

## Palliative Care of Patients with Brain Tumors

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It is estimated that 20,000 new cases of primary malignant central nervous system (CNS) tumors were diagnosed in the United States in 2007<sup>1</sup> and that almost 13,000 people with this condition died.<sup>2</sup> The median survival of patients with the most common type of primary malignant CNS tumor, glioblastoma multiforme, has been 12 or fewer months, with a 5-year survival rate of about 3%.<sup>3</sup> Although newer therapies such as temozolomide<sup>4</sup> and bevacizumab<sup>5</sup> are improving both disease control and survival, most patients will ultimately succumb to their illness. Specifically, with the addition of temozolomide,<sup>4</sup> survival at 2 years was improved from 11.2% to 27.3%, at 3 years from 4.3% to 16.7%, and at 4 years from 3.8% to 12.9%,<sup>6</sup> demonstrating both a four-fold improvement in our ability to treat this disease and a stark reminder of how far we still have to go. Factors that predict longer survival include younger age and good overall physical and cognitive functioning.<sup>7</sup> It is worthwhile to note that the incidence of glioblastoma increases with each decade of life, peaking in the 80s with a median age at diagnosis of 64 years.<sup>3</sup> Consequently, many patients are older and have significant comorbidities, which limits aggressive treatment options.

About 170,000 to 200,000<sup>8,9</sup> new diagnoses of secondary or metastatic tumors to the CNS occur annually in the United States. The likelihood of brain metastases varies based on tumor type (Tables 1-3<sup>10-12</sup>) and stage of disease. Overall, the development of brain metastases is an ominous sign because survival is poor, averaging only several months for most patients. The addition of whole-brain radiotherapy improves survival only modestly.<sup>13</sup> Although some patients with documented

brain metastases can be long-term survivors, this is unusual. Positive prognostic factors include younger age; good functional status; and controlled, as well as limited, extracranial disease.<sup>14</sup> Because most patients with metastatic disease of the CNS will die as a result of progressive systemic disease (and not from CNS progression), advances in CNS-directed treatments (eg, stereotactic radiosurgery, improved neurosurgical techniques) will benefit only a small number of patients.

Symptoms that are common in the last month of life in patients with primary brain tumors include seizures (30%), headache (36%), dysphagia (85%), and drowsiness (85%).<sup>15</sup> In patients with metastatic tumors to the CNS with CNS progression, clinical symptoms often are similar to those of patients with primary brain tumors. Typically, the first sign of tumor progression

is recurrence of presenting symptoms (eg, weakness, speech, seizure). With continued tumor progression, these symptoms intensify, although temporary palliation with corticosteroids may be achieved. The tempo of decline becomes more rapid within weeks to months before death, with heightened fatigue and more time spent sleeping, along with decreased endurance and activity levels. Appetite decreases, short-term memory often becomes impaired, and global cognitive functioning declines. In the last hours to days, most patients have increased difficulty with swallowing, ultimately becoming comatose and dying a relatively peaceful death. Terminal agitation and delirium can be seen occasionally; management typically includes antipsychotics and, rarely, benzodiazepines.<sup>16</sup>

### Pain

Patients with brain tumors and their families often fear that having a brain or spinal tumor is associated with pain and that pain means the tumor is progressing. For clinicians, the etiology of pain, especially headache-type pain, is often multifactorial and may be related to treatment side effects (ie, headache is secondary to serotonin antagonists) or secondary effects of the

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**Table 1. Frequency of Brain Metastases by Tumor Histology<sup>22</sup>**

Colon	5%
Melanoma	10%
Unknown primary	10%-15%
Breast cancer	15%-20%
Lung cancer	50%

**Table 2. Incidence of Brain Metastases in Several Cancer Cohorts (All Stages)<sup>23</sup>**

	Patients with Diagnosis (n)	Brain Metastases (n)	% with Brain Mets
Colorectal	720	10	1.2%
Breast	802	42	5.0%
Melanoma	150	12	7.4%
Kidney	114	12	9.8%
Lung	938	156	16.3%

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**Table 3. Estimates of Presence of Intracranial Spread of Tumor at Autopsy by Specific Tumor Type<sup>24</sup>**

Colorectal	7%
Urinary organs	23%
Breast	30%
Lung	34%
Melanoma	72%

tumor (ie, diplopia leading to eye strain, leading to headache). Fifty percent of patients with brain tumors report headache pain during the course of illness,<sup>17</sup> and this pain is present in 36% of patients during the last month of life.<sup>15</sup> In general, pain will respond to nonsteroidal antiinflammatory drugs or opioid titration. Additionally, corticosteroids (usually dexamethasone), which are potent antiinflammatory agents that decrease peritumoral swelling, can be extremely effective agents in controlling painful symptoms attributable to intracranial and spinal lesions. Dexamethasone can be initiated in doses of 4 mg to 8 mg in one or two divided doses per day. The starting dosage is typically doubled every 2 to 4 days until symptoms are controlled (but usually not exceeding 30 mg to 40 mg per day). At the end of life, when patients can no longer tolerate oral medications, opioids can be switched to the sublingual route. Opioids and dexamethasone can be administered subcutaneously or rectally, as well.

### Seizures

Seizures are a dreaded complication of primary and metastatic brain tumors. Interestingly, as many as 60% to 85% of patients with low-grade primary brain tumors (ie, well-differentiated astrocytomas and oligodendrogliomas—tumors that often grow very slowly) will present with seizures, as compared to 20% to 40% of patients with glioblastoma multiforme. About 10% to 20% more patients will develop seizure activity later in the course of their disease.<sup>18</sup> Patients with brain metastases will present with seizures in up to 20% of cases, and another 10% will develop seizures during the course of disease.<sup>19</sup> Seizure risk depends on location and is highest when tumors are located in the parietal, frontal, or temporal lobes.<sup>20</sup> Although there is solid evidence for the efficacy of antiepi-

leptic drugs (AEDs) to reduce the risk of seizures in patients who have experienced a previous seizure, there is also compelling evidence that the prophylactic use of AEDs in patients with brain tumors who have never had a seizure is ineffective. In a consensus statement from the American Academy of Neurology, the recommendation for patients with brain tumors with no history of seizures is to discontinue or taper any AED after the first postoperative week.<sup>21</sup>

Most patients with a seizure history are already taking an AED when they transition to palliative and hospice care. Patients without a history of seizures are often maintained on AEDs as well, reflecting prescribing practices that differ from consensus recommendations. Although it is less common for a seizure-free patient to develop seizures at the end of life, it can happen. Benzodiazepines can help abort seizure activity, and dosing can be achieved via oral, intravenous (IV), intramuscular, subcutaneous, and rectal routes. For initial AEDs, consider oral phenytoin, 300 mg per day, or levetiracetam—the former because of its ease of loading and wide familiarity, the latter for its favorable side-effect profile and wide therapeutic range. Both can be administered orally or intravenously (some data suggest phenytoin can be administered subcutaneously). When patients are no longer able to take oral medications, alternatives include placing a peripherally inserted central catheter (PICC) line for IV administration and considering intramuscular fosphenytoin or phenobarbital, and rectally administered valproic acid, phenobarbital, or carbamazepine.<sup>19</sup>

### Ability to Drive a Motor Vehicle

One of the most challenging social issues that patients with CNS tumors must face is the ability to drive a motor vehicle. Losing the ability to drive significantly affects independent functioning outside the home as well as a patient's psychological well-being and the family dynamic. For many patients, the timing of driving discontinuation is fairly straightforward; for example, those who have severe physical or cognitive impairments and simply can no longer control a motor vehicle and those who have had seizures cannot drive according to state

laws. For some patients, however, when to make a medical recommendation to cease driving may not be so clear. It is important for families to have a discussion early in the disease course that includes the patient and all family members. During this discussion, the clinician must detail the consequences of seizure risk and the anticipated effects of declining physical and cognitive functioning on the ability to safely operate a motor vehicle. Medications including opioids,<sup>19</sup> sedatives, and chemotherapy also can affect driving ability. Repeated clinical evaluation throughout the course of illness, along with input from physical and occupational therapists and continued discussions with family, can help identify patients whose ability to drive safely has declined. Some rehabilitation centers offer closed driving tests, during which therapists can test for reaction time, driving skills, and other limitations that may be difficult to assess in the clinic setting.

### The Phenomenon of Double Loss

Patients with brain tumors face not only the social stigma of having a cancer diagnosis but also the frequent challenges related to cognitive dysfunction (including memory loss, usually short-term), impaired focus, difficulty with the thought process, and, at times, personality changes. Cognitive impairment to some degree was identified in almost 80% of subjects in one study of patients with high-grade gliomas, although most patients had completed radiotherapy or chemotherapy.<sup>23</sup> Although these symptoms can be caused by a direct or indirect tumor, they can also be affected by treatment (surgery, radiation, or chemotherapy) and a number of less common conditions (endocrine abnormalities or psychiatric causes). These cognitive changes can be present at initial diagnosis or develop during the treatment course and frequently will fail to improve, even with radiographic tumor response. We have observed a phenomenon of double loss in which caregivers and family members lose, to varying degrees, the essence of the patient well before physical death occurs. Signs of double loss include caregiver frustration (“Why can’t [the patient] do a simple task?”) and anger (“This isn’t the person I married” or “This isn’t my father/mother”). Guilt about mixed emotions toward the loved one is common. This double loss can make care of the patient, caregiver, and family more challenging in this popula-

tion compared to the general oncology or general hospice population. Research on interventions related to this phenomenon are ongoing. Regarding patient cognitive difficulties, research is beginning to show that intervention (both cognitive and physical) can improve functioning.<sup>24</sup> This likely will become increasingly important as newer therapies improve tumor control and increase long-term survivors.

With the recent diagnoses of brain tumors affecting several prominent Americans, there has been heightened awareness of primary brain tumors among the general public. This awareness highlights some of the advances and ongoing research in treatment for these patients. Improved surgical and radiotherapeutic techniques, along with the use of chemotherapies, molecularly targeted therapies, and vaccine therapies, are improving our ability to treat patients today as well as offer hope for a cure tomorrow. Although many patients will benefit from these advances, most ultimately will succumb to their cancer. This likelihood makes the need for palliative care that maximizes quality (as well as quantity) of life so important—not just at the end of life but throughout the course of disease. Although patients with brain or spinal-cord tumors can have complex symptom constellations and challenging psychosocial problems, aggressive symptom management and family care can offer good control of these issues and allow for the highest possible quality of life during the time our patients have left.

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