

## Mini Review

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# Glioblastoma, the Neurosurgeon, and Neuro-Palliative Care

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## ABSTRACT

Primary malignant brain tumors, such as Glioblastoma multiforme (GBM), carry a poor survival prognosis and lead to a high burden of symptoms for the patient and his/her family. While advances in treatment modalities have led to increased survival rates for patients with GBM it remains a terminal diagnosis. Recent data has demonstrated that patients who receive early palliative care in addition to standard oncological therapies for non-neural cancers have a better quality of life, receive fewer aggressive treatments, and live significantly longer than those who do not receive early palliative care. To date, palliative care has arguably been an underutilized approach to assist in the management of GBM patients. Patients living with brain tumors have symptoms that differ from patients suffering with non-neural cancers, which raises the future possibility of physicians that are dedicated to palliative management of patients with neurological conditions, such as GBM. Common symptoms for patients actively dying with GBM include headaches, seizures, somnolence and fatigue, dysphagia, focal neurological deficits, and cognitive deficits. Neurosurgeons often have early contact with newly diagnosed brain tumor patients. Therefore, it is of utmost importance for the neurosurgeon to have an appreciation of palliative care for this specific patient population and to also have an understanding of the full spectrum of care that these patients will encounter while living, and dying due to GBM. The purpose of this paper is to review the existing literature surrounding palliative care for patients with malignant brain tumors particularly from the perspective of the neurosurgeon and because of the unique symptoms faced by this patient population introduce the concept of neuro-palliative care.

**KEYWORDS:** Neurosurgery; Glioblastoma; Brain tumor; Palliative care; Neuro-palliative care.

**ABBREVIATIONS:** GBM: Glioblastoma multiforme; ICU: Intensive Care Unit.

## INTRODUCTION

The neurosurgeon is well versed in end of life scenarios.<sup>1,2</sup> Traumatic head injuries, massive intracranial hemorrhages, and brain tumors are common situations that neurosurgical teams are tasked to deal with, and often, palliative management is appropriate. A unique end of life situation for the neurosurgeon, that spans the full spectrum of care from the operating room to palliative care, is the treatment of highly malignant brain tumors such as glioblastoma multiforme (GBM).

Glioblastoma multiforme (GBM), the most common adult primary brain cancer carries a median survival of less than 18 months with available therapies.<sup>3,4</sup> Much of the effort to understanding treatment of GBM has been from the perspective of molecular biology.<sup>5-7</sup> Despite laboratory discoveries and the progression of survival due to advances in surgery, radiotherapy, and chemotherapy,<sup>3,8-10</sup> GBM remains a devastating disease that essentially ensures a very poor long-term survival.<sup>11</sup> However, several studies have identified patients who have lived longer than 10 years after their initial diagnosis of GBM.<sup>3,12,13</sup> The rare numbers of patients on the tail

of the survival curves may contribute to a sense of therapeutic optimism that is maintained by physicians and hoped for by patients, which may contribute to a lack of early involvement of palliative care physicians. Despite patients receiving the terminal diagnosis of GBM, palliative care has not been thoroughly utilized as a means of care for patients suffering with GBM or other malignant brain tumors.<sup>14</sup>

The term ‘palliative care’ was initially coined by Canadian oncologic surgeon Balfour Mount<sup>15</sup> who set up the first North American palliative care unit in the 1970’s after being inspired by early work done in Britain. The use of the term ‘palliative care’ was an intentional decision in order to distinguish the field from that of hospice care, which was typically associated with hospices run by religious groups dedicated to end of life care when no further treatments remained.<sup>16</sup> Palliative care is a relatively young field of medicine that has now expanded its scope to manage chronic conditions such as chronic obstructive lung disease or progressive neurological conditions such as motor neuron disease and dementia. However, the genesis of palliative care is strongly rooted in the care of oncology patients. Despite its recent introduction, palliative care has progressed quickly from end of life care to become an actual treatment option itself. A landmark study by Temel, et al.<sup>17</sup> demonstrated that lung cancer patients randomized to early palliative care in addition to standard therapy had a better quality of life, received fewer aggressive treatments, and lived significantly longer than patients undergoing standard therapy alone. The study by Temel and colleagues demonstrates that benefits of comprehensive medical care (standard therapies with simultaneous palliative care) for patients diagnosed with non-small cell lung cancers. Malignant non-small cell lung cancer is known to afflict patients with a high burden of symptoms, leading to a poor quality of life, and a prognosis of less than one year survival.<sup>17</sup>

GBM is also a malignant disease associated with a high burden of symptoms and a very poor survival prognosis. Despite the abysmal prognoses for these patients, palliative care has not been explored as an adjuvant treatment to the standard therapeutic regime for GBM. Treatment of GBM is dependent upon a multidisciplinary approach that includes neurologists, oncologists, radiation-oncologists, and neurosurgeons.<sup>18</sup> Typically, palliative care is left out of this multidisciplinary approach until near the end when all treatment options are exhausted.<sup>14</sup> However, given the recent high quality data from Temel, et al. demonstrating that early palliative care can provide multiple benefits to cancer patients, including significantly longer survival, it is a possibility that early palliative care may also be implemented to care for GBM patients.<sup>19</sup> Although the implementation of early palliative care for brain cancer patients is possible there is little existing data on how best to navigate that route.

The primary purpose of this paper is to review and discuss the existing palliative care literature specifically relating to primary brain tumor patients and particularly from the perspective of the neurosurgeon. A second aim of this paper is

to introduce the concept of neuro-palliative care. Patients living with brain tumors have symptoms that differ from patients suffering with non-neural cancers, which raises the future possibility of physicians that are dedicated to palliative management of patients with neurological conditions, such as GBM. Neurosurgeons often have early contact with newly diagnosed brain tumor patients. Therefore, it is of utmost importance for the neurosurgeon to have an appreciation of palliative care for this specific patient population and to also have an understanding of the full spectrum of care that these patients will encounter while living, and dying due to GBM.

### End of Life Symptoms of Patients with Brain Tumors

Examination of symptoms at end of life for GBM patients is the most studied aspect of end of life care in this patient population<sup>20</sup> and there is a broad range of symptoms experienced.<sup>21</sup> Common symptoms for patients actively dying with GBM include headaches, seizures, somnolence and fatigue, dysphagia, focal neurological deficits, and cognitive deficits.<sup>21-25</sup> While pain and fatigue are associated with many types of malignancies, other symptoms such as seizures, cognitive dysfunction, and focal neurological deficits are more common in the neuro-oncology population. The studies evaluating end of life symptoms in GBM patients are limited by their small sample sizes and retrospective designs that hinder treatment recommendations for management of these symptoms. Common methods for treatment of end of life symptoms include anti-epileptic medications for seizures, steroids to manage raised intracranial pressure causing headaches, and opioids for pain management.<sup>21,26,27</sup> Even with limited data to direct treatments for GBM patients at the end of life there are aspects of care that are successfully managed.

A recent survey of caregivers of GBM patients indicated that there are high levels of satisfaction with treatment of dysphagia and epilepsy but cognitive deficits were deemed to be treated less effectively.<sup>22</sup> On one hand these findings may be attributed to side effects of medications such as steroid induced agitation or anti-epileptics leading to cognitive dysfunction.<sup>20,28</sup> On the other hand, an intrinsic disease of the brain, such as GBM, is likely to impart cognitive dysfunction on patients that manifests as lethargy, seizures, confusion, and delirium regardless of treatment side effects.<sup>23</sup> Occasionally, palliative sedation is employed in the end of life period to combat the distressing cognitive changes associated with GBM.<sup>20,21,28</sup> Unfortunately the use of palliative sedation is complicated due to the fact that treating physicians may not know the patients’ expressed wishes and that many patients, during the end of life, are unable to participate in making decisions about their care.<sup>26</sup>

### Perspectives of GBM Patients During End of Life

Of course the most important aspect in the management of GBM, from diagnosis to palliation, is the patient. Several studies have examined patient opinions related to quality of

life while receiving palliative care for GBM. Quality of life encompasses functional status, emotional well-being, and may be thought of as a marker of contentment that is different for each patient.<sup>20</sup> Clinical trials typically assess imaging progression, performance status (Karnofsky Performance Status), or handicap (modified Rankin Scale). Assessing a patient's well-being in a standardized manner is a challenging endeavor and therefore the existing studies in GBM patients have been qualitative in nature. Mummudi and Jalai,<sup>20</sup> highlight that a GBM patient's quality of life depends on multiple variables such as their performance status, tumor grade<sup>29</sup> (high-grade gliomas lead to worse quality of life), tumor location<sup>30</sup> (frontal or temporal-parietal lesions may be associated with mood disturbances), and treatment factors such as radiation dose.<sup>31-33</sup>

Given the myriad of factors that influence quality of life when patients are dying with GBM, Pace, et al.<sup>23</sup> attempted to focus strictly on the management of end of life symptoms (headache, dysphagia, etc.). Pace, et al. demonstrated that patients were often unable to participate fully in end of life decisions as about 50% of patients in their cohort were not fully aware of their prognosis, however capacity was not formally assessed in this study. To complicate matters, it was also revealed that only 6% of these GBM patients had advanced care directives. Together, the decreased awareness surrounding prognosis and the lack of advanced care directives contributes to exceedingly challenging clinical scenarios which are compounded by family members being left to make decisions due to the fact that most GBM patients exhibited a progressive loss of consciousness in the last weeks of life.<sup>23</sup>

Quality of life is a concept that, for GBM patients, may be the most important aspect of their care. To investigate the attitudes of death and dying in patients diagnosed with terminal brain cancer, Lipsman and colleagues<sup>34</sup> interviewed a sample of patients who were cognitively intact, suggesting that each patient was not in the very final end stages of life. This study highlights the premium that patients put on quality of life, rather than prolongation. To demonstrate this, patients in their study overwhelmingly would choose a surgery that would prolong life by three months with fewer deficits than an operation that would extend life by a year but leave the patient highly disabled. Additionally, patients who are faced with terminal brain cancer place a very high value on mental function and cognition and the possibility of losing those faculties would be a reason to decline further treatment.

#### Care Giver Opinions of Palliative Care

Neurosurgeons commonly assist in managing end of life scenarios for patients, particularly in the Intensive Care Unit (ICU). A survey of caregivers who had a family member pass away in the ICU rated the quality of death as very favorable when cared for by a neurosurgeon, as compared to other specialties.<sup>1</sup> These differences likely reflect the fact that neurosurgeons are often faced with end of life scenarios and are reasonably well

versed at navigating those difficult scenarios. Despite the high satisfaction levels that patients' families have of neurosurgical teams during end of life care in the ICU it remains very rare that neurosurgeons are involved with end of life care for GBM patients. Several studies have attempted to gauge the satisfaction of caregivers (typically family members) with the palliative care received by relatives living with GBM. Using surveys to assess caregiver satisfaction, several studies have demonstrated high rates of caregiver satisfaction during end of life care (54-90% were satisfied).<sup>22,26,28</sup> Although palliative care for GBM patients is associated with satisfaction it is still an immense challenge to effectively manage symptoms in this patient population. Dedicated neuro-oncology teams could be a potential strategy to deal with the myriad of challenging symptoms experienced by brain cancer patients. A European survey revealed that less than ten percent of such patients were supported by neuro-oncology teams during the end of life,<sup>22</sup> which may underscore or exacerbate challenges faced by physicians delivering treatment in this patient population.

#### Decision Making of Physicians Providing End of Life Care to GBM Patients

Utilizing a retrospective questionnaire Sizoo, et al.<sup>26</sup> surveyed physicians in The Netherlands who cared for glioma patients in the last three months of their lives, with particular attention paid to the last week of life. The aim of the survey was to assess the end of life preferences of patients and also the medical decisions carried out by physicians during this time. This study highlights that only 60% of physicians caring for GBM patients at the end of life knew of explicit end of life decisions that the patient would have wanted. For the majority of physicians responding to the survey they did not know their patient's wishes relating to life prolonging treatment, admission to hospital, palliative sedation, or euthanasia. Surveyed physicians reported that about 50% of patients were deemed not capable of making end of life decisions in their last weeks of life due to progression of their cancer leading to cognitive disturbances, somnolence, aphasia, and delirium. Interestingly, 10 patients from this study requested euthanasia and seven were granted this request. This study demonstrates the immense challenges to be faced in managing end of life scenarios for GBM patients. Furthermore, this study highlights the need for early discussions surrounding advanced care directives for patients diagnosed with GBM, a role that the neurosurgeon as an early point of contact may be well positioned to initiate.

#### Cost Effectiveness of Palliative Care for GBM Patients

A substantial portion of health care expenditure occurs towards the end of patients' lives.<sup>35,36</sup> Although the cost of treatment for an individual patient should not necessarily be forefront in a physician's mind, it is nonetheless prudent to consider cost-effectiveness for treatments, especially when palliative in nature. Pace, et al.<sup>25</sup> examined 72 GBM patients enrolled in a palliative home-care program (after no further treatments were

offered) and compared the cost-effectiveness of this approach to 71 patients not enrolled in the program. Patients enrolled in the palliative home-care program were less likely to be admitted to hospital and when admitted spent significantly fewer days in hospital. Together, these differences led to significantly lower hospitalization costs for patients with palliative care during their last months of life (517 Euros vs. 24,076 Euros).<sup>25</sup>

### Survival of GBM Patients with Palliative Care

In studies of cancer therapies survival is the gold standard for outcome measures. The study of early palliative care for lung cancer patients by Temel, et al.<sup>17</sup> was deemed a landmark trial not because the treatment group had a reduction in their symptoms but because they were deemed to have statistically and clinically longer survival. Pace, et al.<sup>25</sup> examined a small sample of GBM patients, in the end stages of their lives, who were enrolled in a palliative home-care program and compared their survival to a cohort of GBM patients who were not enrolled in the program. It should be mentioned that none of these patients were enrolled in early palliative care starting at the time of GBM diagnosis. There were no statistical differences in median survival times between the two groups but a trend favoring palliative care was shown (Palliative care: 13.2±16 vs. comparison cohort: 11.2±7.7 months).

### DISCUSSION

Advances in laboratory science have been translated into increased survival for patients diagnosed with GBM.<sup>5-7</sup> Despite these advances the prognosis for patients living with GBM is very poor and remains essentially a palliative diagnosis, but little is known about the palliative phase in this patient population. Here we have discussed the existing literature surrounding palliative care of patients with GBM. Symptoms experienced by this patient population have been studied, in a retrospective manner, by several groups.<sup>21-25</sup> Other aspects that have been examined during the palliative phase of life for GBM patients include patient perspectives at end of life, caregiver opinions, physician decision making, cost-effectiveness, and survival duration.

Although limited by a small number of studies, several interesting points that directly impact patient care have arisen by reviewing the palliative care literature of GBM patients. The first is that symptoms experienced by patients as they are passing away with GBM have been well documented.<sup>21-25</sup> Understanding the full spectrum of GBM as a disease allows the neurosurgeon to fully inform their patients of the treatment options and progression of GBM to maximize quality of life. The second important piece garnered from the literature surrounds decision making at end of life. Pace, et al.<sup>23</sup> reported that only 6% of patients in their cohort study had advanced goals of care. Goals of care can change for patients as their disease progresses but the neurosurgeon, as an early point of contact for those diagnosed with GBM, can be vital in starting this discussion. Early and

regular discussion regarding goals of care is associated with a higher quality of life for the patient as well as increased survival rates.<sup>17</sup> An additional benefit of early discussions regarding care during the end of life for GBM patients is less stress for family members.<sup>28</sup> Additionally, quality of life is increasingly being suggested as an end point in clinical studies.<sup>20</sup>

The majority of patients with a terminal cancer diagnosis will experience symptoms that are distressing to them such as pain, nausea, and vomiting. The literature suggests that patients with GBM face symptoms that patients with other cancers will routinely not. Due to direct involvement of the brain by GBM and other malignant brain tumors patients will suffer symptoms such as seizures, headaches, and somnolence leading to alterations in their cognitive status,<sup>23,24</sup> as compared to patients with malignant abdominal or thoracic cancers who would not be, unless they have brain metastases. Perhaps due to the terminal nature of a GBM diagnosis patients will choose quality of life, especially intact cognitive performance, over a life prolonging treatment that would be associated with disability.<sup>34</sup>

Due to the unique symptoms faced by patients living and eventually dying with serious neurological diseases the needs of these patients often differ from other palliative patients. Management of these complex situations should ideally be performed by practitioners with expertise in symptom management of terminal neurological conditions, leading to the formation of neuro-palliative care as a subspecialty of palliative care. Physicians dedicated to neuro-palliative care would aid in the management of patients with terminal neurological conditions in several ways. First, physicians who focus their practice on neuro-palliative care will ultimately provide better care to those who need it from the perspective of symptom management as well as discussions of goals of care. Second, a neuro-palliative care approach could also be employed with patient populations in resource limited settings or pediatric patients. Third, physicians with an interest and practice in neuro-palliative care would be able to conduct research in the area to improve symptom management strategies for patients with GBM and other neurological conditions throughout their disease. Given the recent high quality data from Temel, et al.<sup>17</sup> demonstrating that early palliative care, in conjunction with standard oncologic care, for patients with metastatic lung cancer led to significant improvements in quality of life and longer survival it suggest that a similar trial would be worthwhile in GBM patients. Current literature in palliative care of patients with GBM indicates that patients are highly satisfied with a neuro-palliative approach,<sup>22,26,28</sup> that it provides potential cost saving benefits, and that there may be a potential for increased survival,<sup>25</sup> although no study has examined early palliative care in conjunction with standard therapies for GBM patients. The current studies in palliative care for GBM patients are also limited by small samples and retrospective study designs. Together, these results suggest that a trial comparing early neuro-palliative care in conjunction with standard oncologic therapies to standard therapies alone for GBM treat-

ment would be well warranted.

In conclusion, studies of palliative care for patients diagnosed with GBM are limited in numbers and are usually retrospective in nature but have clearly described a constellation of symptoms that are unique to patients with malignant brain tumors at the end of life. These symptoms, often impacting cognitive domains lead to challenging delivery of care for the patient and family as well as the physician. The unique and difficult symptoms faced by patients with malignant brain tumors underscore the need for three simple recommendations to be considered for the care of this patient population.

1. Palliative care should be involved early on in the journey of a patient diagnosed with GBM.
2. Neuro-oncology teams should be involved throughout the duration of a patient's illness with GBM, including the final stages.
3. Palliative care physicians with expertise and interest in nervous system diseases should optimally be involved in the care of such patients (e.g. multiple sclerosis and motor neuron disease) and specifically for patients with malignant brain tumors their palliative physicians should be embedded with neuro-oncology teams during treatment.

#### CONFLICTS OF INTEREST

The authors have no conflicts of interest with respect to this work.

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