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Impact of brain tumour treatment on quality of life

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Abstract Measurement of Health Related Quality of Life (HRQL) in brain tumour patients is important because brain tumours and brain tumour treatment usually affect physical, cognitive as well as emotional functioning. Measurement of HRQL is important for the understanding of disease burden and for the impact of specific tumour treatment. Quality of Life is a multidimensional concept consisting of physical, psychological and social phenomena. A large number of Quality of Life instruments have been developed. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the MOS Short-Form Health Survey are two frequently used general HRQL instruments. A specific brain tumour scale is the Brain Cancer Module, which is designed to be used in combination with general questionnaires.

HRQL measurement and neuropsychological examination were used to investigate the impact of radiotherapy and surgery in low-grade glioma patients and the influence of tumour volume, tumour localization, performance status and age in both low-grade and high-grade glioma patients.

Key words primary brain tumour · glioma · quality of life · cognitive function

Introduction

The assessment of Health Related Quality of Life (HRQL) in cancer patients has become increasingly important during the past decades. Usually, the primary aim of measuring HRQL in oncological patients is to better understand the impact of a specific tumour or a specific treatment on the functional, psychological and social health of the individual. Especially in patients with breast cancer and patients with lung cancer HRQL measurements have been made. Relatively little attention has been paid to the impact of a primary brain tumour on HRQL. This might be very relevant because glioma patients not only have to cope with the diagnosis of incurable and (almost always) fatal disease, but they are usually also confronted with a decrease in cognitive and emotional functioning as a result of cerebral disease.

Outcome measures in brain tumours: impairment, disability, performance, handicap

Osoba and co-workers [20] used the term "disease burden" to encompass the symptoms and limitations in physical functioning and emotional well-being imposed by the illness. They refer to Levin et al. [13] when summarizing the most common initial symptoms in brain tumour patients: these include headache, anorexia, nausea, vomiting (particularly in children), seizures, sleeping longer at night and drowsiness with napping during

the day. Most of these symptoms are thought to be secondary to increased intracranial pressure and may also occur at tumour recurrence.

Apart from these "general tumour symptoms" brain tumour patients may suffer from focal neurological deficits, such as motor deficit, aphasia or visual field defects. Further, Osoba emphasized the fact that personality changes, mood disturbances or decrease in mental capacity and concentration may prove to be as, or more, burdensome to patients and their proxies than some of the "focal" neurological deficits. Disease burden has varying effects on overall well being and HRQL.

Evaluation of cancer therapies traditionally focusses on outcome measures such as tumour size, time to tumour progression (TTP) and overall survival. In brain tumour patients, the severity of neurological impairment should also be recorded. Grant and co-workers [8] pointed out the importance of distinguishing between impairment, disability and handicap. Impairments are direct consequences of pathology which can be demonstrated on physical/neurological examination. In brain tumour patients impairments may be hemiparesis, dysphasia or memory loss. Disabilities are the consequence of impairments: the inability to climb the stairs, to write a letter, to eat or to dress without help. Handicap is how disability affects the patient's well-being and social interactions, such as work, family, marriage and leisure pursuits.

Probably, the impact of therapy is best evaluated by measurement of impairment: the level of impairment provides investigators with more or less objective outcome parameters which reflect a change in underlying pathology. However, the aspects most important to the patient are disability and handicap.Assessment of one aspect of neurological impairment can be achieved by the MRC grading scale for muscle strength.

Examples of disability (or performance) scales are the Barthel and the Karnofsky rating scales. The latter is an ordinal scale that is frequently used in cancer patients. The Karnofsky scale can be insensitive to changes in neurological impairment, such as memory disturbances, speech disturbances and epileptic seizures.

For the measurement of handicap the Modified Ranking Handicap Scale (MRHS) is frequently used; this is a six-tiered scale ranging from 0 (no symptoms) to 5 (severe handicap/totally dependent; requiring attention day and night).

Grant et al. [8], who considered impairment an important and objective outcome parameter, measured neurological impairment in glioma patients by the following simple timed tests:

1. The "nine hole peg test" was employed to measure upper limb function. Nine pegs should be placed in nine holes within 120 seconds.
2. The "ten metre walk" was used to measure lower limb function: if the patient needed more than 8 seconds to complete a walk of ten metres, lower limb function was considered abnormal.
3. Short term memory was measured by means of the Williams Delayed Recall Test. This test consists of a sheet of paper with nine easily identifiable objects or animals, which have to be remembered after six minutes. If the patient is unable to recall some of the objects, he is given a predetermined prompt and if he is still unable to recall the object he is shown a sheet containing fifteen pictures and is asked which of these pictures were on the first sheet. Two points were given for each item not recalled spontaneously, three points for each item not recollected with a prompt and four points for each item not recognized from the visual prompt. A total score of > 12 was considered abnormal.
4. Boston aphasia severity rating scale. This is the subjective rating of speech disturbances by a neurologist on an ordinal scale ranging from 0 (no useful communication possible) to 6 (no speech difficulties).

A "limb functional impairment score" was calculated from the nine hole peg test and the ten metre walk.

The correlation between this limb functional impairment score and the Barthel Disability Index was only moderate, which reflects the poor sensitivity of the Barthel Index at identifying physical disability. The correlation of the limb functional impairment and the MRHS was slightly better. Further, Grant emphasized that the Karnofsky Performance Scale is not a very suitable scale for studies of glioma and he recommended the use of the four tests of neurological impairment in combination with questionnaires of mood, disability and performance. He did not envisage that all these tests should replace the measurement of quality of life.

Quality of Life measurement

In relation to health, quality of life is defined as a multidimensional concept consisting of at least physical, psychological, and social phenomena.

HRQL assessment has become an important part of clinical research in cancer patients and, in fact, is advocated by research groups both in the US and in Europe. In 1994 already 159 Quality of Life instruments had been developed [6]. Standardized HRQL measurements are nowadays also used in clinical practice to monitor changes in the symptom experience and in self-reported functioning. HRQL can be measured by means of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) or the MOS Short-Form Health Survey (SF–36). The latter is a self-report questionnaire developed in the United States [26]. It is composed of 36 items, organized into 8 multi-item scales assessing: 1) physical functioning, 2) role limitations due to physical health problems,

3) bodily pain, 4) general health perception, 5) vitality, 6) social functioning, 7) role limitations due to emotional problems, and 8) general mental health.

This illustrates that Quality of Life measurement as a routine part of daily practice implies that both patients and physicians are aware of the value of discussing a wide range of issues which are not directly related to the illness, but also to emotional and social functioning. Apparently, patients have a high expressed desire for information on their illness and treatment possibilities although the type of information-seeking behaviour may vary widely among patients. In general, younger, better-educated, and female patients ask for more information from their doctors than do older, less well-educated, and male patients. But what about the preferences of patients for disclosing information about themselves? Generally speaking, patients want to feel to be understood by their physician which implies that the doctor should be aware of the influence of the illness on emotional and social aspects of life. But are patients willing to discuss the full range of psychosocial issues with their doctors? This willingness seems to be influenced by the attitude of the doctor toward the psychosocial aspects of patient care [14].

The attitudes and preferences of cancer patients and of oncologists to discuss a range of HRQL issues were investigated by Delmar et al. [4]. They found that more than 95% of cancer patients had the desire to discuss physical aspects of their disease and almost all of them were willing to initiate such a discussion. Over 90% of patients also wished to discuss problems in daily life and emotional aspects, but one quarter of them were only willing to do so at their doctor's initiative. Moreover, one quarter of patients preferred not to discuss their family and social life and one third of patients indicated that they would do so only if their doctor raised the issue. Striking was the finding that female patients were more reluctant to talk to their physician about their partner and friends than were male patients. Similar sex differences were found for other domains of HRQL. A possible explanation for these differences is that women are more inclined to discuss such aspects within their own informal social network. This would be in line with the finding that female cancer patients have larger networks of support and are more likely than male patients to rely on friends and family for emotional support [9].

Patients over 60 years of age were more likely than younger patients to prefer that their physician took the initiative to discuss HRQL issues. Two out of ten physicians who participated in this study disagreed with the statement: "I encourage my patients to raise psychosocial issues during outpatient consultations". The discussion of the patients' emotional functioning was usually left up to the patient and the patients' social functioning was usually not discussed at all. In some cases this might lead to what the authors call "a conspiracy of silence": both the patient and the doctor wait for a clear signal of the other. The reason that specific topics are avoided is not quite clear and it would be important to know if patients would feel more comfortable to discuss certain items with other health care providers than their doctor (eg, oncology nurses, social workers or psychologists).

Test/retest studies have been performed in HRQL questionnaires: The EORTC QLQ-C30 seemed to yield high test/retest reliability in patients with various cancer diagnoses whose condition is not expected to change during the time of measurement [10].

Quality of Life measurement in brain tumour patients

A specific brain tumour quality of life tool is the Brain Cancer Module, which is designed to be used with the QLQ–30 or other general questionnaires [18]. This scale assesses problems specific to brain tumour patients. The module has been modified into the Brain Cancer Module–20 in order to eliminate the overlap with emotional distress items on the QLQ–30. The module contains four multi-item scales: future uncertainty, visual disorder, motor dysfunction, and communication deficit. Furthermore it contains seven single items: headache, seizures, drowsiness, hair loss, itching, weakness of both legs, and difficulties with bladder control. Another brain tumour-specific instrument is the PRESTON profile [15]. Several different domains are addressed by this instrument: physical, emotional, and social functioning. However, it does not evaluate cognitive impairment and has not undergone validity and reliability assessment [5].

The core Functional Assessment of Cancer Therapy (FACT) addresses physical, family, social, emotional, and functional well-being. The FACT brain module is a subjective instrument which measures substantially different quality of life items than the core instrument [27].

Osoba et al. [19] studied HRQL in patients with high grade malignant glioma of the brain. They used the EORTC QLQ-C30 and the aforementioned Brain Cancer Module and found that newly diagnosed patients and patients with a Karnofsky Performance Score of 80–100 had significantly better physical, role and cognitive functioning and global quality of life with less fatigue, visual disorder, motor dysfunction, communication deficit, weakness of both legs and trouble controlling the bladder than did those patients who suffered from recurrent disease and the patients who had a Karnofsky Performance Score of 50–70. Patients with dysphasia, motor deficit and confusion reported lower levels of physical, role, cognitive, emotional and social functioning and global quality of life than did patients who did not have these symptoms. Deteriorating neurological status correlated well with decline in cognitive, physical,

role, emotional and social functioning and with global quality of life.

Quality of life self-reports from brain tumour patients had already been compared with Karnofsky Performance Scores in 1992 [16]. These authors found that for patients with KPS between 90 and 100 (which was two thirds of the population tested) "well-being" was strongly related to freedom from depression, active social life, energy, and fewer symptoms. The lack of a relationship between KPS and quality of life in these patients showed that the KPS lacks sensitivity at this level. The other one third of the population had KPS ranging from 50 to 80. Age appeared to have a considerable effect on KPS scores: older patients tended to have lower KPS scores. In fact, age had a greater effect on KPS than any other variable, such as depression, memory, neurological symptoms, cognition, energy, leisure or socializing. Nevertheless, in this group of patients with low KPS, the KPS was related to impairment in well-being, energy, sex life and leisure. It appeared to be insensitive to depression! This is important, because mood disorders and psychological distress in patients with intracranial tumours may be sufficient to warrant psychological and/or pharmacological intervention. Prevalence figures for mood disorders in brain tumour patients vary widely between studies. Anderson et al. [1] found that only two of 40 patients tested had clinically significant levels of anxiety as assessed by the Clinical Anxiety Scale. Six of these 40 patients had clinically significant levels of depression as assessed by the Hamilton Rating Scale for Depression. Psychological morbidity was associated with high levels of physical disability and also with cognitive dysfunction, but not with the grade of the tumour or with the extent to which the patient was aware of the prognosis of his or her disease.

Quality of Life in low-grade glioma

Taphoorn et al. [24, 25] examined low-grade glioma patients and compared the results with control subjects with low-grade haematological malignancies. They found that patients with low-grade glioma experienced more drowsiness, fatigue, memory and concentration difficulties, and speech problems than did control subjects. Patients with left hemisphere tumours reported more concentration difficulties than patients with right hemisphere involvement. They used the Profile of Moods State (POMS) to assess the actual affective status. This is a mood-adjective checklist, commonly used in studies on the subjective well-being of patients. Affective disturbances are measured along five dimensions: depression, anger, fatigue, tension, and vigor. The test consists of 32 items to be scored by the patient, with respect to the past few days, on a 5-point scale, which ranges from "not at all" to "very much". Patients with low-grade glioma appeared to score higher on the subscales depression, anger, fatigue and tension than did control patients. Further, they scored lower on the vigor dimension. Patients with right hemisphere tumours scored significantly higher on the POMS tension scale than did patients with a left hemisphere glioma. Further, it appeared that women compared to men had more mood disturbances.

These two studies by Taphoorn et al. specially focused on the effect of radiotherapy in low-grade glioma patients. Twenty low-grade glioma patients had been treated with early radiotherapy, whereas 21 other low-grade glioma patients had undergone surgery or biopsy only. Although this was not a prospective study, it is important to conclude that no differences between the two groups were found with respect to quality of life or mood disturbances. Further, extensive neuropsychological examination took place by means of a test battery that was designed to detect possible deficits in the domains of attention, memory, language, visuospatial function, and executive function. No significant differences were found between the two groups, although the combined glioma group (irradiated and not irradiated patients) scored less well than did control patients on most neuropsychological variables, indicating that the tumour itself has a negative influence on cognitive performance.

In a randomized phase III trial in low-grade glioma patients a comparison was made between high-dose (59,4 Gy in 6,5 weeks) and low-dose radiotherapy (45 Gy in 5 weeks) with conventional techniques [11]. The primary endpoint was survival. Quality of life was evaluated by means of a questionnaire constructed for this study. This questionnaire consisted of 47 items assessing a range of physical, psychological, social and symptom domains. Patients who received high-dose radiotherapy reported more fatigue and insomnia immediately after radiotherapy and poorer emotional functioning at 7–15 months postrandomisation.

24 patients with suspected low-grade glioma, in whom surgical treatment was deferred were compared with 24 patients (matched for educational level, handedness, age and gender) with a histologically proven low-grade glioma [23]. Both groups scored worse on quality of life scales than healthy control subjects. Unoperated patients scored better on most items than patients with proven low-grade glioma. An important conclusion of this study was that uncertainty about the future did not differ between the two patient groups and that, therefore, a definite diagnosis does not lead to a substantial reduction of these feelings.

Quality of Life in high-grade glioma

Klein et al. [12] studied 68 newly diagnosed high-grade glioma patients and compared these with 50 lung cancer

patients and matched healthy controls. In both glioma patients and lung cancer patients health related quality of life was significantly lower than that of the healthy controls. In glioma patients neurologic and objective and subjective neuropsychologic functioning were lower than in the lung cancer patients. Cognitive impairment was observed in all glioma patients. Extent of resection was not related to neuropsychological functioning and antiepileptic drug use was correlated negatively with working memory capacity. Bampoe and coworkers [2] studied quality of life in patients with glioblastoma multiforme who participated in a randomised study of brachytherapy as boost treatment. The core instrument of the multidimensional QOL questionnaire they used was derived from the Sickness Impact Profile. No statistical difference between the two treatment arms (conventional radiation plus a brachytherapy boost versus conventional radiotherapy alone) was found regarding quality of life parameters. However, a significant deterioration in KPS and in some HRQL items was found during the first year of follow-up: self care, speech, concentration, cognitive functioning and physical experience deteriorated. Also in this study it appeared that the correlation between KPS and HRQL scores was low.

In a recent Italian study [7], HRQL was evaluated in 57 patients with high-grade malignant gliomas, who had stable disease after multimodality-treatment (surgery, radiotherapy and chemotherapy). The Functional Living Index – Cancer (FLIC) was employed. This is a self administered visual analogue scale exploring different dimensions of quality of life (physical, emotional, social and occupational aspects as well as drug side-effects). It showed that quality of life in this selected group of glioma patients was satisfactory and did not differ from the quality of life in patients with chronic neurological illnesses. The study suggests that aggressive combination treatment (including adjuvant chemotherapy) does not necessarily affect quality of life more than cancer therapies for other tumours. Quality of life in brain tumour patients was significantly associated with depression and state anxiety.

Weitzner et al. [28] evaluated quality of life in a group of 50 brain tumour patients (mainly anaplastic astrocytomas). They found that quality of life in glioma patients is most affected by 1) the extent of tumour involvement, bilateral being worse than unilateral; 2) poor performance status; 3) being a woman; 4) having been divorced; 5) undergoing aggressive treatment, including chemotherapy; and 6) being not able to work. Tumour grade and age were not related to quality of life in this study. The study shows how both tumour-related and non-tumour-related factors may influence quality of life in individual patients. It also indicates that adjuvant chemotherapy may negatively affect HRQL, although the effects of several treatment modalities on HRQL only can be appreciated in prospective randomised trials. In this respect, it is important to realize that therapeutic nihilism, resulting in refraining from therapy, may have a negative impact on HRQL as well.

The effect of treatment in recurrent glioma may be measured by tumour response but also by a change in HRQL. HRQL was assessed using the EORTC QLQ-C30 and the Brain Cancer Module (BCM20) in two clinical trials enrolling a total of 366 patients with recurrent glioblastoma multiforme; 288 patients provided HRQL data that could be analysed. One hundred and nine patients received temozolomide in a phase II study; 89 patients received temozolomide and 90 patients received procarbazine in a randomized phase III trial. Before disease progression, patients who were treated with temozolomide were found to have an improvement in a number of HRQL domain scores compared with their pre-treatment scores. Patients who were treated with procarbazine reported deterioration in HRQL [22].

The same instruments were used in a phase II study in patients with recurrent anaplastic astrocytoma who were treated with temozolomide. After six months of treatment, those patients who were free of disease progression reported either an improvement or maintenance of all the preselected HRQL domains scores [21]. The prognosis of patients with glioma greatly depends on age, performance status, cognitive status and tumour grade [4]. Generally speaking, gliomas cannot be cured by standard treatment. Therefore, experimental approaches are an important consideration. Moots [17] states that for these reasons, individualization of treatment planning for malignant glioma is important. Further, the patient and his proxies must have a clear concept of the nature of the disease and of the possibilities and limitations of various treatment modalities. It should be realized that cognitive impairment as well as emotional distress often make it difficult to convey a clear overview of the exact nature of the illness and the details of the treatment options. The prognosis should be discussed, including the average time to progression, and the treatment possibilities of tumour recurrence. Generally, several specialists (neurologist, neurosurgeon, radiation oncologist, medical oncologist) are involved in the treatment of glioma patients. This places a great premium on the development of a team that can deal with all the (oncological and neurological) issues. The already mentioned therapeutic nihilism, which is often associated with the treatment of primary brain tumours, may limit enrolment in clinical trials. Nevertheless, treatment efforts may have a positive (albeit temporary) impact on HRQL.

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