindfulness, cognitive behavioral therapy, and meditation techniques

may improve sleep. Studies evaluating circadian rhythms in PMBT and assessing the efficacy of such interventions in this population are ongoing (NCT04919993, NCT04669574) [60].

Mood disorders such as adjustment disorder, acute stress disorder, major depression, and anxiety may manifest at any time during the disease trajectory [61]. Anhedonia or agitation from frontal or temporal lobe tumors can contribute to reduced QOL and additional caregiver burden, and depression is associated with a worse prognosis, though minimal data exists to guide management [62]. Per NCCN guidelines, all cancer patients should be screened prior to clinic visits, using a tool such as the NCCN Distress Tool [63]. Mild or "expected" distress can be managed by the primary oncology team and addressed by psychosocial interventions [63]. Moderate or severe distress should prompt referral to a mental health professional or PC clinician. A Cochrane review of pharmacological treatment of depression in patients with primary brain tumors identified no high-quality studies on which to base recommendations [64]. Limited data available suggests that various antidepressant classes, including selective serotonin reuptake inhibitors (SSRIs), increase seizure frequency [65]. Bupropion carries the greatest risk and its use is discouraged in this population, but given the high prevalence of depression and anxiety in the population, the other agents are necessary and used in a range of prescribing patterns [66]. In our practice, we evaluate drug-drug interactions and side effect profile to select antidepressants on a case-by-case basis, and monitor closely for seizures.

## Communication

Clinic visits during initial treatment are often focused on tumor-directed treatments and their side effects, while the cancer itself may be relatively stable. Clinicians may hesitate to bring up ACP at this early phase, and indeed patients and caregivers commonly express trepidation around discussions of death [67, 68]. Yet qualitative studies have found that many patients and caregivers believe these discussions are important and should be preferably initiated by familiar, trusted clinicians. In our experience, making these conversations a standard part of visits early, rather than bringing them up only when crises arise, may help deflect some of the fear and discomfort surrounding these topics. This can also encourage patients and caregivers to continue these conversations at home and allow patients to express their preferences while their cognition is relatively intact.

Topics identified by patients and caregivers as being important include details of their current medical condition; worries and fears about the future; supportive treatment; financial concerns; needs of the proxy/caregiver; and preferred place of care and death [67, 70]. A randomized controlled trial using a video approach to introduce code

status in HGG patients found that patients and caregivers were highly receptive to this method of discussing ACP options, although this technology is not easily available to be incorporated in practice [71]. To structure ACP discussions during the initial treatment phase, we recommend the use of the PAUSE (Pause and make time, Ask permission, Understand big picture, Suggest choosing surrogate, Expect emotion) tool (Table 2) [72]. PAUSE includes ACP as a part of the visit agenda, asking for permission to explore what the patient might want in the rare event they be unable to speak for themselves, and bringing up the topic of advance directives, living wills, and designated surrogate. Another option can be using hypothetical “what if” questions (e.g., “what if the treatment does not work?”), which allows patients or caregivers to discuss fears, hopes and worries [73].

### Phase III: Recurrence

#### Symptoms

At the time of disease recurrence, patients often report increased symptom burden, often associated with worsening functional status. In a cohort of 207 patients with recurrent PMBT, nearly half reported having three or more moderate-to-severe symptoms, one-third reported fatigue, drowsiness, and problems remembering, and one-fifth reported hemibody weakness, difficulty speaking, distress, or irritability [74]. Any new symptom generally prompts concern for disease recurrence, but alternative processes such as infection, medication side effects, hydrocephalus, radiation necrosis, and tumoral edema should be considered.

Urinary incontinence can be highly distressing for patients and caregivers. It may due to tumor effect on the frontal lobe, leptomeningeal spread, urinary tract infection, or functional incontinence due to motor or cognitive dysfunction. Tumors involving the thalamus or spinal cord may cause central neuropathic pain refractory to interventions [75]. Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentinoids are recommended as first-line treatments. Non-pharmacological options may include peripheral nerve block, ganglion/nerve injection, epidural steroid injection, neurostimulation, intrathecal delivery of drug, acupuncture, massage, ultrasound, laser, and cognitive behavioral therapy [76].

As with urinary tract infections, the etiology of gait impairment may be protean. We recommend that clinicians keep a broad differential and consider workup for alternate, potentially reversible causes. Referrals to physical and occupational therapy for optimizing function and the use of assistive devices as well as safety strategies can be crucial for not only improving and maintaining the quality of life but preventing serious injury from falls and accidents [29, 30].

### Communication

The recurrence phase offers a critical opportunity to introduce SPC and how it is distinct from hospice, if this has not already been done. Patients with PMBT prefer to be informed about palliative care, despite feelings of fear [69]. Recurrence presents a critical time for patients to express their EOL case wishes to express their EOL care wishes as a means of preserving autonomy, agency and control, while relieving their caregivers of guilt, uncertainty, and anxiety about medical decision-making, especially in the event of rapid decline [77•]. The topic may be introduced using the REMAP communication tool: Reframing the status of a patient’s disease and clinical state in terms of recurrence, Expecting and managing the emotional response, Mapping out the patient’s current goals and Aligning with those goals, proposing a Plan (Table 2) [78]. Tangible ACP products may include a durable power of attorney for healthcare and a living will indicating which medical interventions, treatments, and care the patient would find acceptable.

### Phase IV: End-of-Life

#### Symptoms

The EOL phase has no standardized definition, but may be identified prospectively in a patient experiencing irreversible decline and with an expected prognosis on the order of months. In HGG, the EOL period is marked by neurologic decline, which often leads to late hospitalization in the final weeks of life [79]. Seizures affect up to 56% of patients at EOL and may occur de novo or recur in patients already on anticonvulsants [80]. Abrupt discontinuation of anticonvulsants can lead to breakthrough seizures and should be avoided [81]. For patients who can no longer take oral medications and are admitted to a medical setting, many anticonvulsants are available intravenously (fosphenytoin, phenobarbital, valproate, levetiracetam, and lacosamide) [82]. For patients at home, rectal formulations of some anticonvulsants exist, but may not be practical to administer. Thus, many patients at EOL will require scheduled benzodiazepines (available in buccal, intranasal, and rectal formulations), acknowledging that this may lead to increased sedation. In addition to counseling families about the likelihood of seizures, which can cause substantial distress, management should include evaluation and removal of triggers and development of a rescue plan if seizures occur [82].

Up to 85% of patients with brain tumors have dysphagia at EOL [80]. Along with consideration of non-oral medication formulations, dysphagia should prompt discussion of artificial nutrition and hydration. This can be an emotional and charged subject for families, but it must be noted that

artificial nutrition is unlikely to be of benefit in this population and may even prolong or cause discomfort in the dying process [83].

Delirium is another common EOL issue, occurring in up to 90% of patients with HGG, often accompanied by alterations in consciousness, highlighting the importance of ACP while patients are still able to participate. Neuroleptics and benzodiazepines are often used to achieve comfort, though limited data are available to guide their dosing. While there is no specific data in HGG, a small, randomized trial in patients with other advanced cancers who were at EOL found benefits in reducing agitation using haloperidol dose escalation, alternation between haloperidol and chlorpromazine, or combination therapy with haloperidol and chlorpromazine [84].

## Communication

Along with symptom control and dying in their preferred place, satisfaction with information provided has been associated with better QOL according to a survey of 207 relatives of decedents with HGG [85], yet other studies have indicated that patients and caregivers often do not receive comprehensive information, particularly about prognosis [34]. Additionally, perception of prognosis may fluctuate throughout the disease course and is often discordant between patients, caregivers, and clinicians [86•]. Recognizing and discussing EOL with patients and caregivers may promote more goal-concordant care [87]. Despite the sensitive nature of these discussions, many patients and caregivers wish to discuss them with their medical teams [70, 88•]. We recommend that when clinicians recognize that a patient is approaching EOL, they offer opportunities for open and supported discussion to facilitate informed decision-making. The “REMAP” framework, as discussed above, can provide a helpful structure for these conversations [78]. Common issues to be addressed in the “MAP” portion of the conversations include discontinuation of cancer-directed therapies and other life-prolonging treatments, hospitalization, code status, and hospice referral [89]. Patients and caregivers may fear abandonment by the oncology team at the end of life, particularly if they enroll in hospice, so they should be reassured that the team will still be available for questions [90].

Although the majority (60–70%) of patients with PMBT including HGG enroll in hospice [91•, 92], many of them do so late (in the last 3–7 days of life) when they may not receive maximal benefit from the service. Thus, familiarity with hospice is important for clinicians. In contrast to PC, which is provided concurrent with cancer-directed therapies at any time after diagnosis, hospice in the USA is an alternative to cancer-directed therapy available to patients with a life expectancy of 6 months or less. It is a Medicare insurance benefit that covers multidisciplinary EOL care and

bereavement services at home (with most hands-on care provided by families or privately hired aides), in a facility, or in an acute hospital [93]. Of note, pediatric hospice allows concurrent care (patients may continue receiving cancer-directed therapy) [94], as does the Veterans Administration [95], and concurrent care is being piloted at select sites by the Centers for Medicare and Medicaid Services through the Medicare Care Choices Model. Receipt of hospice is associated with improvements in symptom control and quality of EOL care, and bereavement support, as well as greater alignment of care with patient preferences [96].

## Phase V: Bereavement

This section focuses on the bereavement and grief of caregivers after the death of the patient. Caregivers may neglect their own physical, mental, and spiritual health, with heightened intensity at the late stage of disease as the patient develops increasingly complex symptoms, needs further assistance with daily living, and/or becomes cognitively disengaged [97]. Caregivers of HGG patients have significant distress both before and after the patient’s death, stemming from fears surrounding the patient’s death, changes in relationship dynamics as the patient declines cognitively and becomes more dependent, and worries about meeting the patient’s care goals [98, 99•, 100, 101•]. Literature on interventions to support caregivers in neuro-oncology remains limited and is an area of active investigation. Clinical care and management recommendations are therefore based on data from the general cancer population.

Prolonged or complex grief is persistent, pervasive, and interferes with the bereaved’s daily functioning. Younger age, higher economic burden, and lower social support, spirituality, and caregiver mastery are associated with increased distress in caregivers of patients with primary brain tumors [102]. These are similar to risk factors for complex grief described in bereaved spouses of patients with other serious illnesses [103]. Anticipatory (pre-loss) grief is also associated with greater prolonged grief disorder and depressive symptoms 6 months after the loss [104]. Predictors of greater anticipatory (pre-loss) grief in family members of patients with advanced cancer and dementia include history of post-traumatic stress, higher caregiving burden, and female gender [105].

Screening tools for identifying at-risk caregivers in the general oncology population may be useful in HGG. For example, the Bereavement Risk-Screening Tool (BRST) can help social workers identify bereaved family members with prolonged and complicated grief [106], and the PG-13 is used to identify at-risk caregivers prior to the patient’s death as well as to identify bereaved caregivers with prolonged and complicated grief disorder [107]. Caregivers report being

receptive to bereavement screening as early as at the time of diagnosis, when it is conducted in a sensitive manner by a mental health professional or social worker and includes a clear description of the purpose [107].

Potential barriers to addressing bereavement include insufficient time, training, patient privacy, and competency, which may be resolved through referral to interdisciplinary team members [108]. Clinical social workers are skilled in using family systems theory to assess for bereavement, evaluating psychosocial stressors, and providing bereavement counseling [109]. For some caregivers, spiritual assessment and chaplaincy support may be appropriate and meaningful [110]. Caregivers also may benefit from early referral to SPC, which includes interdisciplinary support [101]. Early hospice enrollment can also assist caregivers in navigating complex symptom management and is associated with better outcomes in caregiver bereavement [97].

## Conclusion

HGG has a devastating impact on patients and caregivers, with substantial palliative care needs throughout the disease course, with limited evidence, particularly from clinical trials, to guide palliative management. Additional studies are needed to develop symptomatic treatments and optimize the timing and type of ACP interventions. Neuro-oncologists are often primarily responsible for the majority of ACP - in this population, and thus may benefit from additional communication training, which is not typically a part of neuro-oncology curricula [111, 112]. Sources of focused training include the End-of-Life and Palliative Care for Neurology (EPEC-Neurology) curriculum, which is a series of lectures on palliative care topics tailored to neurology, and VitalTalk, an organization that teaches evidence-based communication skills for serious illness [113].

Referral to SPC may also be needed in cases of refractory symptoms, complex dynamics or challenging communication. Recent studies have identified multiple barriers to early referral in this population, including decreased familiarity of SPC providers with brain tumor patients, the small number of specialists with training in both neurology and PC, the stigma associated with PC within the field of neuro-oncology, overwhelming burden of appointments for patients and caregivers, and early cognitive impairment [114, 115]. While all patients diagnosed with HGG may not require immediate referral to SPC, a screening tool may be helpful to identify those patients most likely to benefit based on low functional status or high symptom burden at presentation, early steroid dependence, unresectable tumors in eloquent or sensitive areas (thalamus, brainstem), or poor tolerance of radiation and chemotherapy due to side effects [116]. Results of a randomized prospective phase III trial of early PC in

patients with glioblastoma are pending [117]. Other models of PC delivery (e.g., embedded SPC clinicians in a neuro-oncology clinic or structured PC interventions build into the neuro-oncology clinic workflow) may also warrant investigation [118]. Establishing an effective PC delivery model for patients with HGG and other PMBTs is likely to yield substantial improvements in QOL in this unique population.

## Declarations

**Conflict of Interest** The authors declare no competing interests. ICJME disclosure forms are submitted separately.

**Ethics Approval** All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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●● Of major importance

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