

THE PALLIATIVE CARE GUIDE IN NEUROLOGY: BEST PRACTICE GUIDELINES IN COMMUNICATION, SYMPTOM MANAGEMENT, AND END OF LIFE CARE OF PATIENTS WITH BRAIN TUMORS AND OTHER LIFE LIMITING NEUROLOGICAL DISORDERS

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Palliative care is a multidisciplinary approach to practicing medicine that addresses symptom management, alleviation of pain, assessment of psychosocial and spiritual distress or suffering, and practical support for patients and their caregivers with a goal of improving quality of life for patients with serious and life-threatening illnesses. Although palliative care has gained acceptance as an important part of comprehensive cancer care at the end of life, early integration of palliative care is less common, despite the scientific proof that patients with cancer who receives palliative care not only live better, but longer. In a landmark study, patients with metastatic non-small cell lung cancer were randomly assigned to receive early palliative care integrated with standard oncology or standard oncologic care alone. Early palliative care was associated with improved quality of life, improved symptom management, reduction of aggressive tumor-directed therapy at the end of life and, improved survival.

Despite extraordinary advances in neuro-oncology most brain tumors remain non-curable. Competent neurologic practice is therefore all about improving the quality of life of brain tumor patients, from diagnosis onward. In 1996, the Ethics and Humanities Subcommittee of the American Academy of Neurology (AAN) recognized the importance of competence in the palliative medicine when it emphasized, "It is imperative that neurologists understand and learn to apply the principles of palliative care as...many patients with neurologic disease die after long illnesses during which the neurologist acts as the principle or consulting physician."

Symptom Management in Brain Tumor Patients

While the primary neuro-oncology treatment is geared to extend life and progression-free survival, there is increasing focus by patients, families, and physicians that maintaining quality of life is as important as increasing survival time. Brain tumors can present with many signs and symptoms that have immediate impact on the patients' quality of life. These symptoms can be either caused by the location of the brain tumor or by oncologic treatment (surgery, radiation, chemotherapy). Proactive symptom management is essential to maintain the patient's quality of life and at the same time to support caregivers and families.

Seizures

Epileptic seizures are common in neuro-oncology and affect 30–80 % of all patients with brain tumors. Seizures can be potentially life threatening and can cause significant morbidity especially in patients with otherwise controlled tumors. The seizure frequency is generally higher in patients low-grade glioma (WHO grade II) (60–80 %) and less prevalent in glioblastoma (WHO grade IV) (29–49 %). Approximately 40 % of brain tumor patients present with a seizure as a first symptom and these patients remain at an increased risk for recurrent events despite treatment with antiepileptic drugs. The use of antiepileptic prophylaxis for glioma is currently not recommended for patients who have never had a seizure.

Despite good seizure control during treatment, up to 86 % of patients suffer from seizures at the end of life.

Seizures in the end-of-life phase have been associated with non-peaceful death.

The optimization in this setting can be challenging as many brain tumor patients are unable to swallow or to take oral medications due to changes in mental status. If oral or intravenous application is not appropriate, seizure medications can be supplied intramuscularly, subcutaneously, rectally, or via buccal or intranasal application. Diazepam especially can be delivered as rectal suppository and the buccal or intranasal application of midazolam has also been shown to stop seizures.

Fatigue

Many patients report severe impairment due to fatigue throughout the course of the disease, but it is most prevalent around the time of radiation treatment. The underlying mechanism for cancer-associated fatigue remains unclear, but factors associated with higher risk for fatigue include older age, female sex, decreased performance status, and treatment-related factors. Fatigue has significant impact on patients physical, mental, and emotional functioning. Forty-two percent of patients with primary brain tumors report their energy levels to be “quite a bit low” or “very low” at some point in their treatment course. One prospective study found that one-third of patients with brain tumors had clinically significant fatigue at baseline, prior to starting radiation. Further, fatigue is an independent predictor of overall survival. The NCCN guidelines for clinical practice recommend physical exercise as first-line treatment for cancer-related fatigue. The use of stimulants such as methylphenidate and modafinil has been evaluated in several studies for brain tumor patients, but results are overall inconclusive.

Depression and Cognitive Dysfunction

The quality of life of the patient with a brain tumor may be largely dependent upon the competence in palliative care of the care team. Distress in patients with newly diagnosed brain tumors may be manifest by severe anxiety and/or depression and the risk of emotional upset is highest among patients with a premorbid mood disorder. Patients with anterior frontal tumors may have a higher risk for depression than those with tumors in other locations. Depression and anxiety are negatively associated with quality of life, and there is a weak association between depression and reduced survival. Based on evidence in other seriously ill patients and cancer patients, selective serotonin reuptake inhibitors (SSRIs) should be considered as first-line therapy for treatment of depression and anxiety in glioma patients.

Cognitive deficits in adults with brain tumors have been reported at rates of 29%-90%. The etiology of cognitive impairment in patients with brain tumors is often multifactorial and may include the tumor itself, seizures, metabolic disturbances, along with side effects of surgery, radiation, and/or chemotherapy.

Headache

Approximately 50% of patients with brain tumors experience headache pain, with estimates ranging from 33% to 71%. The first step to treating headache in patients with brain tumors is to identify the reason for the headache. Headache may be due to mass effect, increased intracranial pressure, intratumoral hemorrhage, or transient increases in intracranial pressure known as “plateau waves.” Postsurgical pain may trigger headaches, and patients with a history of migraine may experience resurgence or worsening of their typical headaches. Since the brain itself has no pain receptors, headache in patients with brain tumors may be attributed to several possible mechanisms including traction on draining veins, the middle meningeal artery, skull-based arteries, cranial nerves, pain afferent fibers, inflammation, or inflammatory mediators such as leukotrienes. Primary and adjuvant analgesics such as acetaminophen, nonsteroidal anti-inflammatory medications, and anticonvulsants may be helpful. Opioids are generally not as effective for managing headache as they are for somatic, visceral, or neuropathic pain.

Communication Strategies

For patients with brain tumors, the integration of palliative care early into standard neuro-oncologic care is especially important, given the profound and often early losses in language

Function, changes in personhood and decision making capacity. Based on these neurological deficits, it has been suggested to address advanced care planning early during the disease trajectory.

Hope is fostered through the assessment and management of symptoms and the assurance of non-abandonment offered by the treating neuro-oncologist. The “Ask, Tell, Ask” method is a tool for effective communication in which the doctor first asks the patient what he or she knows, wants to know, or is concerned about, then delivers the information, then checks the patient’s understanding of the information that was provided. Utilizing other paradigms such as the SPIKES protocol for breaking bad news assures that doctor-patient communication is effective, patient-centered, sensitive, empathic, and compassionate.

Table 1. The SPIKES Protocol for breaking bad news or giving important medical information

S: SETTING and listening skills

P: Patient’s PERCEPTION of condition and seriousness

I: Invitation from the patient to give information

K: Knowledge – giving medical facts

E: EXPLORE emotions and EMPATHIZE as the patient responds

S: STRATEGIZE and SUMMARIZE

The Empathic Response is a skill, not a feeling. It is not necessary for the clinician to have the same feelings as the patient nor to agree with the patient's view or assessment. What is necessary is that the patient and feeling feel validated and understood. Empathy is best communicated as follows:

- 1) Identify the Emotion
- 2) Identify the cause/source of that emotion
- 3) Make the connection between #1 and #2.

For example, "I can see how sad this news makes you feel. It must feel awful." Listening to patients and families is one of the most important tools a clinician may employ in assuring validation and a compassionate response. Best listening strategies include:

- a) Ask open-ended questions (e.g., Ask "How did you feel when that happened?" vs. "You felt awful, right?"
When taking a family history, ask "And you father...?" vs. "When did your father die?"
- b) Tolerate silence. Ask, "What were you thinking about just then...?"
- c) Use a word from what the patient has said, (e.g., "You use the word embarrassing. Tell me more...")

Word choice may be helpful or may widen a potential gap between clinicians and patients and families. Consider the potential negative impact of the following questions or statements:

- Do you want to be aggressive?
- Do you want to have everything done?
- It's time we talk about pulling back.
- I think we should stop fighting
- Your husband FAILED all of the chemotherapy we provided.

One of the barriers toward delivery of palliative care has been the unfortunate association with palliative and LESS care. Clinicians must never associate palliation or hospice with doing LESS for patients and families. The conversation must shift from doing "everything" vs. doing Less toward a more helpful discussion of a shift in the goals of care.

Some more helpful language might include:

- I want you to know that no matter what happens with your disease, I am here. I will always do my best. You will always be my patient.
- Even if we decide together to stop treating the cancer, I will never stop treating YOU.
- The chemotherapy failed (not the patient!) to provide the response we had been hoping for together. Let's talk about other strategies and what is most sensible now.

Palliative Care Needs At or Near The End of Life

Agitation and Delirium

Throughout much of the course of the disease, palliative care for patients with brain tumors focuses on maximizing cognitive function and minimizing fatigue. Among atypical antipsychotics, quetiapine and olanzapine are often used for agitated delirium or insomnia. For patients unable to swallow pills, haloperidol in an injectable form may be preferred.

Under some circumstances in patients who are imminently dying, sedation may be an important tool for minimizing suffering. Opioids may be used for control of pain or dyspnea, while benzodiazepines and neuroleptics are often added for agitation and delirium (see Table

3). Established legal, ethical, and palliative care guidelines support the use of sedation for patients who are imminently dying to assure comfort and dignity as a last resort. In studies of sedation in the setting of either home or inpatient hospice, there was no difference in the patients' time to death when comparing those who were sedated and those who were not, underscoring the importance of reminding family and loved ones that sedated patients die not from the prescribed sedation, but from the end stages of their disease.

Table 3. Management of agitation and delirium at the end of life

<u>Medication</u>	<u>Route</u>	<u>Starting Dosage</u>
Lorazepam	p.o. i.v. i.m.	2-3mg/day bid-tid
Diazepam	po. Pr. Iv. Im	2-10mg bid-tid
Clonazepam	po, ODT	0.5mg bid-tid
Quetiapine	po	25mg bid
Olanzapine	po, ODT, im	2.5-5mg qhs
Haloperidol	po, im, iv	0.5-1mg every 1-4 hrs, prn

Management during the end of life phase

Patients who are dying from a serious illness often go through stages of grief, loss, and denial. Patients' central concerns often revolve around families and relationships, the patient/s own psychological integrity, and finding meaning in life. There is an opportunity at the end of life to enhance relationships and leave a legacy. In order to meet these challenges, mental distress and suffering must be well controlled.

Near the end of life, the neuro-oncologist must be able to recognize that the patient is dying and advise family and caregivers. In most patients with primary brain tumors, the cause of death is brain herniation due to tumor progression. In a minority of patients, death may be due to complications of the tumor including seizure, intracranial hemorrhage, infection, or pulmonary embolism. Rarely, death may occur due to treatment complications such as bowel perforation from steroids. Understanding how patients with brain tumors die and preparing family and friends about what to expect can ease anxiety and be very helpful to grieving loved ones as they prepare for the inevitable end of life.

A diagnosis of brain tumor impacts the whole person: mind, body, spirit, and the patient's primary relationships. Early integration of palliative care and competency in communication skills may help to lessen the emotional blow of the initial diagnosis and set more realistic expectations for the course of treatment. The emerging practice standard for neuro-oncologists now includes competency in palliative care. Patients and families should expect their doctors to emphasize quality of life as an essential part of delivering the highest quality of care. Neuro-oncologists must be expected to treat the patient, not only the tumor, from diagnosis to bereavement. Comprehensive care of patients with brain tumors requires mastery of symptom management, communication techniques, knowledge of the results of randomized controlled clinical trials to afford patients the opportunity to live as well as possible for as long as possible.

References:

Anderson GD., Saneto RP., Current oral and non-oral routes of antiepileptic drug delivery. *Adv Drug Deliv Rev* 64:911–918, 2012.

Applebaum AJ., et al., Existential distress among caregivers of patients with brain tumors: a review of the literature, *Neuro-Oncology Practice* 2015; 0, 1-13.

Armstrong TS., Gilbert MR., Practical strategies for management of fatigue and sleep disorders in people with brain tumors. *Neurooncology* 14(Suppl 4):iv65–iv72, 2012.

Boele FW., Klein M., Reijneveld JC., Verdonck-de Leeuw IM., Heimans JJ., Symptom management and quality of life in glioma patients. *Future Medicine* 3:37–47, 2014.

Batchelor T., Byrne T., Supportive Care of Brain Tumor Patients, *Hematol Oncol Clin N Am* 20 1337-1361, 2006.

Carver A.C., K.M., Symptom Assessment and Management, in *Neurologic Clinics: Palliative Care*, Vol 19, No, 4, November 2001.

Carver A.C., Vickrey B.G., Bernat J.L., Keran C., Ringel S.P., Foley K.M., End of Life Care: A survey of U.S. neurologists attitudes, behavior, and knowledge, *Neurology* 1999; 53:284-293.

Chochinov HM., et al., Effect of dignity therapy on distress and end of life experience in terminally ill patients: a randomized controlled trial, *Lancet/Onc.*, Vol. 12, August, 2011.

Clayton JM., et al., Sustaining hope when communicating with terminally ill patients and their families: A systemic review, *Psycho-Oncology*, 17:651-659, 2008.

Coyle, N., Schachter S., Carver A.C., Terminal Care and Bereavement, in *Neurologic Clinics: Palliative Care*, Vol 19, No. 4, November 2001.

Diamond E., et al., Prognostic awareness and communication of prognostic information in malignant glioma: A systematic review, *J Neurooncol* 119: 227-234, 2014.

Diamond EL., et al., Rates and risk for late referral to hospice in patients with primary malignant brain tumors, *Neuro-Oncology* 2015; 0, 1-9.

European Journal of Palliative Care – Core competencies in palliative care: An EAPC White Paper on Palliative Care Education – Parts 1 and 2, 2013.

Foley, KM., How well is cancer pain treated? *Palliative Medicine* 25(5) 398-401, 2011.

Gehring K, et al., Interventions for cognitive deficits in adults with brain tumours, *Lancet Neurol* 2008; 7:548-60.

Gofton TE., Graber J., Carver A., Identifying the palliative care needs of patients living with cerebral tumors and metastases: a retrospective analysis. *J Neurooncol* 2012

Granek L., et al., Difficult Patient Loss and Physician Culture for Oncologists Grieving Patient Loss, *J Pall Med.*, Vol 15, No 11, 2012.

Litofsky NS., Resnick AG., The relationships between depression and brain tumors, *J Neurooncol* 2009 94:153-161.

Lobb EA., et al., Patient and caregiver perceptions of communication of prognosis in high grade glioma, *J Neurooncol* 2011, 104:315-322.

Meier D.E., Back Anthony L., Morrison R.S., The Inner Life of Physicians and Care of the Seriously Ill, *JAMA*. 286: 3007-3014 2001.

Mummudi N., Jalali, R., Palliative care and quality of life in neuro-oncology, *F1000 Prime Reports*, 2014, 6:71.

Norals TE., Smith TJ., Advance care planning discussions: Why they should happen, why they don't, and how we can facilitate the process, *Oncology*, 431-440, 2015.

Oberndorfer S., et al., The End of Life Hospital Setting in Patients with Glioblastoma, *J Pall Med.*, Vol 11, No 1, 2008.

Ostgathe C et al., Hospice & Palliative Care Evaluation Working Group in Germany (HOPE), Differential palliative care issues in patients with primary and secondary brain tumors, *Support Care Cancer*, 2009.

Pace A, Lorenzo C., Guariglia L, Jandolo B, Carapella C, Pompili A, End of life issues in brain tumor patients, *J Neurooncol* 91:39-43 2009.

Pace A, Villani V, Di Lorenzo C et al (2013) Epilepsy in the end-of-life phase in patients with highgrade gliomas. *J Neurooncol* 111:83–86.

Peterson K., Neoplasms, in Voltz (eds) et a., *Palliative Care in Neurology*, Oxford Univ. Press, 2004.

Rooney AG., Carson A., Grant R., Depression in cerebral glioma patients: a systematic review of observational studies. *J Natl Cancer Inst* 103:61–76, 2011.

Rooney AG., Brown PD., Reijneveld JC., Grant R., Depression in glioma: a primer for clinicians and researchers. *J Neurol Neurosurg Psychiatry* 85:230–235, 2014.

Rooney AG., Grant R., Pharmacological treatment of depression in patients with a primary brain tumour. *Cochrane Database Syst Rev* 5:CD006932, 2013.

Schubart JR., Caring for the brain tumor patient: Family caregiver burden and unmet needs, *Neuro-Oncology* 10, 61-72, 2008.

Sizoo EM., et al., Symptoms and problems in the end of life phase of high-grade glioma patients, *Neuro-Oncology* 12(11); 1162-1166, 2010.

Smith TJ., Longo DL., Talking with Patients about Dying, *N Engl J Med* 367;17, Oct. 25, 2012.
Taillibert S., Delattre J-Y., Palliative care in patients with brain metastases, *Curr Opin Oncol* 17:588-592, 2005.

Taillibert S., Laigle-Donadey F., Sanson M., Palliative care in patients with primary brain tumors, *Curr Opin Oncol* 16:587-592, 2004.

The American Academy of Neurology Ethics and Humanities Subcommittee, Palliative Care in Neurology, *Neurology* 46:870-872 1996.

Thomas A., Carver A., Essential competencies in palliative medicine for neuro-oncologists, *Neuro-Oncology Practice* 2015; 0, 1-7.

Traeger L., Greer JA., Fernandez-Robles C., Temel JS., Pirl WF., Evidence-based treatment of anxiety in patients with cancer. *J Clin Oncol* 30:1197–1205, 2012.

Von Roenn JH., von Gunten CF., Setting Goals to Maintain Hope, *J Clin Onc*, Vol. 21, No. # 2003: 570-574.

Watanabe K., Macleod R., Care for Dying Patients with Primary Malignant Brain Tumors: Respecting Dignity, *Neurol Med Chir (Tokyo)* 45, 657-659, 2005.

Walbert T., Chasteen K., Palliative and supportive care for glioma patients. *Cancer Treat Res*. 2015;163:171-84.

Walbert T., Khan M., End of life symptoms and care in patients with primary malignant brain tumors: a systematic literature review, *J Neurooncol* (2014) 117:217-224.

Walbert, T., Integration of palliative care into the neuro-oncology practice: patterns in the United States, *Neuro-Oncology Practice*, 2014; 1, 3-7.

Weeks JC., et al., Patients' Expectations about Effects of Chemotherapy for Advanced Cancer, *N Engl J Med* 367: 1616-25, Oct. 25, 2012.

Wolfe J., Grief H.E., Klar N., Levin S.B., Ellenbogen J.M., Salem-Schatz S., Emanuel E., Week J., Symptoms and Suffering at the End of Life in Children with Cancer, *N Engl J Med* 342;326-33 2000.