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Cerebral Gliomas: Treatment, Prognosis and Palliative Alternatives

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Abstract

Malignancies of the brain are complicated matters. The diagnosis of a brain tumor monumentally alters the course of life for the patient, their friends, and their family. Gliomas are the most common type of primary brain tumors in the United States affecting more than 20,000 people annually. Depending on the clinical situation, surgical resection of the mass remains the primary mode of treatment. Adjuvant therapies with external beam radiation and chemotherapy are often utilized. In many cases, the most advanced interventional technologies do not cure or prevent progression of the disease to its final stage - death. The bombardment with multiple treatment modalities is exhaustive for already ill patients, and even more devastating to patients and their families when unsuccessful at providing a quality of life that is in accordance with the patient's desires. In these cases, it is important to incorporate a discussion of living a higher quality of life for the limited time the patient has remaining, rather than pursuing a myriad of experimental treatments. In this manuscript, we present a series of topics necessary to facilitate this communication between the physician, patient, and their families.

Key Words: Brain Cancer, Death, Gliomas, Palliative Care, Hospice, Neurosurgery

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1. Introduction

The brain is a complex organ composed of multiple cell types, layers, and strata. One of the primary cell types of brain tissue includes glial cells which serve countless roles in the human brain. Glial cells can be subdivided into numerous categories, each with a specific function. Gliomas are tumors of glial cells that affect the human brain and spinal cord. They most frequently arise from three cell types: astrocytes, oligodendrocytes, and ependymal cells [1]. Astrocytes are the most abundant glial cell in the brain and act primarily as supporting cells to the neurons. Oligodendrocytes function in myelin production in order to accelerate propagation of action potentials between neurons. Astrocytes give rise to astrocytomas; oligodendrocytes give rise to oligodendrocytomas, and a mix of both cell types gives rise to oligoastrocytomas [2].

Gliomas are the most frequently diagnosed brain tumor, found in 80% of cases [1]. Astrocytomas are the most prevalent type of gliomas affecting children and adults, alike. These cancerous growths can be categorized from Grade I to IV according to the World Health Organization (WHO) grading system. Grade I describes a slow growing or benign tumor with curative possibilities. Alternatively, Grade IV constitutes the fastest rate of malignant growth often described as high grade 3. A glioma is rated on malignant potential according to a multitude of characteristics namely: size, rate of growth, pathology and molecular genetics [1]. The most aggressive form of astrocytoma is glioblastoma and is often categorized as Grade IV. Although there seems to be a pattern in the type and grade of gliomas, in no instance is it implied that a higher and more dangerous tumor cannot occur in the generally less aggressive categorizations of glial cancers [4].

The incidence of brain tumors has been increasing and with that, the rate of glioblastoma diagnosis and mortality. It was observed through a study comparing glioblastomas and other gliomas that the incidence of both occurs more in Caucasians than in any other ethnic group [1]. Males were diagnosed more with other types of gliomas than females, with a ratio of 1.38. Further, the elderly exhibit a higher risk of aggressive gliomas due to genetic modifications [5]. Astrocytomas peak between the age of 75-84 while oligoastrocytomas and oligodendrogliomas peak between the ages of 35-44 [5]. It is also noted that more males than females are diagnosed with a glioblastoma, with a ratio of 1.61. In another study conducted in Northwestern Greece on

488,435 patients presenting with a brain tumor, it was suggested that gliomas most often affect the frontal lobe at a frequency of 46.5%. In the same study, factors such as smoking, alcohol consumption, and cellular phone use had no correlation with the onset of cancer. A slight correlation was found in those that had suffered some cranial trauma years prior, however, the data was not statistically significant [6].

Clinically, patients with a suspected glioma can manifest symptoms of headaches, seizures, numbness of the extremities, slurring or other problems with speech, vision loss, and raised intracranial pressure [7]. This is most likely due to mass effect in the brain secondary to the tumor size altering brain anatomy and physiology. Once a patient presents with any of these issues, a physician can make an accurate diagnosis with a neurological exam or imaging including magnetic resonance imaging (MRI) or computed tomography (CT). A biopsy involves the resection of a sample of the tumor to analyze the cells under a microscope [8]. Biopsy will determine if the tumor is benign or malignant and assist in the staging of the tumor and identification of causal cell lineage.

Prognosis of gliomas is dependent on the grade and pathology of the tumor. Astrocytic tumors have the highest survivorship in Grades II to IV relative to other forms of glial cancers. For example, glioblastomas have 0.05% to 4.7% survival in the span of five years. However, a form of Grade I astrocytoma called pilocytic astrocytoma has a 94.4% survival rate in the same span [4]. Moreover, survival rates decrease significantly as age increases. Other factors that affect survival are the location of the tumor, the treatment administered, and genetic dispositions [9].

Treatment options are patient specific and depend on the severity of the presentation. Gliomas are very aggressive tumors and require intensive treatment to prolong life. Depending on the clinical scenario, a physician can utilize a multitude of therapeutic options including Cyberknife©, surgical excision, radiation, Gamma knife© or proton therapy to eradicate the tumor [1]. External beam radiotherapy or internal chemotherapy may be used as a primary or adjuvant therapy to improve the prognosis. Since 2004, targeted chemotherapy has continued to play an increasing role in the treatment of these cancers [10]. One of the main challenges is that even with utilizing the most advanced treatments available; patients can often experience tumor regrowth or significant iatrogenic neurological impairment. This ultimately challenges the patient's long-term prognosis, and impairs the quality of life. Post-therapeutic quality of life values remain of essential importance when discussing treatment options in patients with brain malignancies with a poor or limited prognosis, yet there are few resources available to guide such discussion. In this paper, we aim to compare and contrast two treatment approaches for gliomas: surgery and radiotherapy. We also attempt to address the central ethical considerations when deliberating the most appropriate therapeutic methods. Lastly, we aim to lay a foundational model to encourage patient-physician discourse of pertinent palliative and hospice-care topics to guide physicians and patient dialogue with regards to quality of life.

2. Treatment Options for Cerebral Gliomas

2.1 Surgical Interventions

Surgical resection of gliomas has various advantages. Not only can an accurate diagnosis be made by direct biopsy of the tumor, but it also facilitates the use of adjuvant treatment options to prevent recurrence and prolong survival. Surgery usually begins with a craniotomy to access the brain. Patients are anaesthetized, intubated, and markers are placed before the head is shaved. Modern neurosurgical procedures are now implementing intraoperative imaging to more accurately resect tumors. Neuronavigation uses CT and/or MRI throughout surgery to assess any shifts in the position of the tumor. Neurosurgeons are able to see a three dimensional (3D) model of the tumor and change their surgical approach accordingly for the patient's safety [11]. 5- Aminolevulinic acid is another method used by neurosurgeons to guide surgeries utilizing its fluorescence as a marker. Using violet-blue excitation light, neurosurgeons are able to detect the fluorescent margins of the tumor to assure safe resection [12]. Moreover, new and improved robotics such as the NeuroArm© can be even more precise than a human hand when incising the margins of a tumor, further decreasing the possibility of damage to the surrounding tissues, thus protecting against neurological deficits [13].

Surgery is often proposed to younger patients that have better ability to withstand possible postoperative complications. However, age is not the only factor surgeons consider to determine if surgery would be the safest and most efficacious treatment option. Factors such as tumor size and location also affect this determination. Larger tumors cannot be successfully treated by radiosurgery; therefore, surgery is most likely the better option for these patients.

Similarly, tumors in close proximity to crucial areas of the brain are particularly dangerous and can ultimately result in major neurological deficits [14]. Surgery in this case is not recommended. Symptomatic patients are also ideal candidates for a surgical procedure [15].

As with any surgery, complications can be encountered during and after surgery. There is risk of intraoperative hemorrhage throughout the tumor resection. Post-surgical complications include neurological deficits including gross motor loss, seizures, unconsciousness, and dysphasia. Patients can also experience respiratory problems, arterial hypertension or hypotension, nausea, vomiting, headaches, and pain. Postoperative infections such as meningitis have been reported as well [15]. In a study conducted analyzing 22 patients, neurological deficits were found in 31.8% of patients after glioma resection. However, most recuperated by the time the patient was discharged [16].

Overall survival after resection is highly influenced by factors such as age and postsurgical complications. The median survival for a group of 1,229 patients treated at the University of Texas MD Anderson Cancer Center was 13.4 months. From this same population, patients that had 100% resection survived an average of 15.2 months while those that didn’t survived only 9.8 months [17]. In addition, a study by the Department of Neurosurgery at the St. Olavs University Hospital reports that 47.5% of 144 patients treated at their facility survived one year post-surgery. Only 16.0% survived to two years [18].

2.2 Radiosurgery Interventions

Unlike typical radiation treatments, radiosurgery minimizes the area exposed by targeting the tumor directly with the use of advanced computer programs and sophisticated technology. It can be delivered as one single treatment, stereotactic radiosurgery, or by fractions over a period of time, known as fractionated radiosurgery [19]. This is accomplished by emitting concentrated beams to the tumor, ultimately destroying the cancerous cells by damaging its DNA while protecting as many healthy cells possible. First developed in the mid-1950s, stereotactic radiosurgery has evolved into three forms of treatment which include Gamma Knife©, Linear Accelerator, and proton accelerator [20].

Gamma Knife© radiosurgery requires the use of a head frame secured to the patient’s head with four pins. The center of the frame helps guide the beams to locate the tumor. The computer software, also known as Leksell Gamma Plan, has the imaging necessary from an MRI or CT scan to create a 3D blueprint of the tumor which eases the focus of beams within the head frame. Varying volumes of energy are delivered using the Gamma Knife depending on the size and position of the tumor [21].

All three modalities of radiosurgery follow almost the same procedure. The Linear Accelerator, also known as LINAC, focuses x-ray energy or electrons to the tumor much like the Gamma Knife. The LINAC system also used a head frame but has developed a frameless technique with the use of lasers to detect movement from the patient. This method has proven just as effective [22]. The proton accelerator uses a similar mechanism but instead uses protons to target the tumor. Before the procedure, patients are numbed at the four areas where the pins will be inserted. Once the head frame is installed, various scans will be used to pinpoint the location of the tumor. After the scans are analyzed by the software and a target plan has been executed, the patient lies down under the machine where their head frame is secured. As soon as the treatment is completed, the head frame is removed and the patient is observed for any adverse effects [23].

Stereotactic radiosurgery (SRS) is a more prudent treatment option for those with tumors too small to be resected by a neurosurgeon. These tumors are typically less than 3.0 centimeters [24]. This less invasive procedure allows for the treatment of tumors in various parts of the body which include the brain, spine, liver, and even the abdominal cavity. Patients are conscious throughout the entire treatment and are allowed to resume all daily activities within two days. However, radiosurgery can be detrimental to the body. Patients can suffer from various side effects like nausea, vomiting, vertigo, and seizures [25]. It is also important to note that while radiation affects the DNA of the tumor it can also affect the healthy cells adjacent to it.

The immobilization of the patient, even with a head frame or mask, is still a major source of complications in radiosurgery. The procedure relies on imaging to pinpoint the location of the tumor and any abrupt movement can force surgeons to start the planning process again. This proves to be quite difficult when treating children; therefore, sedation is used to minimize this issue. Patients with little to no bladder control and those with respiratory problems need to be assessed before treatment because these patients prove to be the most unstable. Even if the machines have an emergency stop option, frequent movement from these patients proves almost impossible to treat [26]. Further, a study conducted with patients diagnosed with high grade gliomas shows that 16% of the sample of 115 patients suffered from radiation necrosis. Necrosis is another complication of radiosurgery that occurs in nearly 30% of cases [27].

Despite the complications and various side effects, radiosurgery has proven very successful in prolonging survival in patients with cancer. In a population of 114 patients treated with SRS, the treatment achieved a survival period of 23 months instead of the 12 expected without treatment. However, in this study SRS was not as successful with grade 3 gliomas due to their larger size [28]. In yet another study with 106 patients treated with LINAC, the average survival was 15.5 months with 58% of patients surviving to one year and 28% to two. Local control was at 91% and 84% after the first and second year, respectively [22]. Outstanding local control was also encountered in patients who underwent Gamma Knife© radiosurgery. A 63 year old male was observed over a 7 year period as he underwent Gamma Knife radiosurgery for his recurrent glioma. For the first radiosurgery, the patient didn't have a recurrence until after 4 months. He repeated the radiosurgery for a second time and no recurrence was observed until after 14 months. The third and final repetition permitted another 69 months before he passed away [29]. Pairing radiosurgery with other treatment options is also feasible for patients and one that may be just as successful.

3. Ethical Considerations in Determination of Treatment Approach

One of the most essential ethical tenets in the practice of modern medicine is that of patient autonomy. This principle is of utmost importance in the determination of the necessity of risky, aggressive surgery. Ultimately, patients bare the power in the shared-decision making model. This is to say, consumers of healthcare are authorized to proceed with medical recommendations, ignore such advice, seek second opinions and manage their own care as they see fit. Patients, as the primary decision makers, receive a significant portion of clinical education from physicians, necessary in order to make the best health decisions for them. In the case of radical surgery, informed consent is the educational modality in which physicians may best enable patients to make such choices.

Informed consent must play a critical role in developing patient understanding of the procedure, its risks and benefits. Any radical procedure mandates a more exhaustive consent than routine evaluation. Rather than merely completing the legally required documentation, physicians need to engage with patients in this preoperative period. The aggression of the consent process must match that of the operation. It is imperative that a more thorough model of informed consent be adopted in cases where the possibility of a positive outcome is less than certain. Meaning, patients must demonstrate understanding not only of the necessity of the procedure and mastery of what an operation entails, but rather exhibit comprehension of the risks, benefits and alternatives of the surgery presented. By expanding consent to include confirmation of appreciation of all of these aspects, whether by restating each element in the consent documentation or verbalizing each aspect in the pre-surgical consultation, the medical community may better prepare patients for radical surgery while ensuring their understanding of the likelihood of success, complications, quality of life after the surgery, morbidity and mortality.

Ultimately, the perception of the physician as a savior of sorts may influence the decisions of patients to proceed with surgical intervention. Often patients in the most dismal states will value a physician who takes a risk with their treatment plan as a personal hero, which may not truly be of benefit. On the other hand, some physicians may promote risky procedures for financial gain in performing a procedure for conditions with a known poor prognosis regardless of therapy. Perhaps it is our efforts as providers rather than our treatment, necessarily, that dictates the perception of effort and aptitude of physicians by our patients. However, it is imperative that we do not take advantage of this relationship. As the principal source of medical counsel for patients, we must provide a breadth of options and truly comprehensive management to prevent patients from feeling limited in the options that exist for their treatment. An area grossly overlooked during these discussions include that of quality of life one can expect post-surgical/therapeutic treatment which is something patients often do not consider pre-treatment. Undoubtedly, the ideation of a bright prognosis and a positive future is conducive for healing. In these cases, the physician’s primary role must be as the bearer of hope.

3.1. Evaluating Quality of Life in the Context of Cerebral Gliomas

Quality of life, though an explicitly individualized perception, is commonly evaluated using a fixed set of metrics. Among these are frustration in completing tasks, perception of decreased family contribution, fear of seizure, lack of independence, inability to drive, less enjoyment in leisure activities, decreased fulfillment from work, and inability to work to assess both brain-specific and functional elements of quality of life [30]. Neurocognitive changes are generally expected in individuals with brain tumors. Changes in cognition that alter decision making capacity are common and may compromise the ability to consent to therapy or treatment, even after resection of the causal mass [31]. Beyond effects on management, this cognitive impact also affects the activities of daily living and independence [31]. In a study conducted by Kvale et al., that aimed to evaluate the quality of life in patients diagnosed with gliomas using the Functional Assessment of Cancer Therapy - Brain (FACT-Br); it was demonstrated that those with a glioma were assessed to experience a lower quality of life (mean 127.34$\pm$ 21.29 St.Dev.) when compared to healthy individuals with a mean score of 86.5 [32, 33]. In this case, a higher the numerical value based upon the FACT-Br assessment corresponds with a reported lower quality of life. Such a lower score was attributed to a lack of functional independence and inability to contribute to family or work life. There was no statistically significant difference between demographic groups when evaluating quality of life. This assessment was similarity reported across all patients affected by gliomas, regardless of sex, color, class, or creed [32].

3.2. Quality of Life Following Surgical Resection

With advances in neurosurgical modalities, diffuse low-grade gliomas are mostly operable malignancies [34]. However, it is well supported that cognitive deficits are common following surgery for resection of brain masses [31]. In patients six week after surgery, new motor deficits, language deficits, ataxia, occipital lesions and lack of use of ultrasonography were all associated with decreased quality of life measured in a multivariate model of a neurocognitive battery [35]. As the field of neurosurgical oncology continues to evolve with the advent of functional mapping, the quality of life for patients after surgery is an increasingly important outcome in the evolution towards “functional neurooncology” [34]. Neuropsychological evaluation as a routine element of care for those affected by gliomas may assist in both the evaluation of capacity and also aid in bolstering executive function in the days and weeks following surgery [31].

3.3. Quality of Life Following Radiotherapy

It has been demonstrated that radiotherapy can cause damage to the white matter, resulting in cognitive impairment, apathy, motor control deficits, memory loss, and executive dysfunction [36]. Though non-specific to gliomas, treatment with radiation demonstrates a decline in neurocognitive performance, regardless of intensity of therapy [36]. However, some studies report that the use of whole brain radiation therapy (WBRT) demonstrates worse neurocognitive outcomes than those treated with stereotactic radiosurgery alone (52% vs. 24% reporting immediate decline in verbal recall) [36]. However, between these two treatments, there was no statistically significant difference in quality of life based on the FACT-Br assessment of the psychosocial aspects of quality of life [36]. These findings are supported by other evaluations that show a larger difference in cognitive function versus quality of life following radiotherapy [37]. Despite these findings, it is argued that there are limitations in the instruments used to assess quality of life in patients affected by brain cancer [38]. Realistically, it is unlikely that any screening questionnaire will ever completely uncover the psychosocial elements that impact the lives of patients affected by glial cancers. Thus, continued neuropsychological support in clinic and at home must continue to evolve as an integral component of care for those affected by gliomas.

4. Clinical Strategies

4.1. Shared Decision Making

When considering surgery, radiation or chemotherapy as a treatment option it is critical to evaluate the risk and benefits of each approach in a patient-centered manner. Further, the time commitment and possible adverse reactions or outcomes must be fully disclosed in order to best prepare patients to make the decisions that are best for them. This said, it is imperative to review the following factors essential in the shared decision making process as identified by Swetz, Kamal and Matlock [39]:

1) The estimated prognosis - quality of life post-surgery vs. global life expectancy
2) Current and anticipated best functional status outcome
3) Expected toxicities or complications

4) Treatment burden - time spent coming to treatment site, time off work for family, and cost.

Shared decision making concedes power of medical choice to patients. Thus, the patients must be informed of their condition, proposed interventions, prognosis, alternatives, risks and benefits in order to fully shoulder this responsibility. When surveying data of patients with glioblastoma status post-surgical intervention, data showed that those with fewer unmet informational needs demonstrated a higher level of self-perceived quality of life [40]. Meaning, the more patients know about their condition, goals and prognosis, the more favorable the quality of life outcomes. However, other studies have demonstrated that further research is required in generating tools to assist in developing the shared decision making process, because patients with gliomas have demonstrated difficulties understanding the complexities of their conditions [41]. It has been shown that shortly after being diagnosed with a malignant glioma; many patients have an impaired capacity to make treatment decisions as compared to healthy patients [42]. More specifically, the impaired medical decision making capacity is directly related to short-term verbal memory deficits; hence, contributing to a potential lack of comprehension or acceptance of their medical condition. Additionally, it is most believed that the imposing gravity of the medical condition itself and its impact on the patients' life and family further erodes mental cognition.

4.2 Preparedness Planning

Preparedness planning is considered practicing an integration of palliation with longitudinal care of seriously ill patients. This conversation can often begin with the process of advance care planning, the "ongoing process in which patients, their families, and their healthcare providers reflect on the patient's goals, values, and beliefs, discuss how they should inform current and future medical care and ultimately use this information to accurately document the patient's future health care" [43].

In the context of radical surgery, advance care planning assists families in working through all considerations-- success of treatment, quality of life, goals of care, concerns, and ethical qualms that may arise in the developmental process. These conversations must be complete and deliberate in order to protect loved ones from the burden of decision making during this immensely stressful time. Among the topics that must be addressed are complications, functional status postoperatively, progression of disease, and deterioration of quality of life amongst others [43].

Often, these discussions are inadequate. Though no advance directive can possibly be comprehensive enough to cover all possible scenarios, recent focus driven by insurance mandates in primary care have focused on life-saving interventions rather than on health status. Far too often these conversations happen in emergency circumstances. Seldom are the risks and benefits of surgery discussed, nor are the options of other interventions or the possibility of forgoing treatment. The approach is far too often the suggestion of only one treatment option and discussing it in a favorable lens without acknowledging the efficacy of other modalities. Ultimately, it is a sophisticated understanding of a patient's wishes that is the most effective, ethical approach for clinicians and families to honor patients. Incorporation of advance care planning into daily practice is critical in allowing for improved care and interventions throughout life that are in accordance with a patient's desires, with respect to their autonomy and dignity.

In the context of cerebral gliomas, it is vital to use advance care planning into patient care plans throughout the course of the disease. Involving palliation early in the progression of disease permits care teams can assist in shared decision making and advance care planning. Understanding the natural history of disease and early definitions of care goals through effective, family-centered communication allows physicians to address barriers in palliative care to improve the quality of life and to allow for death with dignity.

When discussing goals of care, it is important for physicians to not only understand, but appreciate the importance of the subjective meaning of 'quality of life'. Examples of such variability includes being able to watch a baseball on television, being with their family; while others might feel a 'quality of life' is being able to climb mount Everest or flying a plane. Eric Cassell defines suffering as a state of severe distress associated with events that threaten the intactness of personhood or the interconnected physical, social, spiritual, and psychological aspects of self [44].

Physicians tend to focus on the simplest controllable component of suffering - physical distress. However, alleviating suffering not only devalues the important components of personhood, but it also causes loss of empathetic communication skills with the patient, and places a focus on the human body rather than the whole person which includes many other subjective components such emotion, spiritualism, and psyche amongst others. A physician's job is to treat the person's well-being, not limited to the objective disease. Treating the subjective well-being is about the caring for the reasons one wishes to be alive.

5. Conclusion

Credited to the ethos of conventional Western medicine, there is a profound attention to extension of life which would otherwise be shortened without medical intervention. As such, there is often an oversight of extension of life with minor reflections on quality. However, this can be emotionally difficult for the patient, their family and the physician/medical care team alike. There is a growing need to refocus on the quality and well-being of a patient's life undergoing radical therapy for conditions like glial cancer, rather than merely extending life with a poor quality by exploring the central juxtaposition of living vs. existing. This is especially true for patients with brain neoplasms refractory to conventional therapeutic management such as radiation and surgical interventions. In these cases, a care-planning dialogue between the physician with patients and families can be emotionally challenging for both physicians and families. To focus on a more holistic discourse, we have provided a framework that outlines several points of discussion for guiding a family-centered conversation to focus on quality of life and its interconnected physical, social, spiritual and psychological aspects.

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7. Author Contributions

Dharam Persaud-Sharma conceived of the study, participated in its design and coordination and drafted the manuscript; Joseph Burns participated in its design and coordination and helped to draft the manuscript; Marien Govea participated in its design and coordination and helped to draft the manuscript; Sanaz Kashan participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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