The end-of-life phase of high-grade glioma patients

Sizoo, E.M.

2013

document version
Publisher's PDF, also known as Version of record

Chapter 3.1

Health-Related Quality of Life in Patients with High-grade Gliomas

Eefje M Sizoo

Andrew Bottomley

Martin J.B. Taphoorn

Adapted from:

- **Sizoo EM** and Taphoorn MJB. Health-related quality of life in patients with high-grade gliomas. In: M.A. Hayat (ed.), *Tumors of the central nervous system*. Volume 3. DOI 10.1007/978-94-007-1399-4_32, © Springer Science+Business Media B.V. 2011.
- Taphoorn MJB, **Sizoo EM**, Bottomley A. *Review on quality of life issues in patients with primary brain tumours.* The Oncologist 2010; 15:618-626

Abstract

Health-related quality of life (HRQOL) has become an important outcome measure in clinical trials in high-grade glioma patients. HRQOL is assessed using self-reported, validated questionnaires, addressing physical, psychological, emotional, and social issues. In addition to generic HRQOL instruments, disease-specific questionnaires have been developed, including for brain tumour patients. For the analysis and interpretation of HRQOL measurements, low compliance and missing data are methodological challenges. HRQOL in high-grade glioma patients may be negatively affected by the disease itself, as well as by side effects of treatment. But treatment with surgery, radiotherapy and chemotherapy may improve patient functioning and HRQOL, in addition to extending survival. Although HRQOL has prognostic significance, it is not superior to well-known clinical parameters. In clinical practice, assessment of HRQOL improves physician-patient communication and could thereby in turn improve the patient's quality of life. More focused HRQOL questionnaires are needed for common use in daily practice.

Introduction

High-grade gliomas (HGG) are among the most feared diseases. Not only is the patient inflicted by an incurable malignancy, the disease directly involves the brain, thereby threatening the "being" of the patient. Patients diagnosed with a HGG have a poor prognosis and despite intensive treatment with surgery, chemotherapy, radiotherapy, tumour recurrence inevitably occurs. Eventually, patients will die from tumour progression. Thus, in this patient category, the aim of treatment is not only to prolong life, but also to maintain quality of life as long as possible.[80] Combined radiochemotherapy and other new treatment strategies may not only increase the duration of survival, but may also have severe side-effects including a risk of toxicity.[9, 18] Therefore, the benefits of extended survival and/or progression delay have to be carefully balanced against side-effects of treatments and their potential negative impact on functioning and quality of life. Hence, the concept of health-related quality of life (HRQoL) should be included as an outcome measure supplementing traditional end points such as (progression-free) survival time in clinical trials evaluating the effect of treatment. Measuring HRQoL emerged in the early nineties in the medical oncology literature. In brain tumour patients, however, it has long been a neglected issue.[9] Since the beginning of this century, HRQoL has become a secondary outcome measure in a growing number of clinical trials evaluating glioma treatment.[93]

Outcome Measures in Glioma Research

Next to the classic outcome measures such as progression free survival and overall survival, the effect of a brain tumour and its treatment on the patient's functioning and well-being should be assessed. It is important to make a distinction between impairment, disability, and handicap.[94] Impairments are the direct consequences of disease demonstrated by physical examination. Disability is the impact of the impairment on a patients' ability to carry out activities. Finally, handicap is the consequence of disability on the patients' well-being. Impairment is considered to be a "hard" measure compared to disability and handicap, which are more relevant for the patient's functioning. Impairment in a brain tumour patient can be evaluated using neurological and neuropsychological examination. Disability can be determined by using scales, such as the Barthel index (BI), an instrument on a persons' ability for selfcare[95], or the Karnofsky Performance Scale (KPS), an assessment tool to measure a patient's ability to carry out activities of daily living.[96] The Modified Ranking Handicap Scale (MRHS) is frequently used to measure handicap. This is a six-point scale ranging from 0 (no symptoms) to 5 (severe handicap/ totally dependent; requiring attention day and night)[97]. It should be noted that there are no specific disability or handicap scales for brain tumour patients, besides the Spitzer scale[98] which is hardly used.

Although these outcome measures provide information on the influence of the tumour on a patient's functioning in daily life, they do not fully reflect the effect of the tumour on the patient's HRQoL.

Assessing Health-Related Quality of Life: A Patient-Reported Outcome Measure

To measure quality of life, the concept of HRQoL was developed. HRQoL is defined as a person's self-assessed ability to function in the physical, psychological, emotional, and social domains of day-to-day life.[99] This complex patient-reported outcome (PRO) measure demands a multidimensional instrument, and preferably should be assessed using a self-reported questionnaire. As an alternative, a (semi)-structured interview could be undertaken with the patient. At present, no single gold standard tool exists to measure HRQoL. Both generic and disease specific tools have been developed and validated to assess HRQoL, both for cancer patients and in the non-cancer population. For cancer patients, the most common tool in use was developed by the European Organisation for Treatment and Research of Cancer (EORTC) quality of life group: the EORTC QLQ-C30.[100] This is a 30-item measure designed to assess HRQOL of cancer patients. Table 1 shows the construction of this measure.

Table 1 Content of the EORTC QLQ c30 version 3.0

	Number of items	Range item scores	Item numbers	Scale scores
Global health status/QOL				
Global health status/QOL	2	1-7	29,30	0-100
Functioning scales				
Physical	5	1-4	1-5	0-100
Role	2	1-4	6, 7	0-100
Emotional	4	1-4	21–24	0-100
Cognitive	2	1-4	20, 25	0-100
Social	2	1-4	26, 27	0-100
Symptom scales				
Fatigue	3	1–4	10, 12, 18	0–100
Nausea/vomiting	2	1–4	14, 15	0–100
Pain	2	1–4	9, 19	0–100
Single-item scales				
Dyspnoea	1	1–4	8	0–100
Sleep disturbance	1	1–4	11	0–100
Appetite loss	1	1–4	13	0–100
Constipation	1	1–4	16	0–100
Diarrhoea	1	1–4	17	0–100
Financial impact	1	1–4	28	0–100

The EORTC BN20 was specifically developed and validated for patients with brain cancer.[101] It includes 20 items and assesses visual disorder, motor dysfunction, various disease symptoms, treatment toxicity, and future uncertainty (Table 2). This tool should be used in combination with the EORTC QLQ C30 and is often used in clinical trials in glioma patients undergoing chemotherapy and radiation therapy. The items on both the EORTC QLQC30 as well as the EORTC BN20 measures are scaled, scored, and transformed to a linear scale (0–100). Differences of at least 10 points are classified as a clinically meaningful changes in a HRQoL parameter. Changes over 20 points are classed as large effects.

Table 2 Content of the EORTC BN20

	Number of items	Range item scores	Item numbers	Scale scores
Subscales				
Future uncertainty	4	1–4	1-3, 5	0-100
Motor dysfunction Communication	3	1–4	10, 15, 19	0-100
deficits	3	1–4	11-13	0-100
Visual disorder	3	1–4	6-8	0-100
Single-item scales				
Headaches	1	1–4	4	0-100
Seizures	1	1–4	9	0-100
Drowsiness	1	1–4	14	0-100
Bothered by hair loss	1	1–4	16	0-100
Bothered by itching skin	1	1–4	17	0-100
Weakness of legs	1	1–4	18	0-100
Difficulty controlling bladder	1	1–4	20	0-100

Another widely used (brain) cancer specific HRQoL tool is the Functional Assessment of Cancer Therapy (FACT). Next to a general FACT module (FACT-G), a brain cancer specific module was developed (FACT-Br) by Weitzner et al., combining the FACT-G with a brain subscale.[102] Table 3 shows the construction of this measure. Compared to the EORTC questionnaires, the FACT modules are more focused on psychosocial aspects and less on symptoms.

Table 3 Content of the FACT-Br Version 4

	Number of items	Range item scores	Item numbers	Range scale scores
FACT-G subscales:				
Physical well-being	7	0-4	GP1-GP7	0-28
Social well-being	7	0-4	GS1-GS7	0-28
Emotional well-being	6	0-4	GE1-GE6	0-28
Functional well-being	7	0-4	GF1-GF7	0-28
Brain subscale	19	0-4	Br1-Br18	0-76

An alternative recently developed PRO measure for brain tumour patients is the MD Anderson Symptom Inventory Brain Tumour Module (MDASI-BT), which has been validated for both primary brain tumour patients and patients with brain metastases.[103, 104] Given that this questionnaire addresses symptoms, it has similarities with the EORTC QLQ-BN20. The MDASI-BT might be useful to describe symptom occurrence throughout the disease trajectory and to evaluate interventions designed for symptom management.

When patients are unable to self-report, for example due to cognitive disturbances, one might consider using proxies or health care professionals to rate the patient's quality of life. In the past, this method was regarded far from optimal. However, a recent review found moderate to good agreement in various studies evaluating the concordance between patient and proxy measures.[105] Mixed results have been reported for patients and health care providers. Proxies and health care providers tend to report more HRQoL problems than do patients themselves, and proxy ratings tend to be more in agreement with the patients' physical HRQoL domains compared to the psychological domains. Also, the agreement between

patients, and proxy HRQoL reports was evaluated specifically in brain tumour patients. The EORTC QLQ-C30, EORTC-BN20, and the FACT-Br showed moderate agreement between the patients' and proxies assessment of HRQoL, provided cognitive functioning was not severely affected.[106, 107] The use of a nonpatient-based report should, therefore, only be used when patients are incapable of self-report.

One may anticipate that patients with more severe clinical symptomatology and quality of life difficulties are less likely to complete questionnaires because it is too burdensome. Because these patients (noncompliers) will be excluded from the analysis, this may lead to an overestimation of the actual quality of life.[107] Indeed, the interpretation of serial measurements of HRQOL is affected by missing data.[108] Apart from the selection bias due to the clinical condition, in both patients and observers compliance with filling out questionnaires decreases over time. The main cause of missing data, however, is administrative failure. Administrative failure arises, for example, when questionnaires are not distributed by the doctor or nurse, distributed at the wrong moment or handed out without instructions. Methodological and patient-related factors can also lead to missing data. Methodological problems may arise due to the study design, for example, using HRQoL instruments unknown to the clinicians who are supposed to hand these out. Other patient-related factors than the clinical situation encompass lack of motivation on the part of the patient, misunderstanding instructions, and/or filling out questionnaires incorrectly. Several approaches can be undertaken to minimize avoidable loss of data on HRQoL.[108] Of the utmost importance is that research staff and patients understand the relevance of these data to be collected. While writing a research protocol, HRQoL assessment should be explicitly defined as a trial endpoint, the way of data collection should be specified, and the analysis of HRQoL parameters should be described in order to prevent methodological problems. Administrative problems can be challenged by the training staff in charge of data collection to check for completeness of assessments at submission, document reasons for

missing data, and structurally contact patients who miss appointments. To reduce patient-related missing data, it is important to motivate patients. At trial entry, patients should be fully informed regarding the importance of HRQoL assessments, how they will be done, and when they will be done. Multiple questionnaires addressing similar issues in a different format and/or a high frequency of assessments will result in a low overall compliance.

Cognitive functioning versus HRQoL

Cognition encompasses functions such as language, memory, attention, and executive functioning – core functions of the human brain. Cognitive disturbances can be caused not only by the tumour itself or by tumour-related epilepsy, but also by the tumour treatment (surgery, radiotherapy, chemotherapy) as well as by supportive treatment (anti-epileptic drugs, corticosteroids).[109] Cognitive disturbances can cause burdensome symptoms for patients; therefore, it is assumed that impaired cognitive function reduces quality of life. The direct relation between cognitive functioning and HRQoL in glioma patients was only demonstrated in one study.[110]

Health-Related Quality of Life in Patients with High-grade Glioma

As one would expect, the majority of newly diagnosed HGG patients have a significant impaired level of HRQoL compared to healthy controls.[111, 112] In patients with a reduced level of HRQoL at the time of diagnosis, the quality of life will further decrease over time, while in patients not significantly distressed, the HRQoL scores may improve.[12] In comparison to other neurological diseases of the central and peripheral nervous system, patients with HGG experience the same level of HRQoL.[113] When comparing HGG patients to other cancer patients, such as lung cancer patients, again similar quality of life results were found in both patient groups.[112]

Several tumour-related factors in HGG patients can have an impact on perceived quality of life. Patients with HGGs experience worse quality of life than patients who have a low grade glioma.[114] However, between patients diagnosed with glioblastoma multiforme (grade IV) and patients diagnosed with anaplastic astrocytoma (grade III), no differences in HRQoL scores exist at the time of diagnosis.[111] Next to the grade, the size of the tumour and the location in the brain correlate with HRQoL. Large tumours, tumours in the nondominant hemisphere, and tumours located anteriorly in the brain are associated with poorer HRQoL scores.[114]

Disease-specific signs and symptoms have a major impact on quality of life. Neurological signs and symptoms as seizure frequency[90], motor deficits[106] and functional status [110] have proven to diminish HRQoL. Surprisingly, no deleterious effect of dysphasia on HRQOL has been established.[106] As to nonspecific signs and symptoms in patients with systemic cancers,

fatigue and depression are identified as the leading factors diminishing HRQoL.[115] Also, in high-grade glioma patients, fatigue is one of the most common symptoms and, therefore, one of the leading symptoms of decreasing quality of life.[75] Clinically significant symptoms of depression have shown to be present in a significant portion of HGG patients, and are probably higher than the prevalence in the general cancer population. Thus, depressive symptoms are a serious clinical issue negatively affecting HRQoL in these patients.[75] Disease recurrence has a significantly deleterious impact on a patients' life. Patients carry a significant symptom burden and neurological deficits are more severe at the time of recurrence compared to the initial presentation.[110] Not surprisingly, HRQoL of patients with tumour recurrence is more comprised compared to patients without recurrence at the same time from diagnosis.[116, 117]

Effect of (Tumour) Treatment on Health-Related Quality of Life

Effect of Surgery on HRQoL

Reduction of tumour mass may alleviate neurological symptoms and cognitive deficits; thereby, improving quality of life. On the other hand, surgery and perioperative injuries may cause neurological deficits and focal cognitive deficits as a result of damage to normal surrounding tissue.[109] Although these deficits are often transient, they may result in a temporarily lower perceived quality of life. In a nonrandomized study, patients who had undergone a gross-total resection had both a longer survival and a better HRQoL than patients who only had a biopsy.[12] Clearly, these results have been biased because the selection of patients for resection versus biopsy depends on factors as tumour size, tumour location, multi-focality, and performance status. Finally, the HRQOL in patients who had undergone a gross-total resection increased over time. Therefore, it appeared from this study that the benefit of resection in terms of quality of life outweigh the early side-effects of surgery.

Effect of Radiotherapy on HRQoL

The benefit of radiotherapy is well-established in the treatment of HGG patients, because tumour progression is postponed and overall survival extended. By stabilizing disease and delay progression, quality of life can be maintained for a longer period than without radiation. Side-effects of cranial radiotherapy, however, of which cognitive deterioration is most feared, may negatively affect HRQoL. Radiation side-effects in the brain can be divided in acute radiation encephalopathy, early-delayed radiation encephalopathy and late-delayed encephalopathy. Acute and early-delayed radiation encephalopathy, occurring during or shortly following radiotherapy, may result in drowsiness and fatigue. Because these side-

effects are nearly always completely reversible, they may only temporarily affect HRQoL. By contrast, late-delayed radiation encephalopathy which occurs months to years after radiotherapy, may result in progressive cognitive decline.[109] Two randomized studies evaluating the combination of chemotherapy and radiation versus radiation therapy alone included HRQoL as an outcome measure.[17, 20] No negative effects of radiotherapy on quality of life were observed in anaplastic oligodendroglioma patients and patients with glioblastoma multiforme with a good performance status. On longer follow-up, >1.5 year after completion of radiotherapy, HRQoL scores of HGG patients without progression even improved compared to scores at the start of the treatment. In long term (i.e., >2 years from initial treatment) HGG survivors without disease progression who all had initial radiotherapy, even HRQoL scores were observed meeting the level of healthy controls, which may partly be explained by response shift, i.e., that patients over time more readily accept their situation.[117] Specifically in the elderly population (age >70 years), a moderate survival benefit from radiotherapy has been established for patients who had a good performance status at the start of the treatment. More importantly, HRQoL, performance status and cognitive functions did not further deteriorate compared to the observation arm of this study, in which patients only received supportive care.[16]
Reirradiation in HGG patients is increasingly applied because patients live longer following their initial treatment. Reirradiation should be considered in patients with an adequate performance status (KPS ≥70) applying focal radiation treatment after an interval from initial treatment of at least 6 months.[118] The effect of reirradiation, specifically on HRQoL, was only evaluated in one small study[119] with a median follow-up of 9 months. The majority of patients (80%) judged their general health status after reirradiation to be stable or even improved compared to before treatment; in 20% of patients, their perceived general health status declined. Scores for physical functioning, cognitive functioning and fatigue remained stable in nearly all patients.

Effect of Chemotherapy on HRQoL

In 2005, a large randomized controlled EORTC trial showed that the combination of temozolomide chemotherapy and radiotherapy significantly prolonged survival in patients with newly diagnosed glioblastoma multiforme compared to patients treated with radiotherapy alone.[9] The effect of this new treatment modality on HRQoL was evaluated separately.[17] During treatment and follow-up, in both treatment groups changes over time in 7 preselected HRQoL domains were not substantial during the first year of follow-up, provided there was no progression of disease. For several scales, scores even improved over time. However, during treatment, the patients in the combination treatment group reported more side effects (nausea, vomiting, appetite loss and constipation) compared to the radiotherapy only group, which can be attributed to the use of temozolomide and antiemetics. Furthermore, during adjuvant temozolomide treatment, social functioning was

worse in the intensive treatment group. Overall, it can be concluded that the addition of temozolomide during and after radiotherapy significantly improved survival without a long-lasting negative effect on quality of life.
As for treatment of patients with anaplastic oligodendroglioma, adjuvant treatment with combined procarbazine, CCNU (lomustine), and vincristine (PCV) chemotherapy after radiotherapy significantly prolongs progression-free survival, but not overall survival[19]. With respect to HRQoL, patients receiving PCV chemotherapy show a significant increase in nausea/vomiting and appetite loss during and shortly following treatment compared to patients only receiving radiotherapy. Furthermore, patients on PCV chemotherapy report more drowsiness. These differences, however, resolve over time: after 1 year follow up, no longer differences were observed in HRQoL between treatment groups.[20] Overall, there is a short-lasting negative impact of PCV chemotherapy on HRQoL during and shortly after treatment, but no long term effects or HRQoL have been established. More importantly, because PCV chemotherapy postpones tumour progression, the impact of progression on well-being and HRQoL should be evaluated in future studies.
In recurrent glioma, the median survival is short and treatment so far is only modestly effective. Because HRQoL measurements encompass assessment of both functioning ability and toxicity from therapy, HRQoL outcomes are of equal importance as survival in this patient group.[116, 120] Patients with recurrent anaplastic astrocytoma or glioblastoma multiforme successfully treated with temozolomide achieve a statistically significant improvement in a portion of the HRQoL domains while patients with disease progression reported statistically significant deterioration in most HRQoL domains.[116, 120] Thus, there is HRQoL benefit from temozolomide treatment for the period of stable disease due to treatment before disease progression occurs. The effect of temozolomide on HRQoL in recurrent glioblastoma has been compared with the effect of procarbazine in a randomized study. Patients receiving procarbazine showed deterioration in most HRQoL domains during treatment, whereas patients treated with temozolomide improved while on treatment.[116]
Although temozolomide chemotherapy has largely replaced PCV chemotherapy in glioma patients due to fewer side effects and improved tolerability, HRQoL data on chemotherapy in elderly HGG patients with poor performance status, as well as in the recurrent setting are scarce.[18]

Effect of Supportive Treatment on HRQoL

Symptomatic medications prescribed for glioma patients often include anti-epileptic drugs (AED) and steroids (dexamethasone). Because the occurrence of seizures can diminish HRQOL, it can be assumed that treatment with AEDs would improve quality of life. Conversely, an adverse effect of AED on cognition has been demonstrated.[121] This, in turn, can have a negative effect on the quality of life. A study examining the impact of seizures and AED on cognition and quality of life showed both cognitive functions as well as HRQOL

to deteriorate. The cognitive deficits could primarily be ascribed to the use of antiepileptic drugs, whereas the low HRQOL scores were mainly related to poor seizure control. [90] Dexamethasone reduces peritumoural oedema and is prescribed to alleviate neurological symptoms, thereby improving quality of life. On the other hand, common side-effects are myopathy, gastro-intestinal complications, hyperglycaemia, and psychiatric complications (mainly agitation or depression). Because these side-effects are related to the prescribed dosage, steroids should be tapered or maintained at the lowest effective dose.[122]

Health-Related Quality of Life in Clinical Practice

Old age and low functional status (Karnofsky Performance Status <70) have proven to be poor prognostic factors for survival in patients with HGGs. In daily practice, these prognostic factors are used to select patients who will probably benefit from aggressive treatment and patients who will probably not. HRQoL parameters have shown to be independent prognostic factors in various types of cancers.[123] At present, the prognostic value of baseline HRQoL data in predicting survival of HGG patients is questionable. Hitherto, four relatively large studies have been published about this subject. Two analyses using FACT scores for prognosis were performed. The first analysis has demonstrated patients with high scores on the FACT-G to have an enhanced survival compared to patients with low scores.[124] The second one, using the FACT-Br in combination with a five-item linear analogue scale assessment (LASA) also found a relation between high HRQoL scores and improved survival in univariate analysis. However, HRQOL was closely related to functional status and after correction for this in a multivariate analysis, no prognostic significance of HRQoL scores remained. [111] Two EORTC brain tumour studies regarding this issue were analysed by Mauer et al. [123] Classical analysis of EORTC-QLQ C30 subscores, controlled for major prognostic factors as age and performance status, identified cognitive functioning, global health status, and social functioning as statistically significant prognostic factors for survival in glioblastoma patients. In patients with anaplastic oligodendrogliomas, emotional functioning, communication deficit, future uncertainty, and weakness of legs were found to be significant prognostic factors. [125] In a more sophisticated boot-strap analysis, HRQoL scales were added to other predictive factors in a prognostic model. It came out that the HRQoL scales did not improve the prognostic value of known clinical factors. More importantly, fewer parameters are required in the prognostic model using clinical factors compared to the model using HRQoL data. From these analyses it can be concluded that, although various HRQoL scales have prognostic value, they have no additional value over already known clinical factors.

However, HRQoL data may have value in daily clinical practice. Routine HRQoL measurements in oncology patients visiting the outpatient department, with information provided to physicians, have shown to have a positive effect on physician-patient communication. In some patients, these measurements improved HRQoL and emotional

functioning. However, measurement of HRQoL, symptoms, and functioning are still far from being implemented in daily practice. In the future a core set of standard and disease specific questions repeated at key points of the disease trajectory (beginning of treatment, midtreatment, during follow up, at relapse) should be implemented to allow comparison over time. A small set of focused HRQoL questions could be used at each visit (for example, during treatment the focus could be on side effects). Furthermore, clear interpretation of scores is important and decision guidelines should be provided to the clinicians [126].