Health-Related Quality of Life or Quantity of Life: A Difficult Trade-Off in Primary Brain Tumors?

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Health-related quality of life (HRQoL) measurements have become increasingly important in brain tumor research, next to traditional outcome measures such as overall and progression-free survival. Several validated questionnaires have been developed to measure HRQoL in clinical trials, as well as in clinical practice. In brain tumor patients, both the tumor and treatment may have an impact on HRQoL, which can be positive and negative. When determining the net clinical benefit of a new treatment strategy, both the quantity and quality of life (QOL) should be considered.

Because treatment may benefit or harm both quantity and QOL, a trade-off discussion may arise when these two outcomes are conflicting.

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Gliomas are the most frequent primary brain tumors in adults, and the far majority of these gliomas are malignant. Although the yearly incidence of gliomas is relatively low with six cases per 100,000 persons,[1] these neoplasms result in a disproportionate share of cancer morbidity and mortality. Multimodal treatment with surgery, radiotherapy and chemotherapy does not result in cure, but prolongation of (progression-free) survival can be achieved.[2,3] Patients with a low-grade glioma (LGG) usually live longer than patients with a high-grade glioma (HGG). The median survival of LGG patients ranges from 6–15 years,[4,5] partly depending on the genetic profile of the tumor.[6] Patients with a glioblastoma (GBM, the most frequent and most malignant subtype of HGG) on the other hand, have a median survival of only 15 months.[3]

The incurable nature of gliomas has led to the recognition that palliation and the maintenance or improvement of the quality of life (QOL) are at least as important as prolonged (progression-free) survival. Therefore, the management of gliomas is directed not only at maximizing survival but also at improving QOL during the entire disease course, from initial diagnosis until the end of life. This trend also is observed in clinical cancer research: over the last decades, health-related quality of life (HRQoL) has become an important outcome measure in clinical trials of treatment for primary brain tumors.[7–9] Results on HRQoL, in addition to traditional outcome measures such as overall and progression-free survival, may contribute in determining the net clinical benefit of a new treatment strategy. Treatment may benefit or harm both quantity and QOL and a trade-off discussion will arise when these two outcomes are conflicting.

This review starts with a description of the concept of HRQoL and its methods of assessment, followed by a description of several factors that may have an impact on HRQoL. The main focus of this review, however, is to evaluate the benefits and harms of a specific treatment strategy in glioma patients, both in terms of quantity and QOL. Do the results of these clinical trials result in difficult trade-off discussions?

CONCEPT OF HRQoL AND METHODS OF ASSESSMENT

To measure the impact of disease and treatment-related factors on the QOL of patients, the concept of HRQoL was developed. HRQoL is considered a

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multidimensional concept and encompasses physical, psychological, emotional, and social domains.[10] Reflecting the patient's perspective, HRQoL is a patient-reported outcome (PRO) measure and by definition completed by the patient.[11] However, self-reporting can be difficult in glioma patients because of neurological symptoms and cognitive impairments. In that case, proxies (partner or other relatives) may complete the questionnaires from a patient-by-proxy perspective to obtain information on HRQoL of the patient. It should be noted though, that the level of agreement between patient and proxy ratings is not always consistent. Patients and proxies often very much agree on symptom scales but to a lesser extent on psychosocial scales[12,13] and they agree more often when the patient's HRQoL score is in the low or in the high range.[14] Disagreement between ratings is especially evident with increasing symptom severity and cognitive impairments.[14–16] Many types of PROs have been developed, ranging from one dimensional (assessing a single aspect of HRQoL, such as fatigue) to multidimensional measures.

Another perspective from which to look at patients' functioning and health is through the World Health Organization International Classification of Functioning, Disability and Health (ICF 2001) criteria. This ICF system refers to disability as dysfunctioning at one of three distinct levels, (1) impairment, (2) activity limitations, and (3) participation restrictions. *Impairments* are problems in body functions, of which hemianopia is an example in glioma patients. Assessment of impairments is typically done through neurological examination to reveal neurological deficits or with standardized neuropsychological tests to reveal cognitive impairments. Next, the consequences of this impairment in daily life are reflected in the patient's *activity limitations*. In line with our example, the patient with hemianopia is unable to drive a car. To assess these activity limitations, measures of (instrumental) activities of daily living might be used. Finally, the highest level reflects the way the disability affects the patient's well-being and social interactions, the patient's *participation restrictions*. This means that the patient with hemianopia, who is unable to drive a car, is no longer able to go to work or visit friends and family. Measures of participation restrictions are typically embedded in HRQoL questionnaires.

To date, there is no single gold standard instrument to measure HRQoL. Several HRQoL questionnaires are available for use in clinical brain tumor trials as well as in daily clinical practice. A widely used generic instrument to measure HRQoL in cancer patients was developed by the European Organization for Research and Treatment of Cancer (EORTC), the EORTC QLQ-C30.[17] This generic questionnaire includes five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, pain, and nausea and vomiting), a "global health status" and an "overall quality of life" item, and six single items for remaining symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), with a total of 30 items. In addition to this core questionnaire, the EORTC QLQ-BN20 questionnaire is available to measure symptoms and problems that are specific for patients with brain cancer.[18] This brain tumor–specific instrument includes 20 items organized into four scales (future uncertainty, visual disorders, motor dysfunction, and communication deficit) and seven single items (headache, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control). Both questionnaires ask patients to rate their symptoms and problems over a 7-day recall period. With exception of the "global health" and "overall quality of life" items of the QLQ-C30, all items of both the EORTC QLQ-C30 and the EORTC QLQ-BN20 are rated on a 4-point Likert scale, ranging from "not at all" to "very much". Answers to the items "global health" and "overall quality of life" are provided on a 7-point Likert scale, ranging from "very poor" to "excellent". Scores of all single item and/or multi-item scales of the EORTC questionnaires are linearly transformed to 0–100 scales.[19] For functional scales and the "global health" and "overall quality of life" items, a higher score represents *better* HRQoL, whereas on symptom-oriented scales a higher score represents *worse* HRQoL. Difference or change scores of ≥ 10 points on any given scale are interpreted as being clinically meaningful, whereas changes of > 20 points are thought to represent a very large effect.[20]

Another frequently used tool to measure HRQoL is the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire. The FACT-G (version 4) covers four domains (physical, social/family, emotional, and functional well-being) and comprises a total of 27 items.[21] This generic questionnaire can be supplemented with a brain cancer-specific module. This FACT-Br consists of 23 items measuring concerns relevant to patients with brain tumors.[22] The principle for scoring is equal for all items of both questionnaires; items are rated on a 5-point Likert scale ranging from "not at all" to "very much", with higher scores representing a better HRQoL. The smallest difference that can be considered clinically important is established at 3-7 points of the total FACT-G score.[23] Similar to the EORTC questionnaires, both the FACT-G and the FACT-Br employ a 7-day recall period. In contrast, the FACT questionnaires differ from the EORTC questionnaires with respect to their focus. Whereas the FACT questionnaires cover more psychosocial aspects of the