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Review

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

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Abstract

Gliomas are malignant primary brain tumors and yet incurable. Palliation and the maintenance or improvement of the patient's quality of life is therefore of main importance. For that reason, health-related quality of life (HRQoL) has become an important outcome measure in clinical trials, next to traditional outcome measures such as overall and progression-free survivals, and radiological response to treatment. HRQoL is a multidimensional concept covering physical, psychological, and social domains, as well as symptoms induced by the disease and its treatment. HRQoL is assessed by using self-reported, validated questionnaires. Various generic HRQoL questionnaires, which can be supplemented with a brain tumor–specific module, are available. Both the tumor and its treatment can have a negative effect on HRQoL. However, treatment with surgery, radiotherapy, chemotherapy, and supportive treatment may also improve patients' HRQoL, in addition to extending survival. It is expected that the impact of HRQoL measurements in both clinical trials and clinical practice will increase. Hence, it is important that HRQoL data are collected, analyzed, and interpreted correctly. Methodological issues such as selection bias and missing data may hamper the interpretation of HRQoL data and should therefore be accounted. In clinical trials, HRQoL can be used to assess the benefits of a new treatment strategy, which should be weighed carefully against the adverse effects of that treatment. In daily clinical practice, HRQoL assessments of an individual patient can be used to inform physicians about the impact of a specific treatment strategy, and it may facilitate the communication between the physicians and the patients.

Key words Health-related quality of life, brain tumors, glioma, patient-reported outcome

Gliomas are the most common primary brain tumors, with an annual incidence of 6 cases per 100,000[1]. The majority of gliomas are malignant tumors. Despite multimodal treatment with surgery, radiotherapy, and chemotherapy, these patients cannot be cured[2,3]. Patients with low-grade glioma (LGG) typically live longer than those with high-grade gliomas (HGG). The median survival of patients with LGG ranges from 6 to more than 15 years[4,5], especially when there is a favorable genetic profile[6]. In contrast, the median survival for patients with glioblastoma (the most frequent and malignant HGG) is only 15 months[7].

Traditional outcome measures in clinical cancer research have been confined to overall survival, progression-free survival, and radiological response to treatment. Palliation and the maintenance or improvement of quality of life are also important, and this recognition has resulted in that health-related quality of life (HRQoL) becomes an important outcome measure in clinical cancer research[8-10]. This is especially true for patients with incurable cancer, such as glioma.

This review focuses on the concept of HRQoL and its measurement, as well as on the effect of the disease (primarily HGG) and the treatment of the disease on HRQoL.

Concept of HRQoL and Its Assessment

HRQoL is a multidimensional concept covering physical, psychological, and social domains, as well as symptoms induced by the disease and its treatment[11]. By definition, HRQoL is a patient-reported outcome (PRO) measure, reflecting the patient's perspective[12]. Because glioma patients, due to the nature of disease, often experience cognitive deficits, this may (in due course) influence the patient's perspective, diverging from the caregiver's perspective on the patient's HRQoL. Many types of PROs have been developed, ranging from one-dimensional (assessing a single aspect of HRQoL,

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such as fatigue) to multidimensional measures.

Apart from PROs, there are also classification systems for defining patients' levels of functioning and handicap. The World Health Organization International Classification of Functioning, Disability, and Health (ICF 2001) refers to disability as dysfunction at one of three distinct levels. The most basic level is a patient's *impairment*: hemiparesis is an example of such an impairment. A higher level reflects the consequences of this impairment in daily life, the patient's *activity limitations* (e.g., the patient with hemiparesis is unable to climb the stairs). The highest level comprises how the disability affects the patient's well-being and his social interactions, the so-called patient's *participation restrictions*. In line with the example, this means that the patient who cannot climb stairs may have to move to another house.

For brain tumor patients, assessment at the level of *impairment* is typically done with a battery of standardized neuropsychological tests to give more detailed insight into cognitive functioning, as well as with neurological examination to reveal neurological deficits. Measures that assess (instrumental) activities of daily life functioning [(I)-ADL] can be used to assess *activity limitations*. Measures of *participation restriction* are typically embedded in HRQoL questionnaires.

Various HRQoL measures are available for use in clinical brain tumor trials as well as in daily clinical work. The European Organization for Research and Treatment of Cancer (EORTC) developed a generic questionnaire, the EORTC QLQ-C30, to measure HRQoL in cancer patients[13]. This questionnaire consists of 30 items, which are organized into 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea and vomiting, and pain), 1 global health status scale, 1 overall quality of life scale, and 6 single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). This generic or core questionnaire can be supplemented with a brain tumor–specific questionnaire, the EORTC QLQ-BN20[14]. This latter questionnaire includes 20 items, which are organized into 4 scales (future uncertainty, visual disorders, motor dysfunction, and communication deficit) and 7 single items (headache, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control). Almost all items on both the EORTC QLQ-C30 and the EORTC QLQ-BN20 are rated on a 4-point response scale, ranging from "not at all" to "very much." The exceptions are the "global health" and "overall quality of life" items of the QLQ-C30 that employ a 7-point Likert scale, ranging from "very poor" to "excellent." All single item and/or multi-item scales of the EORTC questionnaires are linearly transformed to 0–100 scales[15]. Difference or change scores of ≥10 points on any given scale are interpreted as being clinically meaningful; changes of >20 points represent a very large effect[16].

Another frequently used tool to measure HRQoL is the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire. The FACT-G (version 4) consists of 27 items covering 4 domains: physical, social/family, emotional, and functional well-being[17]. In addition to this generic questionnaire, a brain cancer-specific module, the FACT-brain, is available. This disease-specific questionnaire consists of 23 items measuring concerns relevant to patients with brain tumors[18]. Items on both questionnaires are rated on a 5-point scale, with higher scores representing a better HRQoL. The minimally important difference is established at 3–7 points of the total FACT-G score[19]. FACT questionnaires differ from EORTC questionnaires with respect to their focus. The FACT measures cover more psychosocial aspects of the disease and its treatment, whereas the EORTC measures are more focused on functioning and symptoms.

A more recently developed questionnaire that is used to measure HRQoL in cancer patients is the MD Anderson Symptom Inventory (MDASI) questionnaire[20]. This questionnaire was specifically designed to measure the severity of symptoms in cancer patients (13 items) as well as the interference of these symptoms with activities of daily living (6 items). In addition to the core questionnaire, a brain tumor–specific module (MDASI-BT) has been developed[21], consisting of 9 items (weakness, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel pattern, and irritability). The MDASI-BT is similar to the EORTC QLQ-BN20 in that both questionnaires tend to focus on symptoms. Items on both the MDASI and the MDASI-BT are scored on a numeric rating scale ranging from 0 to 10, with 0 indicating "not present" and 10 "being as bad as you can imagine." A subscale or total score can be calculated by averaging the sum of the items in a subscale or the total questionnaire, respectively. The smallest difference that can be considered clinically important is set at one-half standard deviation[22]. Using this distribution-based interpretation of scores means that a score considered clinically meaningful will vary from study to study (depending on the score distributions).

Effect of the Disease on HRQoL

Not surprisingly, the post-diagnosis and pretreatment levels of HRQoL for glioma patients are significantly lower than that for healthy controls[9,10]. Of note, patients with other neurological diseases of the central nervous system (such as Parkinson's disease and multiple sclerosis) or patients with other diseases without involvement of the central nervous system (such as hematological malignancies) experience similar levels of HRQoL to that of glioma patients[8,23]. This implies that suffering from any illness has a major impact on HRQoL irrespective of nervous system involvement and the nature of the disease.

At the same time, there are several tumor-related factors in glioma that may influence HRQoL, particularly tumor grade, size, and location[24]. For example, HGG patients have a more impaired HRQoL when compared with LGG patients, large tumors are associated with poorer HRQoL than small tumors (although this does not hold for gliomas in the left-dominant hemisphere), and patients with an anterior tumor report poorer HRQoL compared with those with a posteriorly located tumor[24].

Glioma patients experience both general cancer-related symptoms such as fatigue, anxiety, and depression, and disease-specific symptoms including seizures, cognitive deficits, motor dysfunction, and symptoms caused by elevated intracranial pressure[9,10,25], which may impair HRQoL.

Once tumor recurrence or progression occurs, this may also

have a negative impact on HRQoL of glioma patients. Indeed, patients with tumor recurrence have a more compromised HRQoL than those without tumor recurrence[26], and HRQoL worsens as disease progresses[27]. In the end-of-life phase, glioma patients can be expected to have an even more compromised HRQoL.

Effect of Treatment on HRQoL

Both the tumor and its treatment can affect HRQoL, and the relative effects of the disease versus treatment may be difficult to distinguish once treatment has been initiated (particularly outside of the context of randomized clinical trials). Nonetheless, a number of studies point to specific HRQoL effects of surgery, radiotherapy, chemotherapy, and supportive care interventions on glioma patients.

Effect of surgery

Apart from establishing a histologic diagnosis, the goal of glioma surgery is to resect as much tumor tissue as possible. The intent is to alleviate symptoms and prolong survival, while minimizing complications due to the operation itself. Tumor resection may improve HRQoL by a reduction of the tumor mass, resulting in alleviation of neurological symptoms and improvement of cognitive functioning. Alternatively, surgery may damage the normal surrounding tissue and cause (mainly transient) neurological and cognitive deficits[28], thereby decreasing HRQoL.

In a non-randomized prospective study in HGG patients, a significant association was found between the extent of tumor resection and HRQoL[29]. Patients who had undergone a subtotal or gross total tumor resection were more likely to have an improved HRQoL than patients who had undergone biopsy only. Clearly, these results should be interpreted with caution, because bias was introduced by patient selection with respect to tumor size, tumor location, and performance status.

Two studies in HGG patients assessing HRQoL preoperatively and 6 weeks after surgery revealed a slight, non-significant, overall decline in median HRQoL scores at the group level[30,31]. At the individual patient level, 44%–49% of the patients reported deterioration in HRQoL postoperatively[30,31]. Occipital lesions, postoperative ataxia, motor or language deficits, and lack of ultrasonography use for resection control were found to be associated independently with a deterioration in postoperative HRQoL[31]. Also, deterioration in HRQoL soon after surgery was found to be associated independently with poorer survival[30].

Effect of radiation

Treatment with radiotherapy may stabilize the disease and delay tumor progression, thereby preserving a patient's functioning and consequent HRQoL. However, radiotherapy may also have a negative impact on the HRQoL of glioma patients. Both immediate effects of radiotherapy, such as fatigue or symptoms of increased intracranial pressure, and long-term effects, such as a decline in cognitive functioning resulting from irreversible radiation encephalopathy, may negatively affect HRQoL.

Radiotherapy in LGG patients extends progression-free but not overall survival[32]. However, the impact of postponing tumor progression on HRQoL has not been investigated. High-dose radiation may have a more negative effect than low-dose radiation on LGG patients' HRQoL, without adding benefit in terms of survival[33]. In the short-term, LGG patients who underwent high-dose radiotherapy reported a more comprised HRQoL with respect to fatigue/malaise and insomnia than patients who underwent low-dose radiotherapy[33]. Long-term radiotherapy-induced cerebral abnormalities (with atrophy and/or white matter hyperintensities on magnetic resonance imaging) have been reported more frequently in LGG patients who underwent radiotherapy compared with LGG patients who did not. These radiological abnormalities were associated with deterioration in cognitive functioning[34,35]. However, the effects of radiotherapy on cognitive functioning of LGG patients was not unequivocal after 6 years of follow-up[36]. At that point, having undergone radiotherapy was not associated significantly with impaired HRQoL, whereas the presence of neurocognitive deficits and epilepsy was[6]. Long-term follow-up (12 years) of these LGG patients indicated that patients who underwent radiotherapy had significantly worse cognitive functioning compared with patients who did not[34]. Although not investigated, it is likely that these radiotherapy-induced cognitive deficits also have a negative effect on long-term HRQoL.

In contrast to the findings in LGG patients, the benefits of radiotherapy have been demonstrated in the treatment of HGG patients. Previously, standard care of treatment consisted of resection followed by radiotherapy. The last decade, however, chemotherapy was added to this treatment regimen[3]. Two randomized controlled trials in newly diagnosed HGG patients with a good performance status evaluated the effect of these two treatment strategies—radiotherapy in combination with chemotherapy (concomitant and/or adjuvant) versus radiotherapy alone—on survival and HRQoL[9,10]. Even though baseline HRQoL scores were already substantially impaired, no negative effects of radiotherapy on either anaplastic oligodendroglioma or glioblastoma patients were observed. HRQoL even improved slightly over time, which may be partially explained by a so-called response shift; i.e., although patients experience a change in health over time, they become more readily to accept their situation. This change influences their appraisal of HRQoL.

Preservation of HRQoL after radiotherapy was also found in studies on elderly GBM patients and patients with recurrent GBM treated with radiotherapy. Elderly GBM patients (>70 years) often have a poor performance status and have a reduced tolerance and response to treatment. However, the addition of radiotherapy to supportive care in these patients increased the median survival time, without causing a further deterioration of HRQoL[37]. Hypofractionated stereotactic radiotherapy for recurrent GBM resulted in a comparable overall survival time as treatment with chemotherapy, with preservation of pretreatment HRQoL in most patients[38].

Although the treatment regimens in all of the studies mentioned above do not appear to have a negative effect on HRQoL, it is important to note that compliance decreased with subsequent assessments. Patients with a better health status and favorable

treatment response are more likely to remain in a study and will therefore be overrepresented during (long-term) follow-up, leading to an overestimation of HRQoL.

Effect of chemotherapy

Several chemotherapy regimens are used in the treatment of glioma, alone or in conjunction with radiotherapy (concomitant and/or adjuvant). The combination of procarbazine, lomustine, and vincristine (PCV) is a well-established chemotherapy regimen in glioma treatment, as is temozolomide. Chemotherapy postpones tumor progression, with the possibility of maintaining a patient's functioning and consequent HRQoL. Conversely, adverse effects of chemotherapy may result in a deterioration of HRQoL.

Treatment with procarbazine in recurrent GBM patients has been found to be more toxic than treatment with temozolomide, and this is reflected in HRQoL scores; treatment with temozolomide resulted in an improvement in HRQoL, whereas treatment with procarbazine resulted in a deterioration in HRQoL[39]. Compared to radiotherapy alone, adjuvant PCV after radiotherapy in patients with anaplastic oligodendroglioma resulted in significantly longer progression-free and overall survival[40,41]. With respect to HRQoL, the addition of PCV to radiotherapy resulted in increased (although not clinical significant) nausea/vomiting, appetite loss, and drowsiness during and shortly after undergoing PCV treatment. Long-term follow-up, however, showed no differences in HRQoL between the two treatment strategies[10]. Thus, the major impact of adjuvant PCV after radiotherapy on HRQoL seems to be short-term and transient. The combination of temozolomide and radiotherapy led to meaningful and significantly longer overall and progression-free survivals in GBM patients when compared with radiotherapy alone[3]. In the short-term outcome, GBM patients undergoing the combination of radiotherapy and temozolomide reported significantly worse social functioning compared with patients undergoing radiotherapy alone. However, as for other HRQoL scales, differences in scores between the two treatment arms were not significant during follow-up[9]. In a prospective nonrandomized phase II trial evaluating the effect of hypofractionated intensity-modulated radiotherapy with temozolomide in GBM patients, a decline in cognitive and social functioning was reported during follow-up, as well as more appetite loss and communication deficits. A significant improvement was found for insomnia, motor dysfunction, future uncertainty, and drowsiness[42]. Although several aspects of HRQoL improved or deteriorated at some points during follow-up, HRQoL scores over time were more or less stable.

An antiangiogenic agent (bevacizumab) added to the current standard of care (radiotherapy with concomitant and adjuvant temozolomide) was introduced as a possible new treatment strategy for newly diagnosed GBM patients. The addition of bevacizumab resulted in similar overall survival but longer progression-free survival when compared with standard care in two different but parallel trials. However, one trial showed that HRQoL was preserved until progression[43], whereas the other trial showed that HRQoL deteriorated in the bevacizumab arm as compared with the non-bevacizumab arm[44].

A methodological drawback in many of these studies is that HRQoL was no longer evaluated once tumor progression occurs. Important information on HRQoL may therefore be lost, because disease progression may result in deterioration in many HRQoL endpoints. However, because post-progression treatment varies between patients, comparisons between different treatment strategies may become problematic. Moreover, HRQoL assessments of long-term survivors should provide information on possible late adverse effects of different treatment strategies.

Effect of supportive treatment

In addition to antitumor treatment, glioma patients may undergo symptomatic medications such as antiepileptic drugs (AEDs) and corticosteroids (i.e., dexamethasone).

Patients with tumor-related epilepsy experience seizures, which may have a negative impact on HRQoL. AEDs are intended to reduce the seizure frequency, which should improve HRQoL. However, the use of AEDs may also decrease HRQoL due to their adverse effects or interactions with chemotherapeutic agents. The impact of seizures and AEDs on cognition and HRQoL was investigated in a cohort of LGG patients. The use of first generation AEDs was associated with worse cognitive functioning, and the observed decline in HRQoL was associated with a higher epilepsy burden[25].

Although equally effective, second generation AEDs such as levetiracetam and oxcarbazepine cause fewer adverse effects and are less susceptible to interactions with antitumor treatment. Two studies have reported the effect of levetiracetam and oxcarbazepine on HRQoL in patients with brain tumor-related epilepsy[45, 46]. Both studies found that the use of AEDs did not significantly affect HRQoL after 12 months of follow-up. It should be noted, though, that immediate adverse effects would not have been detected in these studies because there was only one follow-up assessment. The exact timing of HRQoL assessments is important for the interpretation of the results (immediate effects versus long-term effects), and modest changes in the timing of an assessment can result in substantially different outcomes.

Dexamethasone is prescribed to alleviate symptoms of elevated intracranial pressure (i.e., headache, nausea and vomiting, visual disturbances, drowsiness, and decreased consciousness) by a reduction of vasogenic edema. The relief of these symptoms may result in an improvement in HRQoL. However, dexamethasone may cause a wide variety of adverse effects, such as proximal muscle atrophy and weakness, gastrointestinal problems, and/or psychological distress, thereby decreasing HRQoL. Most adverse effects depend on the dosage of dexamethasone, implying that dexamethasone should be prescribed in the lowest effective dose to minimize its adverse effects[47]. The exact impact of dexamethasone on HRQoL in glioma patients is not easy to assess because this medication is often prescribed in combination with other (antitumor) treatments or at the time of symptomatic tumor progression.

Considerations and Conclusions

Value of HRQoL assessments in research and clinical practice

During the past decades, HRQoL has become an important outcome measure in brain tumor research. It is therefore expected that the impact of HRQoL measurements on clinical decision-making[48] and healthcare policy development will increase.

Hence, it is important that HRQoL data are collected, analyzed, and interpreted correctly. Several methodological issues may hamper the interpretation of HRQoL data[49], including the timing of the assessments, selection bias, response shift, and missing data. These methodological limitations should be kept in mind when interpreting HRQoL scores derived from clinical trials or from an individual patient in clinical practice.

In clinical trials, the benefits of a new treatment strategy should be weighed carefully against the adverse effects of that treatment, in terms of overall and progression-free survivals, as well as in terms of HRQoL. In daily clinical practice, HRQoL assessments of an individual patient can be used to inform physicians about the impact of a specific treatment strategy, so they can closely monitor and tailor treatment. Moreover, HRQoL assessments can increase the physician's awareness of the patient's functioning and well-being, which may facilitate the communication between the physician and the patient[50].

Conclusions

HRQoL has become an important outcome measure in brain tumor patients, which may help both doctors and the patients and their families to make decisions on (tumor) treatment and clinical care. Over the years, several validated questionnaires have been developed to measure HRQoL. Both in clinical trials and in daily practice, it is expected that its use will even increase now that new (combination of) treatments emerge for brain tumor patients.

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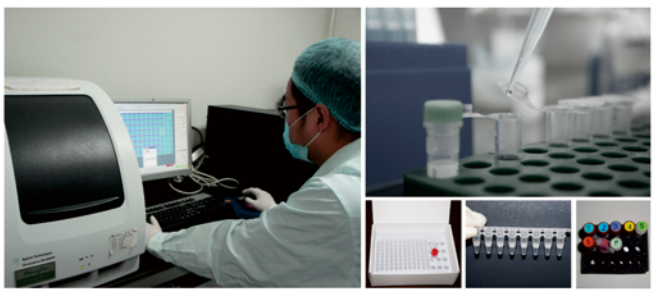
AMOY
DIAGNOSTICS
Molecular tests for personalized medicine
STAY ON TARGET

ADx-ARMS® Real-time PCR Technology

- One-step procedure
- Results in 90 minutes
- Detects 1% mutant allele
- GMP-compliant manufacturing
- ISO13485-certified laboratory
- CFDA approved for clinical use in China
- Compatible with multiple PCR instruments



Amoy Diagnostics Product List

TEST	GENE	TEST	GENE
Mutation Detection	EGFR CE	Gene Expression	RET
	KRAS CE		TP 53
	BRAF CE		ERCC1 CE
	EML4-ALK CE		TYMP
	PIK3CA CE		STMN1
	ROS1 CE		TYMS
	HER2		TOP2A
	MEK1		TUBB3
	JAK2		BRCA1
	BCR-ABL		DPD
	PDGFRA		RRM1
	C-KIT	DNA/RNA Extraction	FFPE DNA
	AKT		FFPE RNA
	RET		FFPE DNA/RNA
	TP 53		Blood DNA

***EML4-ALK* Kit**

***ROS1 Gene* Fusions Kit**

- 21 ALK gene fusions and 14 ROS1 gene fusions can be detected
- Simultaneous testing for ROS1 and ALK with multiple sample types
- ROS1 test kits being used for pivotal clinical trial of Pfizer's crizotinib

***ROS1/ALK Gene* Fusions Kit**

Articles using Amoy Diagnostics

1) The diagnostic accuracy of pleural effusion and plasma samples versus tumour tissue for detection of EGFR mutation in patients with advanced non-small cell lung cancer: comparison of methodologies (*J Clin Pathol 2013*)
2) Targeted resequencing reveals ALK Fusions in non-small cell lung carcinomas detected by FISH, immunohistochemistry, and real-time RT-PCR: a comparison of four methods (*BioMed Research International 2013*)
3) A comparison of ARMS and direct sequencing for EGFR mutation analysis and tyrosine kinase inhibitors treatment prediction in body fluid samples of non-small-cell Lung cancer patients (*Journal of Experimental & Clinical Cancer Research 2011*)
4) Analysis of driver mutations in female non-smoker Asian patients with pulmonary adenocarcinoma (*Cell Biochem Biophys 2013*)
5) Association of EGFR mutation or ALK rearrangement with expression of DNA repair and synthesis genes in never-smoker women with pulmonary adenocarcinoma (*Cancer 2012*)
6) Comparative screening of K-ras mutations in colorectal cancer and lung cancer patients using a novel real-time PCR with ADx-K-ras kit and sanger DNA sequencing (*Cell Biochemistry and Biophysics 2012*)
7) Oncogenic driver mutations in patients with non-small-cell lung cancer at various clinical stages (*Annals of Oncology 2012*)
8) KIF5B-RET Fusions in Chinese Patients With Non–Small Cell Lung Cancer (*Cancer 2013*)

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