

## Essential competencies in palliative medicine for neuro-oncologists

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Palliative care is an 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. Patients with high-grade malignant gliomas have an invariably poor prognosis and high morbidity. With short survival times and complex neurological and systemic symptoms, these patients require palliative care from the time of diagnosis. In this review, we highlight the palliative care needs of neuro-oncology patients at diagnosis, during treatment, and at the end of life. We identify some of the barriers to incorporation of palliative care in standard neuro-oncology practice and equate competency in neuro-oncology with competency in the basic tenets of palliative medicine.

**Keywords:** brain tumor, end of life, glioblastoma, neuro-oncology, palliative care.

Palliative care is an approach to practicing medicine that improves quality of life for patients and families with serious and life-threatening illness.<sup>1</sup> Palliative care includes symptom management, alleviation of pain, assessment of psychosocial and spiritual distress or suffering, and practical support for patients and their caregivers.<sup>1</sup> Although sometimes associated with hospice care, palliative care is a broader specialty with a goal of maximizing quality of life without hastening or preventing death. The delivery of palliative care services often draws on skills from a multidisciplinary team of providers.

Palliative care, and in particular early palliative care, has emerged as a necessary component of comprehensive cancer care. The National Comprehensive Cancer Network (NCCN) recommends that all patients with cancer be screened for palliative care needs at their initial visit. 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 oncological care alone.<sup>2</sup> 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.

Glioblastoma, the most common primary brain tumor, is a highly morbid disease without curative therapy. Among patients younger than aged 70 years with high performance status (Karnofsky performance score above 70%) who are clinical-trial eligible and receive the standard triad of resection followed by radiotherapy and temozolomide, the median overall survival is 14 to 15 months.<sup>3</sup> Among the elderly, standard treatment is

more varied. Radiation may be avoided or abbreviated, and chemotherapy may or may not be offered depending on the patient's functional status. In those patients over aged 70 years who receive radiation, median survival is approximately 7 months.<sup>4,5</sup> Without radiation, elderly patients with glioblastoma have a median survival of only 4 months.<sup>4,5</sup> In a study of 5029 Medicare patients aged 65 years and older with glioblastoma, median overall survival was 4.9 months.<sup>6</sup> Among these patients, 21% were hospitalized for more than 30 days between the time of diagnosis and death, and 22% spent a quarter of their life from diagnosis on an inpatient hospital ward.<sup>6</sup> With such short survival times and an ever-changing composition of neurological and systemic symptoms, patients with primary brain tumors need competent, state-of-the-art palliative care from the time of diagnosis throughout their clinical course.

### Palliative Care Needs at Diagnosis

Integration of palliative care starts in the oncology office. 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, and then asks if it was understood or if there are further questions.<sup>7,8</sup> Information, including bad news, can be delivered in a way that fosters coping and nurtures hope by emphasizing what can be done and by setting and exploring realistic goals.<sup>9,10</sup> Paradigms such as the SPIKES protocol<sup>11</sup> are helpful

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**Table 1.** The SPIKES protocol for breaking bad news or giving important medical information<sup>11</sup>


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S: SETTING and listening skills
P: Patient's PERCEPTION of condition and seriousness
I: INVITATION from patient to give information
K: KNOWLEDGE – giving medical facts
E: EXPLORE emotions and empathize as patient response
S: STRATEGY and SUMMARIZE

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for assuring that communication of bad news is patient centered, effective, and compassionate (Table 1).

At the time of diagnosis of a new brain tumor, patients and caregivers report feeling stressed, distressed, anxious, depressed, and generally emotional.<sup>12,13</sup> Patients may report pain, headaches, weakness, or other neurological symptoms. In patients with high-grade gliomas including glioblastoma, the goal of treatment is to manage symptoms and improve quality life for the greatest duration possible. The goals of care are palliative from the beginning. Hope is fostered through the assessment and management of symptoms and the assurance of nonabandonment offered by the treating neuro-oncologist. The quality of life of the patient with a brain tumor may be largely dependent upon the competency in palliative care of each member of the care team.

The message that patients and caregivers hear and the words that physicians and providers say, particularly at the stressful time of diagnosis, may be different. A national prospective study of 1193 patients with stage IV metastatic lung or colorectal cancer examined patients' expectations about the effects of chemotherapy.<sup>14</sup> As with malignant gliomas, in these advanced cancers, the intent of chemotherapy is palliative and is not intended to be curative. However, 69% of the patients with lung cancer and 81% of those with colorectal cancer did not understand that the chemotherapy was not likely to cure their cancer.<sup>14</sup> Patients in both groups understood that chemotherapy was *more likely* to extend their lives than cure them, but the patients' understanding of the role of chemotherapy was generally more optimistic than the evidence supported. Patients were less likely to give inaccurate responses if their care was provided in an integrated network. Perhaps surprising, patients who rated their physicians as better communicators were also more likely to report that they expected a better outcome from chemotherapy. This may suggest that patients are more likely to perceive physicians who discuss chemotherapy optimistically as being better communicators.

In a qualitative study examining patient and caregiver perceptions of initial communication of a high-grade glioma diagnosis, both patients and caregivers reported feeling overwhelmed and in shock by the diagnosis.<sup>15</sup> The shock made it difficult to process prognostic information. Some felt that delivery of the prognosis took away hope.<sup>5,15</sup> One way of coping was for patients and caregivers to think of themselves as individuals for whom the statistics did not apply. Interestingly, in another study it was found that anxiety was lower in patients who wanted to know everything about their illness and in those who understood information better.<sup>5,15</sup>

The emotional burden of a brain tumor diagnosis is among the highest of all cancer sites.<sup>16</sup> Because of the prevalence of distress

among patients with cancer, the NCCN has developed a distress thermometer (a validated questionnaire to assess distress levels among cancer patients). In a study of 159 patients with newly diagnosed brain tumors, the mean distress score was 5.51 on the 0–10 scale.<sup>13</sup> Based on the recommended cutoff of 6, 48% of patients were distressed, and nearly 75% of patients had a distress score above 4, which has been the cutoff score in other studies.

Distress in patients with newly diagnosed brain tumors is associated with psychological symptoms of anxiety and depression.<sup>13</sup> Risk of depression and anxiety is highest among patients with a premorbid mood disorder.<sup>17</sup> Symptoms of depression in patients with brain tumors include dysphoric mood, feelings of helplessness, worthlessness or guilt, loss of self-esteem, difficulty concentrating, and suicidal ideation.<sup>18</sup> Though the symptoms are similar to depression in the general population, the mechanism may be different. The tumor may contribute to comorbid psychiatric diagnoses that, with proper attention, may greatly improve quality of life and survival. Patients with anterior frontal tumors may have a higher risk for depression than those with tumors in other locations. Depression is associated with poorer performance status and worse survival. In a study of patients with high-grade gliomas and premorbid depression, 12-month overall survival was less than that of patients without premorbid depression (15% vs 41%).<sup>18</sup> Depression may be undertreated in patients with brain tumors, with reports of use of psychotropic medications in this population ranging from 26% to 44%.<sup>5,18</sup>

### Advance Directives

In a European study about end-of-life decision-making, it was found that fewer than 7% of competent patients expressed their wishes in advance.<sup>19</sup> At the end of life, the vast majority of patients with brain tumors may experience a change in their level of consciousness, have difficulty with communication, and/or become confused and delirious.<sup>20</sup> It is therefore essential for their treating neuro-oncologists to incorporate discussion of their wishes including resuscitation, home versus institutional care, and other matters early in the course of their illness. In a retrospective study of 168 patients with brain tumors at Memorial Sloan Kettering Cancer Center among those who died, 79% had a hospice discussion prior to death, 79% had appointed a health care proxy, and 70% had a do-not-resuscitate (DNR) order.<sup>21</sup> The time in which these conversations took place varied widely, with some end-of-life discussions happening on the final day of life.

### Palliative Care Needs Throughout the Course of Illness

#### Cognitive Dysfunction

Cognitive deficits in adults with brain tumors have been reported at rates of 29%–90%.<sup>22</sup> The etiology of cognitive impairment in patients with brain tumors is often multifactorial and includes direct disruption of cognitive systems by the brain tumor, complications of seizures, metabolic disturbances, anemia and endocrine dysfunction, and side effects of surgery, radiation, and chemotherapy. Treatment of cognitive disturbance can be challenging. Pharmacological approaches include the use of psychostimulants (Table 2). Methylphenidate has been shown to improve scores on

**Table 2.** Pharmacological management of cognitive dysfunction

Medication	Recommended Starting Dose
Methylphenidate	5 mg twice daily
Sertraline	25–50 mg daily
Modafinil	100 mg twice daily

neuropsychological testing and subjectively improve cognitive function and mood<sup>23</sup>; however, these results come from an observational study without a control group. Antidepressants such as selective serotonin reuptake inhibitors may also be helpful for ameliorating depression and therefore cognitive dysfunction. Sertraline is a useful agent because of its availability of many strengths and broad therapeutic range (generally starting at 25–50 mg daily). Methylphenidate is usually introduced at 5 mg twice daily and titrated to the maximum tolerated and effective dose. Modafinil has been shown to improve cognitive function and fatigue<sup>24</sup>; the usual starting dose of modafinil is 100 mg twice daily. Nonpharmacological approaches, including cognitive rehabilitation, have been shown to improve function at work and at home.<sup>22</sup> Cognitive rehabilitation has been shown to improve verbal learning, memory, and mental fatigue in patients with brain tumors.<sup>25</sup>

## Seizures

Seizures are a common problem for patients with brain tumors. Seizures are the presenting symptom in 18% of brain metastases and 42% of astrocytic tumors, with an additional 32% of patients with astrocytic tumors developing seizures during the course of their illness.<sup>26</sup> The selection of an antiepileptic medication is often guided by the side-effect profile. Levetiracetam is often recommended for this patient population because of its efficacy, tolerability, and simplicity of dosing with fast loading to a therapeutic dose.<sup>26,27</sup> Following a loading dose of 1000 mg, the usual starting dose of levetiracetam is 500 mg twice daily, and it can be titrated up as high as 1500 mg twice daily.<sup>27</sup> Lamotrigine and topiramate, while both effective, are limited by longer titration times that may be challenging in patients with high-grade or advanced tumors. Enzyme-inducing drugs, including phenytoin, carbamazepine, and phenobarbital, may have interactions with chemotherapy and corticosteroids. Enzyme-inducing antiepileptic drugs are known to induce metabolism of irinotecan, paclitaxel, topotecan, and many of the tyrosine kinase inhibitors.<sup>26,28</sup> Phenytoin can nearly double the metabolism of dexamethasone.<sup>26</sup> Valproic acid, an enzyme inhibitor, can also interact with chemotherapy and has a side effect of thrombocytopenia that may limit its use, although it can be helpful when managing comorbid mood instability. A meta-analysis demonstrated that prophylactic antiepileptic drugs are ineffective for patients with brain tumors without a history of seizures.<sup>29</sup>

## Fatigue

Fatigue is common in patients with brain tumors and affects physical, mental, and emotional functioning. Forty-two percent of patients with primary brain tumors reported their energy levels

to be “quite a bit low” or “very low” at some point in their treatment course.<sup>30</sup> One prospective study found that one-third of patients with brain tumors had clinically significant fatigue at baseline, prior to starting radiation. Further, the fatigue was an independent predictor of overall survival.<sup>31</sup> The NCCN guidelines for clinical practice recommend physical exercise as first-line treatment for cancer-related fatigue.<sup>32</sup> Drug therapy for fatigue is more controversial. Open-label studies have shown improvement in cancer-related fatigue in a general population of patients with cancer with use of methylphenidate.<sup>33</sup> While one small randomized trial of 24 patients with primary brain tumors showed improvement in processing speed and executive functioning with the use of methylphenidate or modafinil,<sup>34</sup> randomized placebo-controlled trials of modafinil<sup>35</sup> and methylphenidate<sup>36</sup> showed equal improvement of fatigue in the treatment and placebo groups. An ongoing phase III randomized control trial is exploring the use of modafinil for cancer-related fatigue in patients with high-grade gliomas (NCT01781468).

## Headache

Approximately 50% of patients with brain tumors experience headache pain, with estimates ranging from 33% to 71%.<sup>37</sup> The first step to treating headache in patients with brain tumors is to identify the reason for the headache. Headache may be due to rapid expansion of tumoral tissue with edema and increased intracranial pressure, intratumoral hemorrhage, or transient increases in intracranial pressure known as “plateau waves.”<sup>37</sup> Postsurgical pain can trigger headaches, and patients with 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.<sup>38</sup> 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 since they are for somatic, visceral, or neuropathic pain, although they may be effectively used in combination with adjuvant analgesics.

## Palliative Care Needs at or Near the End of Life

Patients face a great psychological challenge at the end of life.<sup>39</sup> Patients who are dying from a serious illness often go through stages of grief, loss, and denial.<sup>39</sup> 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 address these issues, physical symptoms and suffering must be well controlled. Optimal end-of-life care addresses physical, spiritual, and psychological integrity to allow patients to “die well” (Table 3).

## Nutrition and Hydration

Some of the most challenging decisions at the end of life can be the decisions about what not to treat. In some situations, it may make sense medically and compassionately to withhold or

withdraw therapies. Discussions about withholding or withdrawing nutrition, hydration, and life support may be particularly difficult and sensitive subjects for families. A randomized placebo-controlled trial of patients with advanced cancer demonstrated no difference in survival for patients receiving hydration and no difference in symptoms of dehydration including pain, hallucinations, myoclonus, depression, and anxiety.<sup>40</sup> Family members may be reassured that when their loved ones die, their death is unquestionably from cancer and not due to the withholding of nutrition or hydration.

### 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. In general, continuous infusions are preferred to prevent any breakthrough or rebound symptoms. Patients require frequent reassessment and dose titration to assume optimal symptom control.

Under some circumstances in the imminently dying, sedation may be an important tool for minimize suffering. Opiates may be used for control of pain or dyspnea, while benzodiazepines and neuroleptics are often added for agitation and delirium (Table 4); longer-acting benzodiazepines are preferable. Established palliative care guidelines support the use of sedation for patients who are imminently dying when necessary to assure comfort and dignity, as a last resort.<sup>41</sup> In some studies of home hospice and in-hospital palliative care units, there was no difference in the patients' time to death when comparing those who were sedated for symptom control and those who were not.<sup>42</sup>

**Table 3.** The five components of "The Good Death"<sup>35</sup>

1. Ensuring optimal physical comfort
2. Maintaining a sense of continuity with oneself
3. Making meaning of life and death
4. Achieving a sense of control
5. Confronting and preparing for death.<sup>35</sup>

**Table 4.** Management of agitation and delirium at the end of life

Drug	Route	Starting Dosage
Lorazepam	p.o. (tablet, liquid), i.v., i.m.	2–3 mg/day divided 2–3 times a day
Diazepam	p.o., p.r., i.v., i.m.	2–10 mg every 3–4 h
Clonazepam	p.o., ODT	0.5 mg 3 times a day
Quetiapine	p.o.	25 mg twice a day
Olanzapine	p.o., ODT, i.m.	5 mg daily
Haloperidol	p.o., i.m.	0.5 mg every 1–4 h, as needed

Abbreviations: i.m., intramuscular; i.v., intravenous; ODT, orally disintegrating tablet; p.o., oral; p.r., per rectum

### Seizures

Seizures are common at the end of life, but loss of swallowing ability may interfere with administration of antiepileptic medications. Phenobarbital is available as an intramuscular injection, which can be given once daily. Likewise, benzodiazepines can be given either subcutaneously or rectally to stop seizures acutely. For management of prolonged seizures or status epilepticus, buccal midazolam (0.3 mg/kg dose) has been used successfully in children<sup>43</sup> and can be applied for patients with primary brain tumors who may have difficulty swallowing.

### Death Rattle

Patients who are dying may exhibit loud respirations due to inability to clear their pharyngeal secretions.<sup>42</sup> This noise, known as the "death rattle," may signify patient discomfort and is often distressing to family and friends in observance. Medications such as atropine drops, glycopyrrolate, or a scopolamine patch can be used to dry secretions and assure the comfort of patients, surrounding family, and caregivers.<sup>42</sup>

### The Process of Dying

Near the end of life, the neuro-oncologist must be able to recognize that the patient is dying and advise family and caregivers.<sup>7,8</sup> In most patients with primary brain tumors, the cause of death is brain herniation due to tumor progression.<sup>44</sup> 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.<sup>44</sup> 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. Family members may have unfounded and frightening expectations from a variety of sources that cause great distress. The willingness of the neuro-oncologist to take the time necessary to understand these fears and gently correct misperceptions can be invaluable to a grieving family.

### Physician Barriers to Providing Competent Palliative Care

Quality care for patients with brain tumors is dependent in part upon the competency of the neuro-oncologist in the principles and practice of palliative medicine. Educational, cultural, patient-related, and other physician-related barriers also affect the delivery and quality of care (Table 5). Since many medical school and

**Table 5.** Barriers to providing competent palliative care<sup>42</sup>

- Physician misunderstanding palliative care as only equivalent to hospice care
- Lack of competency among neuro-oncologist in the best practice standard for palliative medicine
- Patients underreporting due to fear of the significance of their symptoms
- The "culture of cure"

neurology residency curricula give scant attention to palliative medicine,<sup>45</sup> patients with brain tumors and their caregivers are immediately faced with a gap between their symptomatic needs and the competency of their providers.<sup>46</sup> In a recent survey, neuro-oncologists in the United States and Canada reported receiving minimal or no training in palliative care.<sup>47</sup> Twenty-nine percent of US neuro-oncologists and 46% in Europe and Asia reported that they did not feel comfortable dealing with end-of-life issues. Significant deficits have been identified between established medical, legal and ethical guidelines and the care of patients with advanced neurological disease.<sup>45</sup> In addition to inadequate training, the “culture of cure” poses another barrier.

The culture of cure poses additional challenges for integrating palliative care. The curative model emphasizes diagnosis derived from a solid understanding of pathophysiology and treatment proven by empirical research on clinical outcomes.<sup>48</sup> With a heavy emphasis on evidence, this model devalues incurable disease and subjective symptoms. The curative model permeates the major cancer centers in the United States, with slogans telling patients to “Conquer Cancer” and “Fight for a Cure.” In a medical culture focused on cure, despite a known inability to cure many cancers from the time of diagnosis, oncologists and other care providers risk contributing to, rather than lessening, the suffering of patients and families.<sup>46</sup>

Inevitably, physicians respond to their patients’ condition and emotions with emotions of their own. The physician’s emotional responses may impede the ability to deliver competent care. When a patient does not do well or his or her health fails to improve, the physician may feel guilty, insecure, frustrated, and inadequate.<sup>49</sup> In some cases, rather than address these feelings, physicians may disengage or withdraw from their patients.<sup>49</sup> This phenomenon is part of compassion fatigue, which can lead to burnout. Compassion fatigue has been loosely defined as “the cost of caring.”<sup>50</sup> Symptoms of compassion fatigue include hyperarousal, avoidance, and re-experiencing. Hyperarousal may manifest as disturbed sleep, hypervigilance, or irritability. Avoidance may include avoiding one’s own thoughts and feelings and avoiding conversations associated with the patient’s pain and suffering. Re-experiencing is defined as intrusive thoughts, dreams, and distress when reminded about work with dying patients. In a study of house staff, oncologists, and nurses at Memorial Sloan Kettering Cancer Center, all groups reported higher mean scores of emotional exhaustion and diminished empathy compared with general medical physicians and nurses.<sup>51</sup> Compassion fatigue can lead to burnout, decreased work performance, and lower job satisfaction.<sup>50</sup> Oncologists, residents, and students may manage their disappointment or anxiety over patient outcomes by unknowingly and unintentionally blaming the patient. Use of language such as “the patient failed chemotherapy,” rather than noting that “chemotherapy failed the patient,” may distance the neuro-oncologist from his or her patient and make the provision of palliative care more challenging.

## Impact of Earlier Palliative and Hospice Care

Early integration of palliative care has been found to be beneficial for quality of life and survival in patients with advanced cancer.<sup>52</sup> In a multisite prospective study of terminally ill patients with cancer in the United States,<sup>53</sup> end-of-life discussions were associated

with lower rates of ventilation, resuscitation, ICU admission, and earlier enrollment in hospice programs. Longer hospice stays were associated with better quality of life for both patients and caregivers.

In an Italian study, 324 patients with brain tumors discharged from the hospital between 2000 and 2005 were enrolled into a comprehensive neuro-oncological home care program and retrospectively analyzed.<sup>54</sup> The patients received neurological assistance, nursing, psychosocial support, and home rehabilitation with a staff of a neurologist, a psychologist, 5 nurses, 2 rehabilitation therapists, and a social worker. The staff had weekly meetings to discuss home care plans. Through this system, 65% of the patients who died were able to die at home and were assisted at home through the end of life. A concurrent prospective study of comprehensive palliative care for patients with brain tumors demonstrated that, of the 529 patients who died, 323 (61%) were assisted at home until death, 16.8% died in hospice, and 22.2% died in the hospital.<sup>55</sup> There was a significant reduction in hospital readmission rates, increased quality of life, and increased patient satisfaction among patients treated in the comprehensive palliative care program compared with a control group of patients discharged from another institution in Rome who did not receive home assistance.<sup>55</sup>

## Conclusions

A diagnosis of brain tumor impacts the whole person: mind, body, spirit, and the patient’s primary relationships. Malignant brain tumors have an invariably poor prognosis and high morbidity during the course of illness. In addition to evidence-based disease modification and participation in clinical trials, patients with malignant brain tumors have a right to receive increasingly evidence-based palliative care from diagnosis to death. 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. Throughout the illness, consistent reassessment of symptoms can meet the evolving palliative care needs of patients with brain tumors. Intertwining palliative care with oncological care throughout the course of the disease may help to ease the inevitable painful transition to end-of-life care. Ultimately, transition to hospice-based palliative care improves quality of life for patients and families. 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 whole patient, not only the tumor, from diagnosis to bereavement. Comprehensive care of patients with brain tumors requires mastery of symptom management, communication techniques, and 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. The time has come.

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