Quality of Life and Outcomes in Glioblastoma Management

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KEYWORDS

• Glioblastoma • Health-related quality of life • Ethics

KEY POINTS

- Uniform evaluation of health-related quality of life (HRQOL) in patients with glioblastoma multiforme (GBM) is currently not in place.
- HRQOL can be altered by the patient's perception.
- Presurgical dialogue of the ultimate dismal outcome of GBM is very important.
- Discussion of postoperative QOL must be performed during the preoperative phase, to avoid misunderstandings and conserve patient expectations.
- Novel treatments for GBM should focus on improving survival while protecting HRQOL.
- Palliative services should be integrated into the overall multidisciplinary plan of treatment.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common primary brain tumor and unfortunately the most difficult tumor to effectively treat, despite the significant advances in recent research.[1,2] Because of this, unknowingly, many medical professionals might advocate for aggressive interventions that may adversely affect the quality of life (QOL) and outcome of these patients. Given the various neurologic deteriorations and psychopathological impairments that these patients tend to suffer during the course of this rapidly progressive disease, not all of these patients stand to benefit from certain of these therapies, at least from a QOL standpoint. In addition, there are few robust trials that have evaluated the QOL in patients with high-grade glioma.[3–6]

The goal of treatment for the cancer patient should go beyond increasing survival.[7] Rather, maintenance or improvement of the health-related QOL (HRQOL) must be a physician's prerogative when evaluating this goal. Hence, the benefits of the cancer treatment must be weighed against the adverse effects and potential psychopathological impairments. HRQOL, a multidimensional concept that includes self-reported measures of physical and mental health has become a tool to support clinical decision-making in patients with cancer that cannot be cured, such as GBM. Specifically, HRQOL evaluates physical, psychological, and social aspects of human functionality.[3,7]

Previously, the use of the Karnofsky Performance Status was a common method to evaluate QOL. However, this measure did not incorporate a multidimensional approach to cost, QOL, and return to work, all of which are gaining importance as outcome measures, especially because of the intense resource use that brain cancer treatment demands. Better technology and therapeutic

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interventions have yielded a marginal increase in survival after surgery, radiation, and chemotherapy for GBM, and the attention is shifting toward evaluation of the QOL gained by these therapies during those additional weeks or months.[3,8]

Depending on tumor location, surgical intervention, and radiation therapy and chemotherapy administered, certain patients benefit from this marginal increase in survival, but may sustain a decline in their HRQOL. Other patients might do quite well after receiving treatment both clinically and from an HRQOL standpoint, which urges further research and clinical interventions.

The most commonly used metrics to evaluate HRQOL in patients with brain cancer are role participation, social functioning and global QOL, visual disorder, motor dysfunction, communication deficit, and drowsiness (**Box 1**).[9,10] Most papers agree that improvement in QOL is demonstrated by a 10-point positive change in HRQOL score from baseline.[11]

Divergent views of the HRQOL model exist, and there are several other formulations to evaluate physical and social functioning, and role participation that conceptualize disruptions caused by a disease to the community, family and work.[12] Because these formulations or metrics may vary by societal beliefs or norms, at least 1 paper has sought to establish equivalence of language and interpretation of the metric.[13] To add to this complexity, Herdman and colleagues[13] found 19 different types of equivalence, but these standards were not clearly defined, and the theoretical framework for equivalence lacked. Their literature review revealed vague or conflicting definitions to define HRQOL, particularly in the case of conceptual equivalence definitions of equivalence in the HRQOL literature. They concluded that conceptual equivalence definitions are cultural in nature, and there existed an urgent need to establish universalist standardized terminology within the HRQOL field, which would require substantial changes to guidelines and more empiric work on the conceptualization of HRQOL in different cultures.

Box 1
Common metrics used to evaluate quality of life in GBM

- Role participation
- Social functioning
- Global QOL
- Visual disorder
- Motor dysfunction
- Communication deficit
- Drowsiness

RADIOLOGICAL CONSIDERATIONS ON THE QUALITY OF LIFE AND OUTCOMES IN GBM

Radiological predictors of poor prognosis in GBM have been studied in multiple articles.[14–16] Intensity of enhancement of the tumor nodule and extent of peritumoral edema are commonly cited factors that portend a poorer prognosis (**Table 1**). Interestingly, location and tumor volume have not correlated as predictors of survival.[14]

Hobbs and colleagues[17] found that in GBM, the intensity of contrast enhancement on magnetic resonance imaging (MRI) correlated with differences in gene expression. The expression of certain genes has been used to determine the most appropriate individualized treatment. This intratumoral heterogeneity noted on MRI highlights the need for multidisciplinary multimodal treatment, to adequately address all aspects of the biology of GBMs and possibly extend the long-term HRQOL.[18] In summary, GBM patients with little or no necrosis and with less tumor nodule enhancement on preoperative MRI survive longer than patients with greater amounts of necrosis and greater degrees of tumor enhancement.

An increasing body of evidence demonstrates the utility of expression profiling in stratification of patients with GBM in terms of tumor classification and survival.[19]

SURGICAL CONSIDERATIONS ON THE QOL AND OUTCOMES IN GBM

Surgery in glioblastoma is mainstay treatment for both histopathological tissue diagnosis and tumor debulking.[20] Extent of tumor resection slightly increases survival, but this must be weighed against the removal of eloquent cortex, resection of which would decrease postoperative QOL. It is the opinion of the authors, that in cases where the malignant glial tumor invades eloquent cortex, a discussion of postoperative QOL must be performed during the preoperative phase, to avoid

Table 1
Radiological predictors on the QOL

Poor Predictors	Good Predictors
Intense tumor enhancement	Low degree of tumor enhancement
Significant peritumoral edema	Little peritumoral edema

misunderstandings and conserve patient expectations. Many patients prefer to preserve functions like speech and movement, even at the expense of leaving behind significant amounts of tumor. Importantly, the continuum of open dialogue of specialists within a multidisciplinary team when caring for patients with GBM is key, since loss of communication among providers may result in delayed treatment. Interdisciplinary discussions are imperative, since aggressive early intervention retards tumor progression and leads to improved survival.[20] Surgery should be combined with chemotherapy and radiation, as both add survival benefit. Continuous communication of all parties involved with care of these patients is vital.

A presurgical consideration to preserve the QOL in patients with malignant glioma depends on 2 factors;

1. Location of the tumor
2. Aggressiveness of the tumor.

Tumors located within the left hemisphere, primary speech area, or primary motor areas are associated with decreased QOL. Preoperatively, patients with tumors located in the speech area of the brain may present with aphasia, or if in the motor area, with paresis, leading to the need for continuous dedicated care in the postoperative phase.

Rapidly progressive tumors are associated with a rapid decline of cognitive function. Early reoccurrence of tumors usually portends a poor prognosis, but pseudoprogression must be excluded.

Cognitive Impairments

Cognitive impairments that prevent return to work are more common than physical disability. It is unknown how many of the patients diagnosed with a GBM return to work for any period of time. Cognitive impairments are appraised through evaluation of role participation, social functioning, global QOL, communication deficit, and drowsiness. Cognitive impairments are greater when the tumor reoccurs, affects the left hemisphere, or is present in areas of the brain that facilitate comprehension.

Physical Disability

Presurgical consideration of potential postsurgical physical disability is central when trying to protect the QOL for these patients. This presurgical discussion of potential adverse outcomes in the postsurgical phase is crucial and creates improved patient expectations. Studies evaluating patient expectation scores to QOL are unknown, but based on the authors' experience, honest discussion of postoperative expectation during the presurgical phase may improve postoperative role participation, social functioning, and global QOL scores.

According to Furlong and colleagues,[21] HRQOL is the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy.

However, since HRQOL can be altered by patient perception, presurgical dialogue of the ultimate dismal outcome of GBM is so important. For example, expectation of worsening weakness exists postsurgically, when the tumor invades the primary motor cortex and when preoperative weakness is present. Discussion of this fact can modify the patient's intrinsic perception of the weakness with improved HRQOL scores.

From another perspective, if a patient has a strong belief in the advancement of science despite shortcomings in current treatments, he or she may wish to become the subject of a clinical trial supporting scientific experimental technique that may or may not improve outcome or HRQOL. Thus, this calls for the incorporation of a universal HRQOL measurement tool into experimental studies, to begin to better understand outcomes of treatment from a patient's perspective. For example, a treatment that improves survival by 2 months, but causes the patient severe nausea and lethargy throughout the treatment period of 6 months, may not be seen and appraised favorably by the patient. On the other hand, without these trials, scientific advancement might not be made. Medicine thus becomes the science of balances, advancing scientific knowledge and novel treatments counterbalanced against potential patient suffering because of the experimental therapy.

RADIOTHERAPY CONSIDERATIONS ON THE QUALITY OF LIFE AND OUTCOMES IN GBM

Cognitive Impairments

Attention and psychopathological impairments are commonly associated with radiotherapy of the central nervous system (CNS). Most are dose-dependent and constitute limiting factors in the administration of treatments. Radiation-induced neurologic complications occur in 3 forms: acute, early delayed, or delayed (**Table 2**). Acute radiation necrosis is now uncommon, given improvements in accurate dose administration through advances in the design of safer radiation modalities.[22]

To preserve HRQOL, the clinician should be aware of 2 facts. First, patients harboring large GBMs, particularly with signs of increased intracranial pressure, should likely be treated with small

Table 2
Radiation-induced encephalopathy

Stages	Timing	Common Clinical Symptoms
Acute	Minutes to days	Increased intracranial pressure—headache, nausea, vomiting
Early delayed	2 wk to 4 mo	Prolonged drowsiness, somnolence syndrome
Late delayed	4 mo to 24 y	Dementia

doses per fraction (doses of 200 cGy per fraction or less appear to be better tolerated). Second, all patients undergoing brain irradiation should be protected with corticosteroids (8–16 mg of dexamethasone daily or more if increased intracranial pressure is symptomatic), preferably for at least 24 hours before the start of radiation therapy.[23]

The amelioration of the adverse effects of radiotherapy is fundamental in preserving long-term HRQOL. This also maintains patient satisfaction while undergoing further cancer treatment.

Physical Disability

Radiation of tumors affecting eloquent areas of the brain may adversely affect motor, speech, or sensory function over time. Precise stereotactic radiotherapy treatments, such as Gamma knife or Cyberknife demonstrate advantages over other radiotherapeutic modalities and assist in preservation of HRQOL.[24,25] However, such treatments are generally not recommended in large diffusely infiltrative GBMs. Because of its infiltrative characteristic, after surgical debulking, a margin of the surrounding brain should be included in the radiation treatment.[24] Effects of radiotherapy in GBM are usually seen in a semidelayed fashion (4–9 months), and it is paramount to bring up this issue during the initial radiotherapy discussions. It is known that informed patients have improved HRQOL scores despite the presence of significant disability.

CHEMOTHERAPEUTIC CONSIDERATIONS ON THE QOL AND OUTCOMES IN GBM

Cognitive Impairments

Aggressive chemotherapy may lead to cognitive impairment in 20% to 30% of cancer patients. These lasting effects, also known as chemotherapy-induced cognitive dysfunction," may result in decreased HRQOL, especially in the metric of social functioning.[26]

Through targeted chemotherapeutic approaches however, this metric can be improved. Literature suggests that there is benefit to the use of expression profiling in the stratification of patients, as well as the selection of targeted molecular and gene therapies used for successful treatment of malignancy. Although associated with less severe adverse effects than other chemotherapy agents, temozolomide should likely be used cautiously in cases where the tumor is unmethylated, since the tumor is not as responsive to this therapy. Temozolomide is an alkylating agent that adds methyl groups to DNA and is currently the standard of care for first-line chemotherapy for GBM. In a phase 3 study,[27] analysis of O^6-methylguanine–DNA methyltransferase (MGMT) promoter methylation status performed on a subset of tumor samples demonstrated a significant association between MGMT promoter methylation (which decreases protein expression) and improved patient outcome from treatment. Among the patients in the combined temozolomide and radiation therapy arm, those with MGMT promoter methylated tumors experienced a 2-year survival rate of 46% compared with 14% among patients with unmethylated tumors. Yet, MGMT tumor methylation might be a positive prognostic value that is intrinsic to these tumor subtypes, with a prognostic value that is independent from treatment with temozolamide. This is suggested by the fact that patients in this study who had methylated tumors but were treated with radiation alone also had improved survival.[27]

The use of systemic chemotherapy to treat GBM has been met with skepticism because of its limited efficacy and the significant adverse effects demonstrated in clinical trials. Nevertheless, based on findings in randomized trials of new agents, it has been suggested that further evaluation of the role of chemotherapy is warranted.

Temozolomide and Gliadel (carmustine wafers) are generally well tolerated due to their limited systemic toxicity. In addition, these agents appear particularly well suited for incorporation into multimodal treatment strategies.[18]

Although investigations of individual gene or protein alterations are important, because they can provide potentially important clinical markers of outcome or as therapeutic targets, a more powerful approach to stratify therapy while preserving HRQOL would be through the use of gene expression profiling using microarray-based platforms.[20]

This would allow the identification of novel molecular alterations associated with molecular subtypes of tumors or clinical outcome.

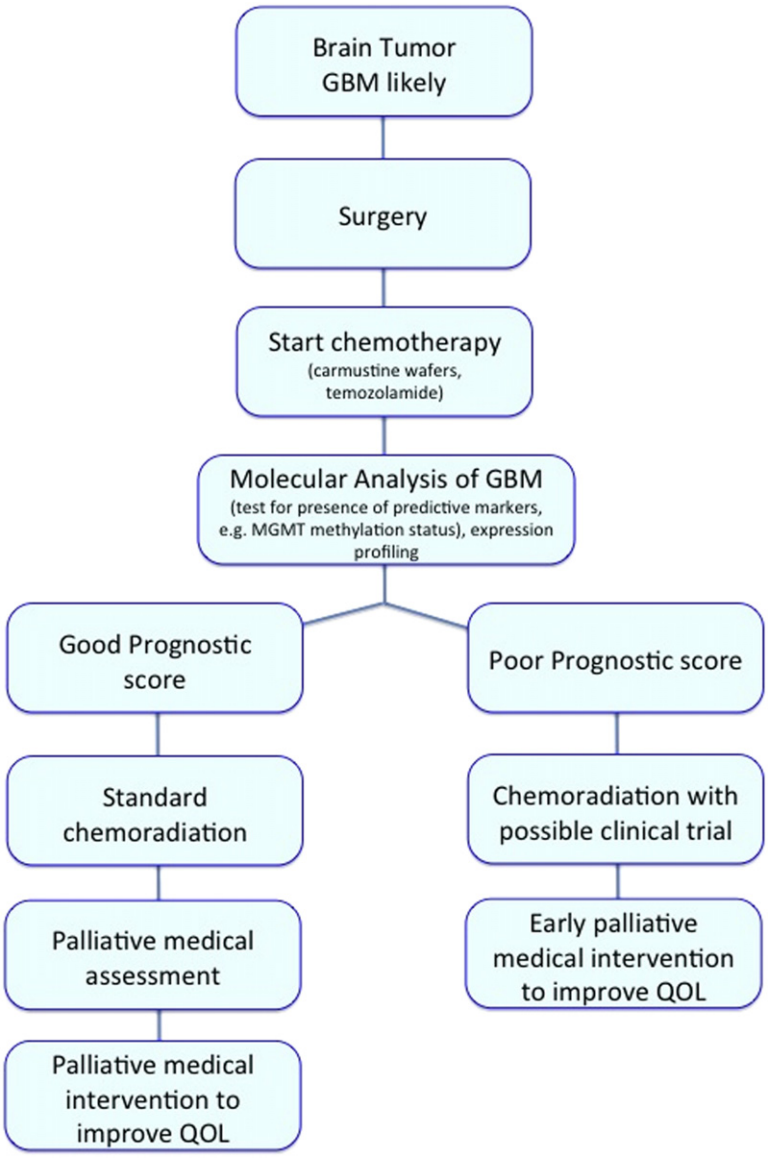

Fig. 1. Flow diagram: multimodal molecular approach to improve QOL.

Physical Disability

Toxic effects of chemotherapeutic agents on the CNS lead to impaired functionality. Central neurotoxicity ranges from acute toxicity such as aseptic meningitis, to delayed toxicities comprising cognitive deficits, hemiparesis, aphasia, and progressive dementia.

In one study,[28] the authors examined for evidence of cell death and cell division in the CNS. This study concluded the presence of chemotherapy-induced cognitive decline even in the absence of radiation. A second study suggested that neural progenitor cells are more vulnerable to DNA cross-linking agents in vitro than are many cancer cell lines. It is becoming increasingly clear that not only CNS irradiation but also chemotherapy alone can cause severe neurotoxicity leading to cognitive decline.[29]

In summary, when discussing chemotherapy treatment, one must balance the need for survival with quality of life.

VALUE OF HOSPICE CARE

Malignant glioma is rapidly progressive despite treatment, and it behooves the physician to discuss this point together with the patient and his or her family. One study suggests that there exists limited provision of hospice care for

supporting individuals in the palliative care stages of such an illness.[30]

Given the progressive illness trajectory of GBM, the complex symptoms experienced by such patients, and the requirement of extensive support, the options for palliative support should be discussed with the immediate family. Issues of those engaged in informal caregiving should be addressed, as this provides ease to the patient and to the family.[31] It is in the opinion of the authors that this topic might be raised by the physician providing immediate care to the patient, but should be formally addressed by a professional in the palliative medical services.

Baseline assessment of patients should be geared to identify 2 factors: first, the range of support services that both caregivers and patients require, and second, the uptake and response to these services. A multimodal molecular approach to GBM has been suggested, and the authors proposed a diagrammatical flow treatment paradigm to improve QOL (**Fig. 1**).[20] Each checkpoint should be documented throughout the illness trajectory. Following this or a similar protocol should improve HRQOL for the patient by relieving stressful tension in the family.[31]

SUMMARY

GBM is the most common primary brain tumor and the most difficult tumor to effectively treat, despite the significant advances in recent research. Uniform evaluation of HRQOL is currently not in place. A universal HRQOL should be adapted to cross-compare advances in clinical trials. Ultimately, excellent novel treatments for GBM should focus on improving survival while protecting HRQOL. Palliative services should be integrated into the overall multidisciplinary treatment plan.

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REFERENCES

1. Colen CB, Shen Y, Ghoddoussi F, et al. Metabolic targeting of lactate efflux by malignant glioma inhibits invasiveness and induces necrosis: an in vivo study. Neoplasia 2011;13(7):620–32.
2. Colen CB, Seraji-Bozorgzad N, Marples B, et al. Metabolic remodeling of malignant gliomas for enhanced sensitization during radiotherapy: an in vitro study. Neurosurgery 2006;59(6):1313–23 [discussion: 1323–4].
3. Mauer M, Stupp R, Taphoorn MJ, et al. The prognostic value of health-related quality-of-life data in predicting survival in glioblastoma cancer patients: results from an international randomised phase III EORTC Brain Tumour and Radiation Oncology Groups, and NCIC Clinical Trials Group study. Br J Cancer 2007;97(3):302–7.
4. Garside R, Pitt M, Anderson R, et al. The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation. Health Technol Assess 2007; 11(45):xi–xii, ix-221.
5. Bosma I, Reijneveld JC, Douw L, et al. Health-related quality of life of long-term high-grade glioma survivors. Neuro Oncol 2009;11(1):51–8.
6. Cheng JX, Zhang X, Liu BL. Health-related quality of life in patients with high-grade glioma. Neuro Oncol 2009;11(1):41–50.
7. Herdman M. The measurement of health related quality of life. Med Clin (Barc) 2000;114(Suppl): 322–5 [in Spanish].
8. Osoba D, Brada M, Yung WK, et al. Health-related quality of life in patients treated with temozolomide versus procarbazine for recurrent glioblastoma multiforme. J Clin Oncol 2000;18(7):1481–91.
9. Torrance GW, Feeny DH, Furlong WJ, et al. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996;34(7):702–22.
10. Yavas C, Zorlu F, Ozyigit G, et al. Health-related quality of life in high-grade glioma patients: a prospective single-center study. Support Care Cancer 2011. [Epub ahead of print].
11. Yavas C, Zorlu F, Ozyigit G, et al. Prospective assessment of health-related quality of life in patients with low-grade glioma: a single-center experience. Support Care Cancer 2011. [Epub ahead of print].
12. Taphoorn MJ, Sizoo EM, Bottomley A. Review on quality of life issues in patients with primary brain tumors. Oncologist 2010;15(6):618–26.
13. Herdman M, Fox-Rushby J, Badia X. A model of equivalence in the cultural adaptation of HRQoL instruments: the universalist approach. Qual Life Res 1998;7(4):323–35.
14. Hammoud MA, Sawaya R, Shi W, et al. Prognostic significance of preoperative MRI scans in glioblastoma multiforme. J Neurooncol 1996;27(1): 65–73.
15. Oh J, Henry RG, Pirzkall A, et al. Survival analysis in patients with glioblastoma multiforme: predictive value of choline-to-N-acetylaspartate index, apparent diffusion coefficient, and relative cerebral blood volume. J Magn Reson Imaging 2004;19(5): 546–54.
16. Li X, Jin H, Lu Y, et al. Identification of MRI and 1H MRSI parameters that may predict survival for

patients with malignant gliomas. NMR Biomed 2004; 17(1):10–20.
17. Hobbs SK, Shi G, Homer R, et al. Magnetic resonance image-guided proteomics of human glioblastoma multiforme. J Magn Reson Imaging 2003; 18(5):530–6.
18. Ashby LS, Ryken TC. Management of malignant glioma: steady progress with multimodal approaches. Neurosurg Focus 2006;20(4):E3.
19. Wiesner SM, Freese A, Ohlfest JR. Emerging concepts in glioma biology: implications for clinical protocols and rational treatment strategies. Neurosurg Focus 2005;19(4):E3.
20. Stupp R, Hegi ME, van den Bent MJ, et al. Changing paradigms—an update on the multidisciplinary management of malignant glioma. Oncologist 2006;11(2):165–80.
21. Furlong WJ, Feeny DH, Torrance GW, et al. The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies. Ann Med 2001;33(5):375–84.
22. Kondziolka D, Flickinger JC, Bissonette DJ, et al. Survival benefit of stereotactic radiosurgery for patients with malignant glial neoplasms. Neurosurgery 1997;41(4):776–83 [discussion: 783–5].
23. Keime-Guibert F, Napolitano M, Delattre JY. Neurological complications of radiotherapy and chemotherapy. J Neurol 1998;245(11):695–708.
24. Crowley RW, Pouratian N, Sheehan JP. Gamma knife surgery for glioblastoma multiforme. Neurosurg Focus 2006;20(4):E17.
25. Combs SE, Widmer V, Thilmann C, et al. Stereotactic radiosurgery (SRS): treatment option for recurrent glioblastoma multiforme (GBM). Cancer 2005;104(10): 2168–73.
26. Nicholas MK. Glioblastoma multiforme: evidence-based approach to therapy. Expert Rev Anticancer Ther 2007;7(Suppl 12):S23–7.
27. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997–1003.
28. Duffner PK, Cohen ME, Thomas PR, et al. The long-term effects of cranial irradiation on the central nervous system. Cancer 1985;56(Suppl 7):1841–6.
29. Dietrich J, Han R, Yang Y, et al. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo. J Biol 2006; 5(7):22.
30. Faithfull S, Cook K, Lucas C. Palliative care of patients with a primary malignant brain tumour: case review of service use and support provided. Palliat Med 2005;19(7):545–50.
31. Arber A, Faithfull S, Plaskota M, et al. A study of patients with a primary malignant brain tumour and their carers: symptoms and access to services. Int J Palliat Nurs 2010;16(1):24–30.