Health-related quality of life in patients with high-grade glioma

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Health-related quality of life (HRQOL) has become an increasingly important endpoint in cancer studies; however, the research into the HRQOL of patients with high-grade glioma (HGG) is sparse compared with that for patients with other neoplasms. Owing to the specific location and poor prognosis, it is more important and difficult to study HRQOL in patients with HGG than in those with other tumors; furthermore, the study of HRQOL in patients with HGG differs from that for patients with other tumors. In this review, we identified and compared the most frequently used instruments to assess HRQOL; analyzed specific facets and determinants of HRQOL (such as sex, tumor location and histological classification, depression, and cognitive function), as well as the association between HRQOL and survival; and appraised the effects of new treatments on HRQOL in patients with HGG from randomized controlled trials. Furthermore, we detected broadly existing problems and many contradictory outcomes and gave some proper interpretation and suggestions regarding them. Neuro-Oncology 11, 41–50, 2009 (Posted to Neuro-Oncology [serial online], Doc. D07-00255, July 15, 2008. URL http://neuro-oncology.dukejournals.org; DOI: 10.1215/15228517-2008-050)

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Introduction

Cancers of the brain and nervous system account for 189,000 new cases and 142,000 deaths annually (1.7% of new cancers and 2.1% of cancer deaths), although such incidences are probably considerably underestimated because of the lack of sophisticated diagnostic technology.1 Gliomas are the most common primary neoplasms of the CNS, composing over 40% of all such tumors and 78% of malignant tumors of the CNS in adults.2 High-grade glioma (HGG) (WHO grades III and IV) is a severe disease with a poor prognosis. Although current treatment for patients with HGG, including surgical resection, radiotherapy, and chemotherapy, is partially effective, patients are rarely cured of their disease.2 Because life expectancy is brief, with the median survival time ranging from 1 to 3 years after initial diagnosis,3 issues related to quality of life (QOL) are immensely important to patients and their caregivers. The issues of health-related quality of life (HRQOL) for cancer patients have received much empirical investigation in the last two decades. In the field of neuro-oncology, the description, measurement, and management of HRQOL continue to evolve.

In this review, our objectives were to (1) identify and review the literature on HRQOL measurement in trials on HGG; (2) identify and compare the most frequently used HRQOL measure instruments; (3) analyze facets and determinants of HRQOL, as well as the association between HRQOL and survival; and (4) appraise the effects of new treatments on HRQOL.

Search Strategy and Selection Criteria

Published data for this review were identified by searches on PubMed (http://www.ncbi.nlm.nih.gov/pubmed),
using the Medical Subject Headings (MeSH) search terms “glioma” and “quality of life.” Only articles published in English were selected. References from selected articles were also considered.

Conception and Significance of HRQOL

There is no consensus on the definition of QOL as it is affected by health. The terms “QOL” and, more specifically, “HRQOL” refer to emotional functioning, physical functioning, cognitive functioning, social functioning, and spiritual well-being, which are seen as distinct areas influenced by a person’s experience, beliefs, expectations, and perceptions.4 There is general agreement that HRQOL measures should be patient-reported, as they involve the patient’s subjective assessment or evaluation of important aspects of his or her well-being,5 but proxy-reported outcomes are still used to assess HRQOL in HGG patients.

In recent decades, with the debate on whether the survival endpoint alone can provide sufficient evidence of the superiority of one treatment modality over another, HRQOL has become an increasingly important endpoint in cancer studies, next to outcome measures such as overall survival, progression-free survival, and time to tumor progression, and is most relevant in patients who cannot be cured of disease.6 The American Society of Clinical Oncology has suggested that HRQOL should be a primary endpoint in any phase III study,7 and an increasing number of studies have utilized HRQOL to assess the effect of new treatments on patient well-being.5,8–18 However, the relevancy and importance of survival data can hardly be disputed or replaced, and in published articles, survival is always the primary endpoint, with HRQOL secondary.

HRQOL in patients with HGG has been studied for more than a decade, with general agreement that HRQOL measures are important in any assessment of the efficacy of new treatments for gliomas. The research on HRQOL of patients with gliomas is sparse, compared with that for other neoplasms, such as lung cancer, colorectal cancer, prostate cancer, and breast cancer, which have higher incidences.19 The studies of HGG have focused on survival rather than more meaningful endpoints such as QOL or palliative effect, so Gupta and Sarin20 proposed that QOL, palliative effect, and overall survival should be the primary endpoints and ideally reported in all clinical trials involving poor-prognosis HGG.

HRQOL Measure Instruments

HRQOL is a multidimensional construct that considers physical, functional, mental, and social health and is best measured with multi-item instruments that can be scored and quantified. The measurements of HRQOL have developed from simple scales, such as the Karnofsky Performance Status Scale (KPS), the Beck Depression Inventory (BDI), and the Folstein Mini-Mental State Examination (MMSE), to sophisticated generic disease and general cancer scales, such as the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) and the Functional Assessment of Cancer Therapy—General (FACT-G), to cancer-specific scales, such as the Brain Cancer Module (BCM) and the Functional Assessment of Cancer Therapy—Brain (FACT-Br). A large number of multi-item instruments have been developed to report HRQOL in patients with gliomas. The most important and widely used of these questionnaires are the KPS, MMSE, QLQ-C30, BCM, FACT-Br, and the Linear Analog Self-Assessment (LASA) scale.

KPS

The best-known instrument, KPS, has been widely used for many years to measure the physical functioning of patients.21 Scores range from 0 to 100, and high scores indicate a patient’s better ability to perform normal activities of daily living or his or her lesser degree of dependency on others for assistance. In recent years, some have questioned the validity and reliability of the KPS22–24 because it is insensitive to neurologic impairment such as memory loss, speech disturbances, and seizure activity25 and does not emphasize any of the psychological or social impairments that a patient with a brain tumor encounters daily. Mackworth et al.25 found that the relationship between the KPS and QOL was insignificant among patients who were relatively healthy (KPS 90–100) and that the KPS was highly sensitive to age, making it more difficult to be interpreted than self-reported QOL data. Because the KPS is reported by a physician or advanced practice nurse caring for the patient, rather than the patient directly, the outcome may not reflect the true QOL. Although KPS is an inadequate surrogate for HRQOL, it is still extensively used by clinicians because it is simple to manage and is considered an adequate measure of physical performance as well as a stratified factor in randomized clinical trials. The KPS is also an additional external measure that may be useful in studies on HRQOL among patients who are unable to provide reliable self-reported information.

MMSE

The MMSE is a well-validated and widely used screening test for dementia and cognitive impairment,25 the latter being a common problem in patients with gliomas. A decrease of more than three points in the MMSE score is considered to indicate clinically significant deterioration.26 In recent decades, however, the sensitivity and specificity of MMSE have been challenged.27,28 Patients with mild aphasia or agnosia may not be adequately assessed by the MMSE. Articles describing studies that involved the MMSE reported that radiation therapy in patients with high-grade and low-grade gliomas was not associated with cognitive decline despite the extensive literature contradicting this assertion.27,28 The use of such an insensitive tool might indicate that patients with true disability resulting from cognitive impairments would not be identified and offered appropriate inter-
ventions. MMSE is intended to capture only one dimension of HRQOL and hence should be used only in conjunction with other HRQOL questionnaires.

**QLQ-C30 and BCM**

With the development of HRQOL research, the instruments to measure it have evolved from one-dimensional to multidimensional. The QLQ-C30 is one such multidimensional instrument that is most broadly used to assess HRQOL in cancer patients, including glioma patients (http://groups.eortc.be/qol), and has been psychometrically validated in patients with lung cancer, breast cancer, ovarian cancer, head and neck cancer, brain cancer, and others. The QLQ-C30 is a 30-item, self-reported questionnaire containing the following domains: physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items), global quality of life (2 items), fatigue (3 items), pain (2 items), and nausea and vomiting (2 items) and single items for dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact. The average time required to complete the QLQ-C30 is 11–12 min.31

The BCM is a new, supplemental questionnaire developed specifically for use with more general questionnaires, such as the QLQ-C30, for patients with brain cancer.24 This 24-item scale assesses problems specific to brain tumor patients, but four items dealing with “emotional distress” overlap with the “emotional functioning” items in the QLQ-C30; hence, if the QLQ-C30 is also used in a study, the 20-item BCM version (BCM-20) is applied. The BCM contains four multi-item scales (future uncertainty, visual disorder, motor dysfunction, and communication deficit) and seven single items asking about headache, seizures, drowsiness, hair loss, itching, weakness of both legs, and difficulties with bladder control. Both the QLQ-C30 and BCM-20 have been shown to be reliable, valid instruments in the setting of HGG.24,32 However, the QLQ-C30 global QOL scores were shown to have larger variability and smaller discriminative ability than the FACT-G and Functional Living Index–Cancer, because QOL research experts have no consensus on what the QLQ-C30’s global questions really measure and QLQ-C30 uses only two questions to give a global score.33

**FACT-G and FACT-Br**

The FACT-G (http://www.facit.org) is also a validated multidimensional instrument that has been used to assess HRQOL in cancer patients.34 Now in its fourth version, the FACT-G has been translated into nearly 50 languages and has been used extensively worldwide. The FACT-G comprises four subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. Users of the FACT-G are able to generate an overall score and four subscale scores with ranges and distributions that are sample specific.

FACT-Br is a reliable and valid 50-item measure that includes FACT-G (27 items) and a brain subscale (23 items) to assess HRQOL in brain tumor patients.35 The overall time required to complete FACT-Br is about 10–15 min. Each inventory question is scored from 0 (worst possible QOL) to 4 (best possible QOL), with some items being reversed. Researchers successfully applied the FACT-Br to patients with brain tumors (i.e., meningiomas and heterogeneous brain tumors) for assessing QOL, but this questionnaire proved impractical in older patients with glioblastoma multiforme (GBM),11 which may reflect the possibility that brain tumor patients with KPS scores less than 60 may be unable to complete the questionnaire.35 Recently, FACT-G normative data have become available to aid in the interpretation and understanding of clinical and research data.38

Among the HRQOL instruments for cancer patients, the QLQ-C30 and FACT-G are probably the most commonly used,39 but for brain tumor patients, the QLQ-C30 and BCM-20 are employed more broadly than the FACT-Br.40 Most patients included in studies on the development of brain tumor–specific scales had high KPS scores.24,35 Thus, both the BCM and FACT-Br may be suitable to assess the HRQOL only in higher-functioning brain tumor patients. Brain tumor patients with KPS scores below 50 are often too incapacitated to complete the questionnaires. This selection bias and the issue of how to address QOL in neurologically impaired patients should be addressed in future studies. Kemmler et al.30 found that the QLQ-C30 and the FACT-G measure markedly different aspects of QOL despite considerable overlap. Replicability provided, this implies that neither of the two QOL instruments can be replaced by the other and that a direct comparison of results obtained with the two instruments is not possible. Cheung et al.33 demonstrated that, in some aspects, the FACT-G global QOL scores had smaller variability and larger discriminative ability than the QLQ-C30.

**LASA**

LASA consists of five single items asking respondents to rate, on a 0–10 scale, their perceived level of functioning, together with one overall HRQOL. Specific domains include physical well-being, emotional well-being, spiritual well-being, and intellectual well-being. The LASA has been widely used in clinical studies, and data obtained from neuro-oncology patients have demonstrated its validity, reliability, and strong correlation with similar multi-item scales, especially the FACT-Br, Symptom Distress Scale (SDS), and Profile of Mood States (POMS; overall, confusion, and fatigue).41 Compared with other multidimensional scales, the LASA is less time consuming because it is brief. Therefore, it may lessen the burden on HGG patients in completing the questionnaire. Sloan et al.42 have suggested that single items may be sufficient when only a global impression of QOL is needed, when screening is desired to determine if a patient needs a more in-depth assessment, or in a phase II study attempting to assess whether a treatment has any effect on QOL. For higher-functioning patients, however, its simplicity is at the cost of details of QOL;
thus other multidimensional questionnaires are more suitable.41,42 Few studies have compared the different scales that assess HRQOL of cancer patients,33,39 and there has been no research comparing HRQOL questionnaires for patients with brain tumors. HRQOL research of glioma patients should be considered a process, and as a part of this process it seems reasonable to pursue several different lines of questionnaire development rather than trying to construct one “perfect” QOL instrument.

Problems in HRQOL Research

The study of HRQOL in patients with HGG has gained increasing attention, while instruments to measure HRQOL have developed from one-dimensional, generic questionnaires to multidimensional, specific ones. However, multi-item instruments can be lengthy and therefore time consuming for patients to complete, and this time burden may result in poor completion rates, especially among brain tumor patients.11 Missing data is the most severe problem in the study of HRQOL, sometimes rendering data unsuitable for analysis or producing strong bias.11,17 Reasons for missing data are complicated. Walker et al.43 found that the largest single cause of missing data (approx. 70%) was administrative failure, while patient refusal accounted for only 6% of cases; they also found that compliant patients had a significantly greater probability of survival and were younger and fitter relative to the rest of the study population. Therefore, the level of HRQOL concluded from such studies may be better than the factual status of the patients. A number of studies indicate that missed assessments are inevitable and increase as time progresses. Bernhard et al. 44 identified three important sources of potentially avoidable data loss: methodological factors, logistic and administrative factors, and patient-related factors. Walker et al.43 also concluded that studies utilizing HRQOL outcomes should take early consideration to minimize avoidable sources of missing data and should record the reasons for noncompliance, and they warned that HRQOL studies that base conclusions on a complete case analysis should be wary of possible bias.

Because HRQOL parameters are dynamic, HRQOL indices should be reassessed periodically, which leads to another issue: when is the right time to reassess HRQOL so as to optimally reflect changes in patient status? All the studies considered in Table 1 made a baseline assessment of HRQOL during the time between hospitalization and the beginning of treatment, especially after surgery and before chemotherapy or radiotherapy; however, there was no standard time of reassessment. Future studies should identify the optimal time for reassessing HRQOL in HGG patients.

Few of the HRQOL studies of patients with glioma were randomized controlled trials, the gold standard for medical studies. Efficace and Bottomley45 retrieved the literature on HRQOL in adults with primary and recurrent brain tumors published between 1980 and 2001 and identified only five randomized controlled trials that met their criteria.8,46–49 Even among these five trials, three of which studied HGG8,47,48 and two of which studied low-grade and high-grade glioma,46,49 some problems were still detected.8,46–49 When we searched the English-language literature for studies published between 2002 and 2007, using the MeSH terms “quality of life” and “glioma,” we found seven randomized controlled trials reporting HRQOL in HGG patients.10–12,14,15,17,50 Investigators are expected to improve the conduct and reporting of the randomized controlled trials in HRQOL studies of HGG patients. More well-designed randomized controlled trials concerning HRQOL in HGG patients are needed.

The HRQOL outcomes reported may not represent the correct HRQOL level for patients with HGG and may be better than they actually are because eligibility criteria for the studies (e.g., no patients with KPS scores less than 5011,50,51 or even less than 70,8,12,52–55 no patients older than 70 years,17,52,56 and no patients with cognitive dysfunction or aphasia) excluded those patients with lower HRQOL levels, while patients’ non-compliance increased in the follow-up due to disease progression. How to investigate the HRQOL of patients similar to those excluded in previous studies is a challenging problem and needs to be settled in the future. The proxy-reported HRQOL not consistent with the patient-reported QOL has been demonstrated in many previous studies, but the proxy-reported HRQOL should be considered as a succedaneum for those patients who cannot self-report HRQOL. The current valid questionnaires are aimed directly at patient-reported HRQOL, so proxy-reported HRQOL questionnaires need to be developed for those patients who cannot self-report.

HRQOL in patients with HGG is increasingly included as an outcome measure in clinical research. In most of the reviewed studies, HRQOL was used to evaluate the effects of medical treatment, usually after some forms of radiotherapy or chemotherapy; however, few studies were on prediction or determinants of HRQOL in the area of glioma.

Patient-Reported Outcome versus Proxy-Reported Outcome

Patients are the best primary source of information about their individual HRQOL, with proxy assessments considered to be less reliable. However, a considerable number of HGG patients cannot complete HRQOL measures because they have cognitive impairments or communication deficits, because they are in grave distress, or because the measures are too burdensome. It is precisely these patients for whom information on HRQOL is most needed to inform decision making, but who should measure a patient’s quality of life? Addington-Hall and Kalra57 thought that proxies—both healthcare professionals and lay caregivers—can provide useful information, particularly on the more concrete, observable aspects of quality of life, even though scores from proxies may be influenced by their own feelings and experiences of caring for the patient. Other studies also...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Patient Eligibility</th>
<th>Disease Stage/ Diagnosis</th>
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<th>Timing of Assessments</th>
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<th>HRQOL Outcome</th>
<th>Medical Outcome</th>
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<tbody>
<tr>
<td>Keime-Guibert et al.12 2007</td>
<td>85</td>
<td>Age ≥70 years; KPS ≥70</td>
<td>GBM</td>
<td>Supportive care alone vs. supportive care plus radiotherapy</td>
<td>QLQ-C30; BCM-20; MMSE; NPI; MDRS</td>
<td>QLQ-C30, BCM, and MMSE at baseline, every month during the first 3 months, and then every 6 weeks; MDRS and NPI at days 60 and 135 and then every 3 months</td>
<td>Yes</td>
<td>No statistically significant differences</td>
<td>Longer median survival with radiotherapy plus supportive care</td>
</tr>
<tr>
<td>Henriksson et al.15 2006</td>
<td>140</td>
<td>WHO performance status: 0–2; adequate hematological, renal, and hepatic functions</td>
<td>Newly diagnosed GBM or gliosarcoma</td>
<td>Surgery and radiotherapy vs. surgery, radiotherapy, and estramustine</td>
<td>QLQ-C30</td>
<td>Baseline, 3 months later</td>
<td>Not reported</td>
<td>No statistically significant differences</td>
<td>No statistically significant differences</td>
</tr>
<tr>
<td>Levin et al.14 2006</td>
<td>162</td>
<td>Age ≥18 years; life expectancy &gt;12 weeks; KPS ≥70; adequate bone marrow, liver, and renal function</td>
<td>Newly diagnosed GBM or gliosarcoma</td>
<td>MT vs. placebo</td>
<td>FACT-Br; KPS</td>
<td>Baseline, week 8, week 16, week 24</td>
<td>Not reported</td>
<td>No statistically significant differences</td>
<td>No statistically significant difference in survival; more musculoskeletal toxicities in MT; longer median survival time when disease recurrence in PCV and MT (82.9 weeks vs. 37.6 weeks)</td>
</tr>
<tr>
<td>Taphoorn et al.17 2005</td>
<td>573</td>
<td>Age 18–70 years</td>
<td>GBM</td>
<td>Radiotherapy alone vs. radiotherapy and temozolomide</td>
<td>QLQ-C30; BCM-20</td>
<td>Baseline, during radiotherapy at week 4, 4 weeks after completion of radiotherapy, at the end of the third and sixth cycle of temozolomide, and every 3 months thereafter until disease progression</td>
<td>Yes</td>
<td>No statistically significant differences, except social functioning at the first follow-up favoring the radiotherapy-only group</td>
<td>2.5 months longer in median survival; 37% relative reduction in the risk of death in radiotherapy and temozolomide group</td>
</tr>
<tr>
<td>Roa et al.11 2004</td>
<td>100</td>
<td>Age ≥60 years; KPS ≥50</td>
<td>GBM</td>
<td>RT vs. abbreviated course of RT</td>
<td>KPS; FACT-Br</td>
<td>Baseline, 3 weeks after starting RT, the conclusion of RT, and 3-month intervals thereafter</td>
<td>Yes</td>
<td>No differences in KPS; severe FACT-Br data missing</td>
<td>No statistically significant differences</td>
</tr>
<tr>
<td>Souhami et al.30 2004</td>
<td>203</td>
<td>Age ≥18 years; KPS ≥60; life expectancy ≥3 months</td>
<td>GBM</td>
<td>SRS, EBRT plus BCNU vs. EBRT and BCNU</td>
<td>MMSE; Spitzer QOL Index</td>
<td>Before therapy, during EBRT, and at each follow-up visit</td>
<td>Yes</td>
<td>No statistically significant differences in QOL and cognitive function</td>
<td>No statistically significant differences</td>
</tr>
<tr>
<td>Phillips et al.10 2003</td>
<td>69</td>
<td>ECOG performance status: 0–3</td>
<td>GBM or AA</td>
<td>35 Gy in 10 fractions of irradiation vs. 60 Gy in 30 fractions of irradiation</td>
<td>A brief neurological function questionnaire designed for the study</td>
<td>Baseline, at weeks 2 and 6 of RT, and at each clinic review thereafter</td>
<td>Yes</td>
<td>No formal QOL comparison due to data missing</td>
<td>No statistically significant differences</td>
</tr>
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Abbreviations: HRQOL, health-related quality of life; GBM, glioblastoma multiforme; QLQ-C30, European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire; BCM, Brain Cancer Module; BCM-20, BCM 20-item version; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; MDRS, Mattis Dementia Rating Scale; MT, marimastat; FACT-Br, Functional Assessment of Cancer Therapy–Brain; PCV, procarbazine, CCNU (lomustine), and vincristine; RT, standard radiation therapy; SRS, stereotactic radiosurgery; EBRT, external beam radiation therapy; BCNU, carmustine; QOL, quality of life; ECOG, Eastern Cooperative Oncology Group; AA, anaplastic astrocytoma.
reported that patients and their significant others provided similar ratings for the patients’ QOL. Therefore, it is reasonable to use proxy-reported scores when patients lose their ability to self-report HRQOL.

**Facets and Determinants of HRQOL**

Because HRQOL is a broad and controversial definition, the factors affecting it—including age, sex, location and classification of tumor, moods, treatment strategies, expectation and experience, the relationship of patients and so on—are complex. In the following part, we will discuss some contradictory research outcomes.

**Sex and HRQOL**

Mainio et al. using a 1-year follow-up and both pre- and postoperative measurements, reported that the level of QOL in female brain tumor patients was lower than in males. Rogers et al. and Janda et al. also found that females seemed to be more susceptible to reductions in QOL. The studies on the sex difference in HRQOL among brain tumor patients are few, although it is known that HRQOL in female patients with many somatic diseases (such as chronic lymphocytic leukemia, inflammatory bowel disease, chronic arterial disease, and myocardial infarct) is significantly worse than in males. The reasons for the lower HRQOL in female patients have remained inexplicit. It may be caused by elevated levels of anxiety and depression in females or due to overall worse psychosocial profiles in females. The causality of the gender difference in the level of HRQOL among brain tumor patients deserves special attention in future research.

**Tumor Location and HRQOL**

Whether patients with left or right hemisphere tumors have worse HRQOL is broadly controversial in many studies. Some studies reported that left-sided tumors were associated with more depressive symptoms, more memory problems, poorer verbal fluency, and more neurocognitive deficits on extensive testing, and more difficulties with communication, whereas others reported that right-sided tumors caused more tension and had a negative effect on HRQOL in multiple dimensions. Still others have reported that tumor laterality had no effect on KPS, cognitive outcome, or HRQOL. There are two possible explanations for this uncertain relationship between tumor location and HRQOL. One is that tumor laterality itself is not a sufficiently sensitive variable for analysis of HRQOL, the other is that insensitive instruments, such as KPS and MMSE, are used. Therefore, a larger number of patients and more effective scales may be needed to truly study the effect of laterality and specific tumor location on HRQOL.

**Histological Classification and HRQOL**

The effects of classification of gliomas on HRQOL also show many contradictions. Some findings reported no significant differences in HRQOL between patients with grade III and grade IV astrocytoma, whereas others reported that GBM patients had poorer HRQOL than patients with other histologic features because of the more aggressive characteristic of GBM. Despite GBM being more aggressive than anaplastic astrocytoma, the lack of differences in HRQOL may be explained by the greater importance of facets and determinants such as neurocognitive function and disease status on HRQOL, or there may be only a temporary lack of difference in HRQOL. However, there is consensus that GBM would be expected to have a briefer period of stable HRQOL because of its shorter time to tumor progression and quicker neurocognitive deterioration.

**Depression and HRQOL**

Symptoms of depression are common in patients with HGG and increase over time. Depression has been thought to be the main predictor for worse HRQOL as well as survival in patients with brain tumors. Decreased HRQOL is strongly associated with depression among patients with glioma. Among brain tumor patients, the relation of depression with lowered HRQOL has gained a great deal of interest in studies during this decade. Unfortunately, only a few studies have investigated the contemporary assessment of depressive disorder and HRQOL by clinically valid tools. Concordance between physician recognition of depression and self-reports of depression by patients was low; furthermore, even if physicians diagnosed depression, pharmacological treatment was somewhat inconsistent with recognition. Patients may have declined treatment. The effective treatment of clinical depression among brain tumor patients and the effect of treatment on the patients’ chances of better HRQOL and survival should be a focus of future research.

**Neurocognitive Function and HRQOL**

HGG causes dysfunction of the brain, producing neurological and cognitive signs, symptoms, and impairments that all affect patients’ well-being. Neurological function is one of the facets in HRQOL and can be evaluated by a comprehensive neurological examination, the use of specific psychological and neurological tests, and some items of multidimensional questionnaires of QOL. Cognitive evaluation showed significant deterioration over time in elderly patients with HGG. Deterioration in neurological function was accompanied by significant deterioration in a range of HRQOL domains in patients with newly diagnosed or recurrent malignant glioma. Few studies have adequately detailed the cognitive and psychosocial functioning of HGG patients, with most studies instead focused primarily on relatively insensitive measures of outcome, including MMSE, IQ scores, performance status, and neurologic examinations. The use of well-accepted and psychometrically...
sound HRQOL instruments and more specific tests of cognitive functioning need to be included in clinical trials because most current treatments have a limited effect on the length of survival.

Analysis of HRQOL data from patients with HGG demands consideration of the potential effect of cognitive impairment. Since many cognitively impaired patients cannot complete HRQOL instruments, there may be substantial amounts of missing data. Information that is gathered only on those patients who are cognitively more intact may bias the explanation of results. The use of proxy reports of patient HRQOL by partners or health care providers when the patient is unable to respond reliably is problematic because HRQOL is subjective by definition, and the results may be of questionable meaning for a person who cannot appreciate his or her circumstances.

**Survival and HRQOL**

HRQOL has become an increasingly important endpoint in studies of HGG patients with short survival and severe functional impairment. The importance of HRQOL scores in predicting survival has been highlighted in different kinds of cancers, including lung cancer, esophageal cancer, advanced breast cancer, and head and neck cancers. Can HRQOL information influence or predict survival of patients with HGG? QOL research to answer this question is breaking new ground. Because traditional outcome measures are unreliable surrogates for patients’ benefit in HGG, assessment of HRQOL seems to be essential. Previous studies in HGG patients have found an association between HRQOL factors, cognitive functioning, depression, and survival but ended with controversial findings. Mauer et al. reported that baseline HRQOL scores add relatively little to clinical factors to predict survival in patients with newly diagnosed GBM. Sehlen et al. found that two variables—living with a spouse and the FACT-G total score—predict survival in patients with either malignant astrocytoma or brain metastases. Meyers et al. documented that HRQOL scores did not predict survival, but cognitive functioning was a significant predictor of survival in patients with recurrent malignant glioma or anaplastic astrocytoma. Klein et al. found that cognitive functioning was associated with significantly poorer survival among older patients with WHO grade IV gliomas but was not an independent prognostic factor for the entire population of patients with newly diagnosed HGG. Mainio et al. demonstrated that depression and decreased HRQOL among patients with low-grade glioma were related to shorter survival. It is also difficult to make comparisons among these trials due to the different HRQOL measures employed and the heterogeneity of the gliomas involved.

The reason for the association between HRQOL and survival is indeterminate. Mauer et al. proposed some hypotheses to explain the mechanisms underlying the relation. Patients’ HRQOL scores might display an early perception of the severity of the disease in a more accurate way than conventional prognostic indices; that is, patients who report worse HRQOL scores are the ones with a worse underlying disease. On the other hand, it is also possible that a better HRQOL score could somehow have a positive effect on the disease process, or vice versa.

**Treatment and HRQOL**

Studies on prediction and determinants of HRQOL in the field of HGG have been mentioned above. More studies used HRQOL to evaluate the effects of medical treatment, usually after some form of radiotherapy or chemotherapy. What are the effects of different therapeutics on HGG patients? First, we need to understand the level of QOL before treatment, to establish a baseline to judge the effect of treatment and intervene more proactively. Few researchers have compared the baseline of HRQOL in HGG patients with a normative population or with patients with other diseases, such as non–small cell lung cancer. Overall HRQOL was impaired substantially in GBM at baseline compared with reference data. Patients with GBM had substantial seizures, fatigue, insomnia, communication deficits, motor dysfunction, leg weakness, impaired emotional and social functioning, and noted uncertainty regarding the future. Fatigue, uncertainty about the future, motor difficulties, drowsiness, communication difficulties, and headache were reported with a frequency >50% by patients with GBM or anaplastic astrocytoma, and visual problems and pain were also reported with frequencies of >50% by patients with recurrent GBM. The HRQOL scores of patients with recurrent HGG are similar to scores for patients with advanced and metastatic cancers rather than patients with localized cancers, but lower than scores for patients with newly diagnosed GBM.

The baseline HRQOL in HGG patients was often evaluated after operation and before radiotherapy or chemotherapy was performed because HRQOL was frequently applied as a second endpoint to assess the influence of new therapeutics. Compared with a normative population, HRQOL was significantly impaired at baseline and follow-up evaluation in patients with HGG. Owing to the different measurements employed and different assessment times used, the HRQOL results for different trials cannot be directly compared. Therefore, it is rather difficult to gain a full view about the HRQOL of patients with HGG.

As the HRQOL is often used as the secondary endpoint to estimate the contribution of new treatments on HGG in clinical trials, we also reviewed the randomized controlled trials indexed in PubMed for the years 2002–2007 and published in English. Seven randomized controlled trials were found, and their results are summarized in Table 1. There was no difference in HRQOL between both treatment groups at baseline in all seven studies or at follow-up evaluation in five, and no meaningful HRQOL comparison was provided in two studies. Two studies found a longer survival benefit, one shortened the time of treatment but without survival deprivation, and four demonstrated no statistically significant survival dif-
ference between the two treatment arms.\textsuperscript{10,14,15,50} After analyzing trials of HRQOL in patients with glioma before 2002, Efficace and Bottomley\textsuperscript{45} distinguished five randomized controlled trials,\textsuperscript{8,46–48} three of which did not show significantly statistical differences in HRQOL,\textsuperscript{46–48} one of which reported that patients with low-grade glioma with high-dose radiotherapy got worse in partial HRQOL domains,\textsuperscript{49} and only one study in which HRQOL improved from baseline in the score of seven preselected QOL domains (role functioning, social functioning, global quality of life, visual disorders, motor dysfunction, communication deficit, and drowsiness) among patients treated with temozolomide who remained progression-free at 6 months.\textsuperscript{8} Whatever new chemotherapy or radiotherapy was offered to patients with HGG, HRQOL improvement was slight. How can such phenomena be explained? HRQOL may not be a sensitive outcome for assessing the effect of new therapies. There is still a possibility that multidimensional HRQOL questionnaires contain too many items that interact with each other and may counteract some effect; that is, the present measurements do not differ from the effect of different HRQOL domains on patients and have less sensitivity. Another possible interpretation is that all patients included in these studies had HGG, including GBM with its fast tumor progression, so tumor progression–related QOL deprivation may have more influence on the QOL.\textsuperscript{40} The new treatments, compared with previous therapy, neither improved HRQOL nor decreased it. Because using HRQOL as the secondary endpoint to judge new treatments for HGG found little statistically significant difference, in the future researchers should identify which factors play more important functions in HRQOL.

### Conclusion

Systematic HRQOL studies are just beginning for patients with HGG, and there are many problems as aforementioned. Therefore, expanded research is urgently needed, especially on sensitive and valid HRQOL measure instruments, on aspects of the paradox of HRQOL, and on key factors of HRQOL. Furthermore, researchers should conduct well-designed randomized controlled trials of HRQOL in patients with HGG and avoid the problem of substantial missing data.

### References


