Towards improving health-related quality of life in glioma patients and their informal caregivers

F. W. Boele

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TOWARDS IMPROVING HEALTH-RELATED QUALITY OF LIFE IN GLIOMA PATIENTS AND THEIR INFORMAL CAREGIVERS

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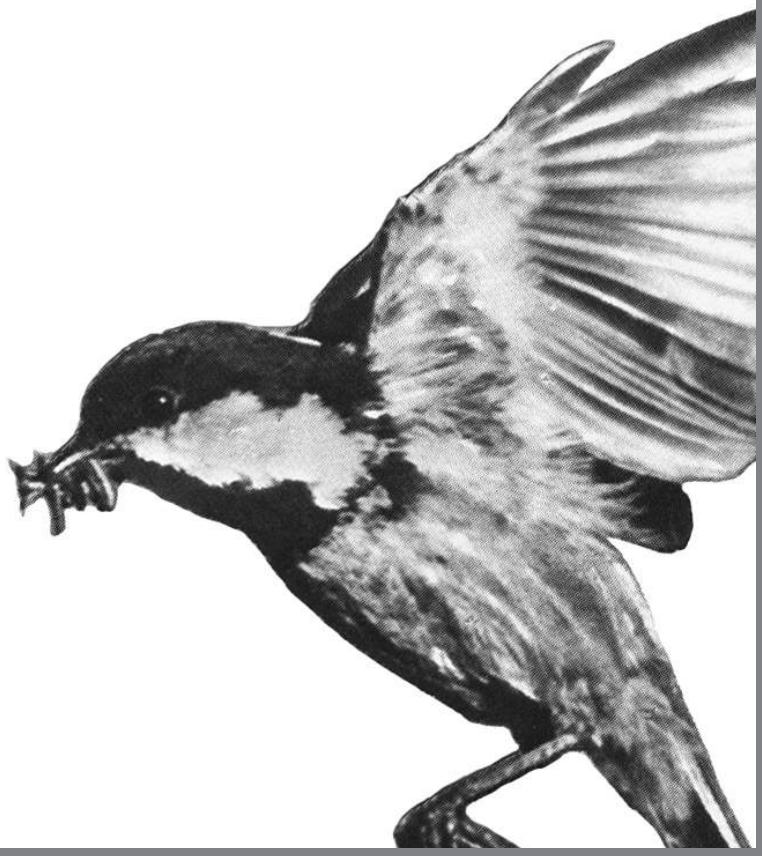
Introduction



1.1 BRIEF BACKGROUND

Gliomas are the most common primary brain tumors, and originate from glial cells within the central nervous system. These tumors have a direct effect on brain functioning. As the tumor progresses, symptoms and problems resulting from the disease often become more pronounced. This can negatively affect not only the patients, but also their direct social environment, such as spouses, family members and close friends. At present, life expectancy of glioma patients is often restricted, depending on the tumor type and grade. Because of the substantial impact of the disease and its treatment on the everyday lives of patients and their loved ones, it is important to pay attention to quality of life and symptom management. In this dissertation, various studies focusing on health-related quality of life (HRQOL) and symptom management in patients with primary brain tumors and their loved ones will be discussed.

1.2 FREQUENTLY USED CONCEPTS IN THIS DISSERTATION

Brain tumors

Primary malignant brain tumors originate from the brain tissue itself. The most common primary malignant brain tumors are gliomas, with an incidence of 5.9 per 100,000 individuals.[1] This means that in the Netherlands, approximately 1000 individuals are confronted with this diagnosis annually.

Treatment decisions and prognosis are primarily based on the malignancy grade of the tumor. Patients diagnosed with a World Health Organization (WHO) grade I glioma may be cured after surgical intervention. WHO grade II gliomas are generally slow-growing and have infiltrative properties. These tumors almost always recur after treatment and can eventually evolve into a higher grade glioma. Anaplastic gliomas (WHO grade III) and glioblastomas (WHO grade IV) are generally rapidly progressive tumors and are typically associated with a poor prognosis.[2] Despite efforts in improving the treatment of gliomas, the median survival of patients suffering from a low-grade glioma is 5-15 years,[3] while patients with a grade III tumor have a median survival of 2-3 years.[4, 5] For patients with grade IV tumors, the median survival does not exceed 12-14 months.[6]

The treatment usually consists of a combination of surgery, radiotherapy and chemotherapy. In making treatment decisions, any benefit from these treatment modalities should be weighed against the expected HRQOL and symptom burden of patients.

Symptoms and problems

As a result of the diagnosis and prognosis, glioma patients can experience psychological distress. In addition, gliomas often give rise to a variety of neurological and cognitive symptoms. Depending on the location of the tumor and the side-effects of treatment, patients can have function loss as a result of paresis or paralysis, other motor dysfunction, problems with speech, sensory loss, and visual-perceptual deficits.[7] Cognitive deficits such as problems with memory or concentration are present in a large number of glioma patients,[8, 9] but more specific (focal) cognitive disturbances may also occur. In addition, fatigue,[10-12] depression[13] and changes in personality and behavior[14] are frequently reported. These symptoms can affect the lives of both patients and their significant others to a great extent, influencing the quality of both their lives.

Informal caregivers

Throughout the disease trajectory, the symptoms and problems described above may cause patients to rely more on their immediate environment for care and support. Consequently, spouses, family members or close friends often have to take on a new role as the primary informal caregiver, providing daily emotional and/or physical support. This caregiving role may invoke positive sentiments, such as a feeling of privilege or satisfaction, but it can also cause substantial burden and stress.[15] In the literature, the nomenclature used to describe these caregivers varies from 'caregiver', to 'informal caregiver', 'family caregiver' or 'neuro-oncology caregiver'. In this dissertation, we will use 'informal caregiver' to clearly distinguish between professional caregivers (e.g. treating physicians, nurses) and those performing their

caregiving activities without financial compensation. In addition, if we did not explicitly select participating spouses, family members or close friends based on their caregiving activities, the term 'significant others' will be used to describe the patients' loved ones.

1.2 Health-related quality of life

Quality of life is a multi-dimensional concept that is by definition self-reported, and therefore subjective in nature. In fact, its very definition is subject of discussion, although the WHO has made efforts to provide a fairly univocal description. The WHO defines quality of life as 'a person's perception of their physical, cognitive, and affective state, as well as their perception of their interpersonal relationships and social roles'.[16] Here, a distinction has to be made between quality of life and health-related quality of life (HRQOL), the latter being related to the impact of health or illness specifically. However, these concepts are often used interchangeably in the literature, which can complicate interpretation. Throughout this dissertation, we will refer to HRQOL consistently as we use instruments designed to measure HRQOL. Instruments assessing HRQOL can be divided into generic or disease-specific instruments. The generic instruments are highly useful to compare HRQOL across different study populations, whereas disease-specific instruments include items assessing symptoms and concerns that are characteristic of certain diagnostic groups.[17] For the brain tumor patient population, valid and reliable instruments assessing HRQOL are readily available.[e.g. 18-23] In clinical trials aimed at improving survival of glioma patients, there is a growing trend towards the measurement and preservation of HRQOL as an important outcome,[24, 25] with the benefits of any form of tumor directed treatment being weighed against the possible harm to patients' wellbeing.

1.3 AIMS AND OUTLINE OF THIS DISSERTATION

The general aim of this dissertation is to work towards an improvement in HRQOL for both glioma patients and their informal caregivers. First, a review is presented to obtain an overview of the impact of symptoms of fatigue, cognitive deficits, depression and changes in personality and behavior on the everyday lives of patients and their significant others in **chapter 1.4.** Here, methods to improve supportive care provision in clinical practice are first introduced.

In the following chapters, the various aspects of HRQOL in patients (**Section 2 – chapters 2.1 to 2.4**) and their significant others (**Section 3 – chapters 3.1 and 3.2**) are illustrated and discussed.

Section 2: Towards improving health-related quality of life in glioma patients

The specific research questions addressed in this dissertation, focusing on patients are: 1) Are cognitive functioning and HRQOL associated?; 2) Is HRQOL compromised in patients with long-term stable disease?; 3) Can interventions reduce symptom burden and improve HRQOL?

Through observational and intervention studies, **Section 2** focuses on tumor and treatment-related symptoms and HRQOL of glioma patients. After the diagnosis and initial treatment, most patients aim at participating in social and vocational activities to their best abilities. This effort may be hindered by the disease-specific symptoms that patients experience which can persist throughout periods of stable disease and may negatively affect their HRQOL.

The associations between cognitive functioning and HRQOL in low-grade glioma patients with stable disease are investigated (**chapter 2.1**), as well as the possible change in HRQOL in stable, long-term survivors of a low-grade glioma over time (**chapter 2.2**). In **chapter 2.3**, the effects of modafinil on brain tumor patients' symptoms of fatigue, cognitive deficits, and mood, as investigated in a randomized placebo-controlled trial are described. Efforts in reducing symptom burden are still ongoing, and the design of a randomized controlled trial to reduce depressive symptoms and improve HRQOL in glioma patients through an online problem-solving therapy is described in **chapter 2.4**.

Section 3: Towards improving health-related quality of life in informal caregivers of glioma patients

The specific research questions addressed in this dissertation, focusing on significant others are: 1) Is there HRQOL compromise in significant others of glioma patients?; and 2) Can a psychological intervention be helpful in improving informal caregivers' HRQOL?

Section 3 focuses on HRQOL issues in informal caregivers of glioma patients. As a result of the burden of caregiving, many informal caregivers experience psychological distress, which can contribute to a compromised HRQOL.

In a cross-sectional study, HRQOL of significant others of glioma patients is compared to HRQOL of significant others of patients with other malignancies that do not involve the central nervous system, but are comparable in terms of prognosis and the impact of the disease on daily life (non-small cell lung cancer and hematological malignancies; **chapter 3.1**).

Subsequently, in order to improve HRQOL and feelings of mastery (i.e. the combined effects of the informal caregiver's self-perception and actual ability to successfully perform the activities of providing care), a psychological intervention was developed. The effectiveness of this intervention on feelings of mastery and HRQOL in informal caregivers of glioma patients is tested in a randomized controlled trial (**chapter 3.2**).

1.3 Section 4: Summary, general discussion and conclusions

In **Section 4**, a general summary is provided (**chapter 4.1**), followed by a discussion on the main findings of this dissertation (**chapter 4.2**). In **chapter 4.3** the methodological limitations are discussed. Finally, recommendations for clinical practice and future research are provided (**chapter 4.4**).

Chapter 1.4

Symptom management and quality of life in glioma patients

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PRACTICE POINTS

- Fatigue is considered one of the most debilitating symptoms after a glioma and is present in a large proportion of patients.
- Cognitive deficits are common in glioma patients and can hinder personal and professional life.
- Clinical levels of depression occur in many brain tumor patients in the six months following diagnosis.
- Changes in personality and behavior are often present and can heavily influence spousal relationships.
- These symptoms impact upon quality of life of patients and their partners.
- Relatively few intervention studies have been performed for symptom management and psychosocial care in glioma patients.
- In clinical practice, a supportive care strategy combining screening followed by adequate referral to supportive care professionals could alleviate disease burden in both patients and their partners.

SUMMARY

Symptoms of fatigue, cognitive deficits, depression and changes in personality and behavior are frequently reported in patients with glioma. These symptoms have a large impact on the everyday life of patients and their partners and can contribute to a decrease in quality of life. While guidelines are available for managing most of these symptoms, these guidelines are often not suitable for the brain tumor patient population, as this population has very specific problems and needs. Obtaining more evidence on the effectiveness of existing and new interventions targeting fatigue, cognitive deficits, depression, and changes in personality and behavior in this population is advised. Screening combined with adequate referral to supportive care professionals has the potential to decrease the disease burden of glioma patients and their partners.

INTRODUCTION

Gliomas are relatively rare, with an incidence of only six per 100,000,[26] but the diagnosis and treatment have an immense impact on the lives of patients and their partners. Patients and their families find themselves not only confronted with the diagnosis of a life-threatening malignancy, but the disease burden is also enhanced by a variety of neurological and cognitive symptoms.[27] Headaches are very common,[28-30] as well as focal neurological symptoms, such as paresis, visual-perceptual deficits, sensory loss, and seizures.[7] Fatigue, cognitive deficits, depression, and changes in personality and behavior are equally common and perhaps form an even larger threat to the daily lives of patients and their partners. Diminished levels of quality of life (QOL) in glioma patients compared with healthy controls as well as with non-CNS cancer control groups have been reported on consistently in the literature.[9, 31, 32] The QOL of partners of glioma patients has also been shown to be worse than that of partners of non-CNS malignancy controls, especially in partners of patients with a recently diagnosed high-grade brain tumor.[33]

With most gliomas currently being incurable despite ongoing efforts to improve treatment, preserving QOL is very important not only for the individual patient but also as a measure of prolonged wellbeing in clinical trials aimed at improving survival.[25] The present review will focus on fatigue, cognitive deficits, depression and changes in personality and behavior, as management of these symptoms could potentially alleviate disease burden and improve the QOL of both patient and partner.[34]

FATIGUE

Fatigue is defined as 'a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion that is not proportional to recent activity and interferes with usual functioning'.[35] This definition emphasizes the multimodal aspects of fatigue; it is both a physiological and a psychological concept, influenced by both social and cultural factors. While cancer-related fatigue is well documented,[36, 37] persisting symptoms of fatigue are also typical symptoms of neurological disease, including traumatic brain injury.[38] With gliomas often being malignant in nature, and causing injury to healthy brain tissue through infiltration and increased intracranial pressure as well as indirectly through treatment, glioma patients may be especially vulnerable when it comes to fatigue. In fact, fatigue is the most commonly reported symptom in high-grade glioma patients who participate in clinical trials[39] and is often thought to be the most debilitating symptom during the course of the disease. Estimates of the prevalence of fatigue in glioma patients vary, but approximately 40% to 80% of patients report severe symptoms of fatigue,[10-12, 40] underlining the immense significance of the problem.

Fatigue can be difficult to distinguish from depression. Biological factors such as elevated levels of cytokines, variations in melatonin production caused by neuroinflammation, and possibly alterations in perfusion and biochemical activity in the brain[41] have been postulated as influencing factors in fatigue in glioma patients. Other factors associated with increased levels fatigue in (brain) cancer populations include older age,[12] female sex, worse performance

status and tumor- and treatment-related factors (e.g. radiotherapy, tumor location, time since diagnosis, disease status, use of antiepileptics and corticosteroids).[10, 12, 38, 40, 42]

Although it is often not possible to determine its precise cause(s), fatigue is known to impact greatly on patients' lives. Following diagnosis and initial treatment, it can be nearly impossible to resume a normal life when suffering from severe symptoms of fatigue as return to work or participating in social activities may become infeasible. In a recently published review by Armstrong and Gilbert, an overview of the National Comprehensive Cancer Network (NCCN) guidelines for treatment of fatigue in the context of brain tumor patients is provided.[41] According to these guidelines, it is recommended to start with an evaluation of contributing and treatable factors in each moderately to severely fatigued patient individually. These factors can include pain, emotional distress, disturbed sleep pattern, nutritional deficits, or imbalance and comorbid conditions. When fatigue persists after treatment for these factors is started, general strategies to manage fatigue can be introduced, including self-monitoring of fatigue levels, energy conservation strategies (e.g. setting priorities, delegating tasks and adding structure to everyday life), and using distraction such as reading a book or socializing with others.

Specific nonpharmacological and pharmacological interventions can be offered to target fatigue. Nonpharmacological strategies include activity enhancement and physically based therapies, such as massage therapy, but also psychosocial interventions, nutrition consultation and cognitive behavioral therapy (CBT). Although potentially promising, Armstrong and Gilbert already point out that many of these types of interventions have not yet been proven to be effective in brain tumor patients.[41] Particularly for patients who suffer from paresis or weakness in the limbs, interventions aimed at activity enhancement may not be feasible, while for those suffering from cognitive deficits, CBT-based programs may not lead to adequate improvement in symptoms of fatigue. Evidence-based nonpharmacological interventions for glioma patients specifically should be developed to explore which interventions work best for glioma patients as a group and which may be most effective for certain subgroups of patients.

Pharmacological interventions include the use of antidepressants, hemopoietic growth factors, and psychostimulants such as methylphenidate or modafinil. There has only been some evidence pointing towards a beneficial effect on fatigue for psychostimulant use in glioma patients. However, the studies showing positive results using methylphenidate or modafinil were not placebo controlled.[43-45] When using a placebo-controlled design, prophylactic methylphenidate failed to show a beneficial effect on fatigue in brain tumor patients.[46] In a study from our own group, we found no beneficial effects of modafinil on fatigue when compared with placebo.[47] Furthermore, these studies seem to show the same difficulties in patient accrual, drop out rates and follow-up. In our own experience, glioma patients show a certain reluctance to try medication for fatigue and attrition is high owing to the experienced side-effects. We feel that since the side-effects that can be attributed to the use of psychostimulants (e.g. having a lower attention span and feeling nervous, fidgety, or depressed) can also be interpreted as early signs of disease progression, development of pharmacological interventions for management of fatigue in glioma patients should be used with appropriate caution.

Some research has been carried out on alternative ways to treat fatigue. Interventions based on yoga have been found to be effective in improving self-reported levels of fatigue in women with breast cancer.[48] Some studies have shown positive results on fatigue using acupuncture, but scientific evidence is required before these interventions can be integrated into clinical practice.[49]

The NCCN guidelines also state that fatigue should be monitored, documented and treated at all stages of disease and that it is best treated by interdisciplinary teams. Furthermore, medical care contracts should include reimbursement for the management of fatigue, and disability insurance should also cover fatigue. While the guidelines are a great help in improving patient care, at present it is not always possible to abide by these guidelines. Many institutions do not have the personal or financial resources to provide the care that fatigued glioma patients require. Moreover, whether or not supportive care is reimbursed by the patients' health insurance differs between and within countries.

COGNITIVE DEFICITS

Cognitive deficits, including dysfunction in the domains of information processing, attention, psychomotor speed, executive functioning, and verbal and working memory, occur frequently in glioma patients. Up to approximately 80% of brain tumor patients experience some degree of cognitive deficits,[7] although estimates of the prevalence of these deficits vary owing to differences in the patient populations studied, the neuropsychological tests administered, or the normative data and cut-off scores used.[50] However, it is clear that the majority of glioma patients experience deterioration in a broad array of cognitive domains.[9, 51]

Cognitive deficits may occur as a consequence of the brain tumor and its treatment (e.g., surgery, radiotherapy, chemotherapy or use of corticosteroids), but epilepsy and use of antiepileptics are also known to affect cognitive functioning.[52] In addition, psychological distress and the premorbid level of cognitive functioning can contribute to the level of deficits a patient exhibits.[52] In glioma patients, worse cognitive functioning has been associated with disease progression and poorer survival.[53-57] However, relatively little is known about the impact of cognitive deficits on the everyday life of patients. With cognitive decline, maintaining functional independence becomes more difficult. Gehring *et al*. already point out that cognitive deficits may be especially burdensome for glioma patients with a more favorable prognosis, as these patients are confronted with the deterioration in functioning when they try to resume their personal and professional life after treatment.[50] Indeed, in long-term survivors even subtle cognitive deficits might hamper patients' autonomy and professional life.[58] Treating cognitive deficits could, therefore, potentially improve patients' QOL.

Efforts in maintaining or improving cognitive functioning consist of both pharmacological and nonpharmacological strategies. Nonpharmacological treatment usually includes restructuring of the environment to aid patients in relying less on their impaired functions, providing advise on using external aids and technology, teaching strategies to cope with their cognitive problems, and retraining specific cognitive skills.[50] Psychoeducation can also be very valuable to both patients and partners. At present, glioma patients can be referred to a neuropsychologist or rehabilitation clinic to receive cognitive rehabilitation. Compared with

patients with traumatic brain injury, brain tumor patients' deficits develop more gradually over time and are often less severe,[59] but they can achieve similar functional gains from participation in a neurorehabilitation program.[60] Currently, the rehabilitation protocols generally used are not specifically designed for the glioma patient population, which gives rise to several problems. Often consisting of several weeks of training, multiple hours a day, these protocols may be too demanding in terms of time and energy required, especially for those with high-grade tumors who are still on active treatment. In addition, although individual programs may be adapted during different stages of the disease, the protocolized programs often focus on improving functioning, while maintaining independent functioning throughout the progressive disease trajectory may be a more realistic goal for a subset of glioma patients.

In a meta-analysis of cognitive rehabilitation studies, the authors conclude that there is still too little evidence for the effectiveness of cognitive rehabilitation strategies in adults with brain tumors in order to make recommendations.[61] Nevertheless, several interventions that show beneficial effects on cognitive functioning have been reported on in glioma patients, providing some support for its effectiveness.[62-64] However, these studies report on rather small groups (less than 20 patients), and all but one[63] did not include a control condition, limiting the conclusions that can be drawn from these reports. To date, one large randomized controlled trial has been conducted in glioma patients, with an intervention consisting of cognitive retraining and compensatory strategies.[65] This study shows promising results, with improved attention and verbal memory and less mental fatigue after six months compared with a care-as-usual group. However, this program consists of six weekly home visits of two hours each with a neuropsychologist plus homework assignments, making it very time consuming for both patients and healthcare professionals. This may limit its feasibility in clinical practice, especially in large countries faced with great distances between the clinic and the patients' homes. Internet-based neuropsychological treatment may potentially form a solution, providing that the patients' cognitive deficits do not hinder them in their use of digital equipment. Alternatively, interventions based on physical exercise show promising results on cognitive functioning and neuroplasticity[66, 67] and deserve further investigation in glioma patients who are not bothered by physical disabilities as a result of the disease.

Pharmacological treatments have also been investigated in brain tumor patients, including methylphenidate,[43, 46] modafinil,[43, 47] memantine,[68] and donepezil.[69] Trials on the effects of armodafinil and liothyronine on cognitive functioning have also been reported on.[50] Many of these studies report difficulties in patient accrual and high drop out rates, and the beneficial effects on cognition were often modest. This mirrors the effects of pharmacological treatment for symptoms of fatigue discussed above, hence we recommend that for treatment of cognitive deficits, attention should perhaps be more focused towards nonpharmacological alternatives.

DEPRESSION

Feelings of distress or depression are common and understandable following a diagnosis of a serious illness. The loss of one's health leads to a process of grief, traditionally described by Bowlby and Parkes *et al*. as going through stages of disbelief, yearning, anger, depression and

finally acceptance.[70, 71] However, when an individual does not reach the acceptance stage but is instead struggling with feelings of depression for a prolonged time, major depressive disorder (MDD) can occur. In the Diagnostic and Statistical Manual of Mental Disorders IV text revision (DSM-IV-TR)[72], MDD is defined as the presence of at least five of the following symptoms for a minimal duration of two weeks: depressed mood; diminished interest in activities; significant weight loss or gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue; feelings of worthlessness or guilt; diminished ability to think or concentrate; or recurrent thoughts of death. At least one of the symptoms should be either a depressed mood or loss of interest or pleasure in order for MDD to be diagnosed.

Diagnosing MDD in glioma patients is difficult because signs of depression can often be explained by direct or indirect consequences of the tumor or its treatment.[73] For example, use of certain antiepileptic drugs is known to cause mood changes.[74] To physicians, a patient's depressive feelings and the expression of a grave outlook on the future may seem a normal reaction to a diagnosis of glioma and the treatment that follows. Mood problems may be interpreted as 'understandable, given the situation' and the treating physician may find it difficult to communicate about these symptoms. [75] In that case, MDD is less likely to be recognized and treated. This leads to an underdiagnosis of depression in cancer patients.[76] It is clear that MDD forms a serious problem in glioma patients with approximately 15 to 20% of the patient population becoming clinically depressed up to eight months following diagnosis.[13, 77] Furthermore, longitudinal data suggests that the proportion of depressed patients continues to increase up to one year after surgery.[78] To compare, the one year prevalence of depression in the general population is 6.6%.[79] There are even indications that glioma patients are at increased risk for developing MDD compared with other cancer patient populations.[80, 81]

Depression or distress has been associated with worse physical and cognitive function in glioma patients, and there is some evidence that tumor volume may be influential.[13] No consistent evidence has been found for the contribution of demographic variables (e.g., gender, age or marital status), or most tumor- and treatment-related factors (e.g., tumor type and histological grade, tumor location, radiotherapy or corticosteroids).[13, 78] The lack of evidence for some of these factors, which are well-known for influencing mood disorders in other populations, could be, in part, caused by the influence of the disease phase. In a recently published study, Acquave *et al*. examined predictors of mood disturbance in patients with brain tumors in several different phases of the disease.[82] In the newly diagnosed patients, mood disturbance was associated with not being married and not using corticosteroids. In patients receiving treatment, mood issues were related with a low income, the use of other medications and having experienced tumor recurrence more than once. In patients who were not on active treatment, women, patients with a lower income and those using anti-depressants were more prone to mood disturbance.[82]

Depression in glioma patients deserves more attention, as it is potentially treatable and successful treatment could significantly alleviate disease burden of patients and their partners. Moreover, the missed diagnoses and undertreatment of depression have economic ramifications,[83] particularly in terms of increasing healthcare costs. At present, the standard of care for the treatment of moderate to severe depression in individuals with a chronic physical condition is

the combination of antidepressants and high intensity psychological treatment, such as CBT or interpersonal therapy.[84, 85] However, these treatment options encounter various problems in the glioma patient population. Gliomas are invasive tumors that cause harm to healthy brain tissue through infiltration and increased intracranial pressure, as well as through anti-tumor treatment, such as radiation therapy. Therefore, it remains to be seen if antidepressants and psychotherapy, the latter often encompassing some form of CBT that requires adequate cognitive functioning, are as effective in these patients as they are in other populations. In addition, glioma patients often use many other medications concurrently, which increases the risk for adverse drug interactions, for example, a lower threshold for epileptic seizures.[86] Although it is now generally believed that depression and epilepsy share risk factors and that prescription of newer antidepressants does not evoke more seizures,[87-89] physicians still seem reluctant to prescribe antidepressants to glioma patients. One study indicated that six months after surgery, only 60% of patients in whom the treating physician recognized depression, received antidepressants.[90]

To summarize, research in this area is so limited that there is at present no evidence from randomized controlled trials for the efficacy of antidepressants or psychotherapy in glioma patients.[91] While stressing the need for investigating antidepressant use in the glioma patient population, we note that the previously described difficulties with pharmacological treatment for fatigue and cognitive functioning could also play a role in pharmacologic treatment for depression. Therefore, the potential effectiveness of psychological interventions in glioma patients merits attention. As CBT is often part of first-line treatment, obtaining evidence for its efficacy in the glioma population would be invaluable. Presently, we are conducting a randomized controlled trial to evaluate the effects of an internet-based guided self-help course on depressive symptoms in glioma patients. Other interventions that are already evidence-based in other patient populations include problem-solving therapy,[92] acceptance and commitment therapy,[93] and mindfulness.[94] When taking into account the cognitive deficits that are common in glioma patients, and where possible adapting existing effective interventions to their needs, much progress in the treatment of depressive symptoms and distress can be made.

CHANGES IN PERSONALITY AND BEHAVIOR

Resulting both from the tumor and its treatment, damage to various brain structures can lead to changes in personality and behavior, which are strongly interlinked. The study of personality has a very long history in psychology and it is an extremely broad concept. In general personality is thought to encompass an individual's behavior towards his or her social environment in different situations[95] – meaning all behavior requiring an interaction. While various studies suggest that changes in personality and behavior are certainly not uncommon in glioma patients,[14, 96-98] including symptoms such as anger, loss of emotional control, indifference and maladaptive behaviors,[99] it is not possible to make an estimation of the prevalence of these problems as very little quantitative research has been reported on in this area. Damage to the prefrontal cortex, in particular the orbitofrontal cortex, has long been associated with increased rigidity in thinking and apathy, as well as impairment in monitoring one's personal behavior.[100, 101] Damage in this

region would, therefore, be expected to be associated with an increased incidence in problems with personality and behavior, a notion that is supported by a study showing that behavioral problems appear to be most evident in patients with frontal lobe tumors.[102] Moreover, although uncommon, drug-induced behavioral problems such as steroid psychosis have also been reported on.[103] However, these problems cannot solely be attributed to the physical aspects of the disease and its treatment, as psychological problems may also add greatly to behavioral problems. Despite its unclear etiology, it is clear that patients are affected by these changes, as these can cause disruption of family life and social relationships both in informal and formal situations. In fact, for partners, these changes are often the most debilitating consequences of the disease.[98] When the patient exhibits a lack of insight in these changes, the distress in partners and others who are closely involved increases.[104] Indeed, awareness, recognition and communication are factors influencing whether couples share certain perceptions or drift apart.[105] Although divorce rates in couples where one partner is diagnosed with a glioma do not differ from divorce rates in couples dealing with other types of cancer, Glantz *et al*. observed a trend towards increased separation in patients with frontal lobe tumors.[106] This suggests a relationship between behavioral changes and increased divorce rates. Separation, in turn, is negatively associated with health outcomes of the patient, such as hospitalization.[106]

As behavioral problems are often very difficult to detect in clinical neuro-oncological practice, but can affect the lives of patients and their partners in a very profound way, these issues form a special cause for concern. With partners most often being the ones requiring help in dealing with the behavioral problems of the patients, referral to psychological help becomes more difficult. After all, during routine hospital visits the emphasis is usually on the patient's functioning and not on the partner's troubles. A series of qualitative interviews in bereaved informal caregivers of glioma patients learned that healthcare professionals could potentially decrease the couples' disease burden by helping in identifying competing demands, providing information on how to use support systems to divide care tasks and by encouraging caregivers to ask for help. In addition, healthcare professionals could provide information on managing cognitive and behavioral problems at home.[107] However, there is no optimal format for the provision of this kind of support. Zwinkels states that clinical nurse specialists in particular should engage in open and honest conversation with both patient and spouse when it comes to behavioral changes to help couples in dealing with these symptoms.[108] Although this approach would be favorable, as nurses have a thorough knowledge of what it means to live with a brain tumor, it is often not feasible to reach every patient in this comprehensive manner in clinical practice due to restraints in time and costs.

If referral is successful, patients as well as their partners can be aided by psychosocial support delivered by institutions specialized in oncological populations. Their treatments focus on dealing with the diagnosis, enduring treatment, and on existential issues for both patient and partner.[109] Individual psychological guidance or support groups can be offered. Dyads in the brain tumor setting require help not only with these oncological issues but also with neurological issues, which at present are often not addressed sufficiently in protocolled treatments. In addition, there is still little evidence of the efficacy of the psycho-oncological interventions that are specifically available in the glioma patient population.

Our own research group has evaluated the effects of a psychological intervention on the wellbeing of spouses of high-grade glioma patients.[110] While providing coping strategies, certain treatment sessions focused on dealing with changes in personality and behavior in the patient. The outcome was encouraging but effects were modest, with partners feeling better capable of handling the disease situation after intervention compared with a care as usual control group. The modest benefit in relation to the large investment of time suggests that other, potentially more effective ways of delivering support could be investigated. When doing so, much can be learned from previous studies performed in other patient populations that are known to struggle with similar difficulties. For example, promoting efficient coping strategies in a different format, as has been demonstrated in the traumatic brain injury population,[111] could prove useful. On a more general note, psychosocial interventions for dementia patients and their partners show that it is highly important to tailor the intervention provided to the specific situation and needs of the dyad in question.[112] With the emergence of e-health, cost-effective interventions requiring minimal guidance of supportive care professionals delivered through the internet or through telephone contact might be a viable alternative, especially for partners not hindered by cognitive or neurological deficits.

SCREENING AND MONITORING SYMPTOMS

Using patient-reported outcomes as screening instruments has been identified as a possible solution in meeting the needs of glioma patients and their partners, when taking into account prevalent neurological symptoms such as cognitive deficits. Screening can help detect a problem, but monitoring symptoms and needs over time paired with some form of feedback to the patient and partner can provide even more insight.[113] To our knowledge, there are no publications on monitoring symptoms in this manner in glioma patients or their partners. There has been a number of studies published focusing on using screening instruments in brain tumor patients.[114-116] However, these projects were conducted in a research setting rather than in clinical practice and outcomes were used only to report on the prevalence of symptoms of distress or depression in a publication.

In routine clinical practice, two studies regarding screening for symptoms in brain tumor patients have been conducted. An Austrian research group conducted a study using routine computer-based screening of QOL, including symptom scales, in clinical practice.[117] The researchers concluded that screening QOL in this manner is feasible and that monitoring QOL profiles over time can lead to improvements in health care provision for patients. However, the publication only reports on implementation issues and feasibility, making it difficult to conclude if patients truly benefited from this screening. More recently, screening for distress and depression in clinical neurosurgical practice was also found to be feasible.[118] In this study, patients received information material with contact information of healthcare professionals or referral to a psychologist if they exceeded the cut-off scores on two screening instruments (the Distress Thermometer and the Hornheide Screening Instrument) and expressed a wish for therapy.

In all studies except for one,[118] results of screening were reported only to the physicians and not to the patients themselves. As physicians often have to cope with lack of time and

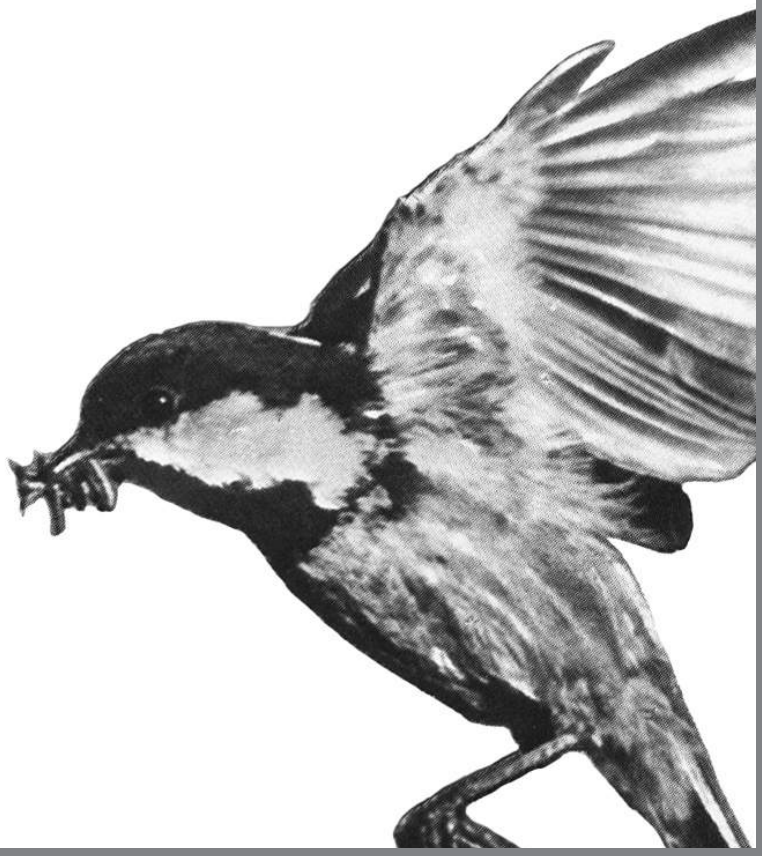
resources,[113] providing feedback to professionals only limits the benefits of screening to patients. In the general cancer patient population, only 20 to 30% of patients received psychosocial care after being screened positive for distress. Linking screening with adequate intervention or referral notably increases the success of screening implementation.[113]

CONCLUSIONS AND FUTURE PERSPECTIVE

While the presence of fatigue, cognitive deficits, altered mood, and changes in personality and behavior have been described in the literature, the treatment or management of these symptoms in routine clinical practice is less frequently addressed. Although many evidence-based pharmacological, behavioral and psychological treatments are available, these are often not developed for the glioma patient population, which poses several practical problems. Much research has been carried out in oncology populations, which are fundamentally different from the glioma patient population in that they do not experience the same prominent neurological and cognitive problems. However, interventions developed for other neurological populations, such as patients with traumatic brain injury, often focus on improving functioning and resuming daily life at a normal level, which unfortunately is unrealistic in a significant proportion of glioma patients. Therefore, interventions developed for patients with neurodegenerative or neuroinflammatory disorders, such as Parkinson's disease or multiple sclerosis, may form a viable alternative, if the fundamental differences between these populations are taken into account.

Meanwhile, in routine clinical practice the provision of, at present, the best available supportive care could be improved significantly. If screening for common problems such as fatigue, cognitive deficits, depression, and personality and behavioral changes, paired with adequate referral to health care professionals and providing feedback to physicians and patients alike could be realized, disease burden of glioma patients and their partners could be substantially alleviated.

Section 2:
Towards improving health-related quality of life in glioma patients



Chapter 2.1

The association between cognitive functioning and health-related quality of life in low-grade glioma patients

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ABSTRACT

Background: Glioma patients are not only confronted with the diagnosis and treatment of a brain tumor, but also with changes in cognitive and neurological functioning that can profoundly affect their daily lives. At present, little is known about the relation between cognitive functioning and health-related quality of life (HRQOL) during the disease trajectory. We studied this association in low-grade glioma (LGG) patients with stable disease at an average of six years after diagnosis.

Methods: Patients and healthy controls underwent neuropsychological testing and completed self-report measures of generic (MOS SF36) and disease-specific (EORTC BN20) HRQOL. Associations were determined with Pearson correlations, and corrections for multiple testing were made.

Results: We analyzed data gathered from 190 LGG patients. Performance in all cognitive domains was positively associated with physical health (SF36 Physical Component Summary). Executive functioning, processing speed, working memory, and information processing were positively associated with mental health (SF36 Mental Component Summary). We found negative associations between a wide range of cognitive domains and disease-specific HRQOL scales.

Conclusions: In stable LGG patients, poorer cognitive functioning is related to lower generic and disease-specific HRQOL. This confirms that cognitive assessment of LGG patients should not be done in isolation from assessment of its impact on HRQOL, both in clinical and in research settings.

INTRODUCTION

Gliomas are the most common primary malignant brain tumors, with an incidence of 5 to 7 per 100,000 persons.[26] A minority of gliomas can histologically be defined as low-grade (WHO grade I or II).

Patients diagnosed with low-grade glioma (LGG) have a more favorable prognosis than those diagnosed with more rapidly progressing tumors,[6, 119] however, the diagnosis and treatment can have a great impact on their lives. In addition, LGG patients find themselves confronted with focal neurological limitations, including loss of motor functioning, visual-perceptual deficits, sensory loss,[7] and epilepsy, which affects approximately 85% of LGG patients.[120] Moreover, cognitive impairment is often associated with LGGs,[51, 121] with patients experiencing deterioration in a broad array of cognitive domains (e.g. information processing, attention, psychomotor speed, and memory) when compared with control groups.[51, 121, 122]

While the prognostic value of cognitive functioning has been demonstrated for survival in glioma patients,[53-56] relatively little is known about its relation to patients' everyday life functioning. A small study among long-term survivors of malignant supratentorial brain tumors suggests that even subtle cognitive deficits might hamper a patient's autonomy and professional life.[58] In addition, indices of neurological functioning, such as epilepsy burden, have been shown to be related to both lower objective cognitive functioning and self-reported health-related quality of life (HRQOL) in LGG patients.[123] With the high incidence of cognitive and neurological deficits and poorer self-reported HRQOL in LGG patients,[31, 124] a relationship between cognitive functioning and generic and disease-specific HRQOL would be expected. However, to our knowledge, these associations have not yet been examined in depth. Previous studies that examined both cognitive functioning and HRQOL did not formulate these associations to be their primary study objective and consequently yielded only brief reports with little detail.[31, 123] However, it is of particular importance to know the clinical and functional significance of cognitive impairment for clinicians and patients. The clinical relevance of cognitive deficits cannot be fully appreciated without assessing their impact on the patient's quality of life. Apart from these possible clinical implications, a separate investigation into the nature and strength of the correlation between these factors is also merited because of the increased value being attributed to both cognitive functioning and HRQOL as secondary endpoints in glioma clinical trials.[24, 25]

MATERIALS AND METHODS

Participants

Data for this study were collected as part of a nationwide study of cognitive functioning and HRQOL of glioma patients. The methodology of these studies has been described in detail elsewhere.[121] In short, LGG patients were diagnosed on average six years prior to data collection and were included in the study if they had: (1) been diagnosed with a histologically confirmed low-grade astrocytoma, oligodendroglioma, or oligoastrocytoma at least one year prior to study entry; (2) no clinical signs of tumor recurrence for at least 1 year after diagnosis and primary treatment; (3) no radiological

signs of recurrence within 3 months before the first assessments were performed, (4) no current treatment with corticosteroids; and (5) basic proficiency in the Dutch language.

In addition, we included data from two samples of healthy controls. Specifically, for comparison on cognitive performance, we employed a reference sample from the Maastricht Aging Study,[125] a large cross-sectional study on the biological and psychological determinants of cognitive aging. Reference data for the HRQOL assessments were selected from a national study aimed at constructing a Dutch version of the Short-Form Health Survey.[19] All healthy controls were matched to the patient group for age, sex, and educational level.

Procedure

Patients were asked to provide information about their sociodemographic background via a structured interview. Clinical data were obtained from the medical records. Patients completed the self-report measures of generic (SF36) and disease specific (BN20) HRQOL and the neuropsychological tests either at home or at their treating hospital. Neuropsychological assessments were performed by a trained test assistant who was supervised by a board certified neuropsychologist (M.K.). The institutional review boards of the participating centers approved the research protocol and all participants provided written, informed consent.

Outcome measures

Cognitive performance was assessed using an extensive battery of standardized neuropsychological tests, described in detail in Table 1.[126-131] Tests included measures of executive functioning (categoric word fluency task[126], concept shifting task[130]), processing speed (concept shifting task[130], letter digit substitution test[129]), verbal memory (visual verbal learning test[128]), working memory (memory scanning test[131]), information processing (letter digit substitution test[129]), and attention (Stroop color word test[127]).

Self-reported HRQOL was measured with the Dutch version of the 36-Item Short-Form Health Survey (SF36).[19] The SF36 yields two component summary scores, one for physical health (PCS) and one for mental health (MCS). The PCS and MCS employ norm-based scoring, with a mean of 50 and a standard deviation of 10. The Dutch version of the SF-36 is a valid and reliable instrument, yielding a mean coefficient alpha of 0.84 across scales.[19]

Disease-specific HRQOL was measured with the Dutch version of the EORTC brain cancer module (EORTC QLQ-BN20).[22] This module contains four multi-item scales (future uncertainty, visual disorders, motor dysfunctions, communication deficits) and seven single items assessing headaches, seizures, drowsiness, hair loss, itching, weakness in the legs, and difficulties with bladder control. Scores range from 0 to 100, with higher scores indicating more symptoms. The BN20 scales have high internal consistency reliability (alpha > 0.70) and show overall adequate psychometric properties.[22] Although the BN20 is often administered alongside the EORTC QLQ-C30, unfortunately, we have no data regarding this cancer-specific HRQOL questionnaire.

Table 1. Neuropsychological tests and corresponding cognitive domains.

Cognitive domain	Content
Executive functioning	**Categoric Word Fluency Task** [21] Measures executive functioning and semantic memory. Outcome variable: number of animals in 60 seconds
	Concept Shifting Test [25] Measures attention, visual search, mental processing speed and the ability to mentally control simultaneous stimulus patterns. Outcome variables: CST A, CST B, CST C.
Processing speed	**Concept Shifting Test** [25] Outcome variable: CST 0
	Letter Digit Substitution Test [24] Measures psychomotor speed that is relatively unaffected by a decline in intellectual ability. Outcome variable: LDST Delta (i.e. number of substitutions read and minus number of substitutions written.).
Verbal memory	**Visual Verbal Learning Test** [23] Examines verbal learning capacity and consolidation of verbal information into long term memory. Outcome variables: Trial 1, delayed recall, delayed recognition, difference between maximum score and trials 1, total score trial 1-5)
Working memory	**Memory Scanning Test** [26] Measures the speed and efficiency of memory retrieval processes. Outcome variables/ items to be stored in working memory: symbol '%', 1, 2, 3, and 4 digits, successively.
Information processing	**Letter Digit Substitution Test** [24] Outcome variables: number of substitutions read and written.
Attention	**Stroop Color-Word Test** [22] Examines information processing speed, selective attention and mental control. Outcome variables: Stroop card I, Stroop card II, Stroop card III.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for Social Science version 20.0 (SPSS). Standard scoring rules were used to convert the data from the questionnaires. The neuropsychological test scores were transformed into Z-scores using the mean and standard deviations (SDs) of the healthy controls, and six cognitive domains were created for the purpose of data reduction (Table 1). To calculate each domain, Z-scores of the outcome variables were summed up and divided by the number of variables per domain. Higher scores indicate better performance in all domains.

Sociodemographic characteristics, HRQOL and cognitive functioning of the LGG group and the control groups were compared using univariate analysis of variance (ANOVA) and the Chi square statistic. A two-sided *p*-value less than 0.05 was considered significant. To examine the associations between cognitive functioning and both generic (SF36 component summaries MCS and PCS) and disease-specific HRQOL (BN20 scales future uncertainty, visual disorders, motor dysfunctions, communication deficits, headaches, seizures, and drowsiness), Pearson correlations were calculated. To adjust for multiple testing, corrections were applied for the six

cognitive outcome measures. A two-sided p-value less than 0.0083 was required as evidence of statistical significance for all Pearson correlations shown.

RESULTS

Demographic characteristics

In total, 239 eligible LGG patients were invited for participation, of which 82% (*N*=195) were included in the study. The main reasons reported for declining participation were the perceived burden of participating and not wanting to be confronted with their disease history. In 5 cases, data were incomplete, leaving 190 LGG patients for the present analyses. No statistically significant differences between the patients and the healthy controls were found for age, gender, and educational level, indicating an adequate matching procedure (see Table 2). Most LGG patients were men (61.5%), and most received middle to high levels of education. The majority of patients were married or lived together with their partner (63.6%).

Cognitive functioning and HRQOL

LGG participants had lower scores than healthy controls on all cognitive domains that were assessed (p<0.001 for all domains except the verbal memory domain (p=0.009)), see Figure 1. Furthermore, we found lower self-reported mental health in LGG patients (MCS; *M*=46.09, *sd*=9.81) than in healthy controls (*M*=49.91, *sd*=9.92, p<0.001). No statistically significant differences were observed in physical health between LGG patients and healthy controls (PCS; *M*=49.92, *sd*=9.11 vs *M*=51.28, *sd*=7.86, p=0.119).

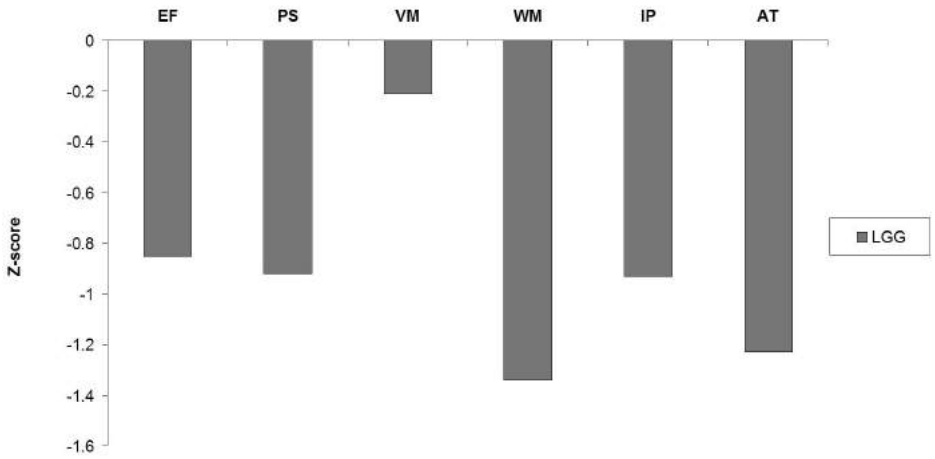

Figure 1. Cognitive performance of LGG patients relative to their healthy controls at the 0-line. Abbreviations: EF, executive functioning; PS, processing speed; VM, verbal memory; WM, working memory; IP, information processing; AT, attention.

Table 2. Demographic characteristics of LGG patients and healthy controls.

	LGG patients (*N*=195)	Healthy controls (cognition; *N*=195)	Healthy controls (HRQOL; *N*=195)	*P*-value
Age in years *M* (SD)	40.80 (11.62)	40.55 (12.01)	39.68 (2.32)	0.494
Gender				
Male	120 (61.5%)	121 (62.1%)	122 (62.6%)	0.978
Female	75 (38.5%)	74 (37.9%)	73 (37.7%)	
Educational level *N* (%)				0.285
Low	58 (29.7%)	55 (28.2%)	61 (31.3%)	
Middle	74 (37.9%)	76 (39.0%)	80 (41.0%)	
High	60 (30.8%)	64 (32.8%)	54 (27.7%)	
Other	3 (1.5%)	N.a.	N.a.	
Marital status *N* (%)				<0.001
Single	56 (28.7%)	27 (13.8%)	29 (14.9%)	
Married/living together	124 (63.6%)	161 (82.6%)	164 (84.1%)	
Divorced	6 (3.1%)	5 (2.6%)	0 (0%)	
Widow(er)	6 (3.1%)	2 (1.0%)	0 (0%)	
Tumor grade *N* (%)		N.a.	N.a.	N.a.
Grade I	21 (10.8%)			
Grade II	174 (89.2%)			
Grade III	0 (0%)			
Grade IV	0 (0%)			
Tumor location *N* (%)		N.a.	N.a.	N.a.
Frontal	47 (24.1%)			
Temporal	33 (16.9%)			
Parietal	19 (9.7%)			
Occipital	5 (2.6%)			
Mixed	89 (45.6%)			
Other	2 (1.0%)			
Tumor lateralisation *N* (%)*		N.a.	N.a.	N.a.
Left	85 (43.6%)			
Right	87 (44.6%)			
Bilateral	9 (4.6%)			
Time since diagnosis *M* (sd) (range)	Months 66.99 (43.96) 0 - 258	N.a.	N.a.	N.a.

* Information on tumor lateralisation was missing in 14 cases.

Associations between cognitive functioning and generic (SF36) and disease-specific (BN20) HRQOL

Cognitive functioning and generic (SF36) HRQOL

Better performance on all of the cognitive domains we assessed was associated with significantly better self-reported physical health (Table 3 PCS; all $p<0.001$). Furthermore, better performance on executive functioning, processing speed, working memory capacity and information processing speed was associated with better mental health (MCS; $r=0.270$, $r=0.318$, $r=0.250$, and $r=0.267$, respectively, all $p\leq0.001$).

Cognitive functioning and disease-specific (BN20) HRQOL

Regarding cognitive functioning and disease-specific HRQOL as assessed by the BN20, many negative correlations of weak to moderate strength were found (see Table 4). All cognitive domains were negatively correlated with the BN20 scales for uncertainty concerning the future, motor dysfunctions, and seizures. This indicates that worse cognitive performance is associated with more symptoms, as assessed by these scales.

Patients who had lower executive functioning, processing speed, working memory capacity, information processing speed, and attentional functioning were characterized by more symptoms of visual disorders. Furthermore, worse performance on information processing tasks and attention tasks was related to more difficulty with communication. Patients who had a lower information processing speed also reported more drowsiness.

DISCUSSION

It is often assumed, but has never actually been demonstrated, that cognitive functioning in brain tumor patients is related to their HRQOL. We tested this assumption in a large cohort of low-grade glioma patients with stable disease, at an average of six years after diagnosis. We found that many aspects of physical functioning, as measured with the SF36 and BN20, were associated with many, if not all, cognitive domains. Furthermore, poorer mental health (MCS)

Table 3. Associations between cognitive functioning and generic HRQOL in LGG patients.

	LGG (*N*=190)	
	Physical health (PCS)	**Mental health (MCS)**
Executive functioning	$r=0.427$, $p<0.001$*	$r=0.270$, $p<0.001$*
Processing speed	$r=0.455$, $p<0.001$*	$r=0.318$, $p<0.001$*
Verbal memory	$r=0.265$, $p<0.001$*	$r=0.184$, $p=0.012$
Working memory	$r=0.393$, $p<0.001$*	$r=0.250$, $p=0.001$*
Information processing	$r=0.436$, $p<0.001$*	$r=0.267$, $p<0.001$*
Attention	$r=0.336$, $p<0.001$*	$r=0.157$, $p=0.036$

*p<.00833

Table 4. Associations between cognitive functioning and disease-specific HRQOL in LGG patients (*N*=190).

	Future uncertainty	Visual disorder	Motor dysfynction	Communication deficit	Headaches	Seizures	Drowsiness
EF	*r*=-0.325 *p*<0.001*	*r*=-0.226 *p*=0.002*	*r*=-0.386 *p*<0.001*	*r*=-0.156N *p*=0.034	*r*=-0.106 *p*=0.152	*r*=-0.316 *p*<0.001*	*r*=-0.181 *p*=0.014
PS	*r*=-0.383 *p*<0.001*	*r*=-0.316 *p*<0.001*	*r*=-0.388 *p*<0.001*	*r*=-0.136 *p*=0.065	*r*=0.174 *p*=0.018	*r*=-0.254 *p*=0.001*	*r*=-0.276 *p*<0.001*
VM	*r*=-0.252 *p*=0.001*	*r*=-0.188 *p*=0.011	*r*=-0.271 *p*<0.001*	*r*=-0.187 *p*=0.011	*r*=-0.149 *p*=0.044	*r*=-0.244 *p*=0.001*	*r*=-0.161 *p*=0.029
WM	*r*=-0.287 *p*<0.001*	*r*=-0.295 *p*<0.001*	*r*=-0.426 *p*<0.001*	*r*=-0.225 *p*=0.002	*r*=-0.154 *p*=0.036	*r*=-0.315 *p*<0.001*	*r*=-0.186 *p*=0.011
IP	*r*=-0.345 *p*<0.001*	*r*=-0.325 *p*<0.001*	*r*=-0.405 *p*<0.001*	*r*=-0.255 *p*<0.001*	*r*=-0.175 *p*=0.018	*r*=-0.255 *p*=0.001*	*r*=-0.209 *p*=0.004
AT	*r*=-0.270 *p*<0.001*	*r*=-0.248 *p*=0.001*	*r*=-0.445 *p*<0.001*	*r*=-0.355 *p*<0.001*	*r*=-0.059 *p*=0.433	*r*=-0.311 *p*<0.001*	*r*=-0.113 *p*=0.130

*p<.00833
Abbreviations: EF, executive functioning; PS, processing speed; VM, verbal memory; WM, working memory; IP, information processing; AT, attention.

and more uncertainty concerning the future were related to lower cognitive functioning. These results suggest that LGG patients in a stable phase of their disease may be bothered by cognitive deficits that negatively affect their everyday life functioning. The present study outcomes concur with those of Giovagnoli and Boiardi,[58] who reported that asymptomatic, long-term glioma survivors may experience limitations in their autonomy, even with subtle cognitive deficits. In addition, severe cognitive dysfunction was related to worse levels of HRQOL in patients with a benign (WHO grade I) meningioma.[132]

This report, as well as our previous report on this LGG patient cohort,[121] demonstrates that cognitive deficits are present in LGG patients in a period of stable disease and that their performance on cognitive tests is statistically significantly worse than of healthy controls. However, the deficits found are, on a group level, relatively mild. In fact, the Z-scores on all domains tested do not exceed 1.5 SD below the mean of healthy controls (the threshold often used in the patient context to define clinically significant cognitive dysfunction). Memory deficits in particular seem less prominently present in our cohort than in other publications on glioma patients.[8, 133] One explanation for this particular difference could be the use of a different neuropsychological test. We tested verbal memory using visually presented stimuli, while other reports frequently use verbal auditory-presented stimuli. While still measuring the same construct (i.e., verbal memory), a bias in results based on this difference cannot be excluded.

In addition, the reduction found in mental health does not exceed a standard deviation below the mean and hence probably reflects only subtle compromise. Nevertheless, while cognitive deficits and compromise in HRQOL may be subtle in nature, the present report demonstrates the highly correlated relationship of cognitive functioning and both generic and disease-specific HRQOL. With most correlations being of moderate strength, it seems likely that LGG patients with stable disease, who resumed their daily activities, may be more aware of

subtle or more pronounced negative changes in their cognitive abilities. We suspect that the priorities of LGG patients may shift along with their view of the immediate and more distant future. However, these hypotheses cannot be confirmed by the present study due to its cross-sectional nature. Thus, additional longitudinal studies are needed.

Alternatively, in part, the associations found may be explained by the nature of the neuropsychological tests and the neurological disabilities of the patients. Visual and motor deficits in particular may contribute to poorer performance on certain cognitive tasks that for a great deal depend on these skills, such as tests assessing attentional functioning. Indeed, poor performance on timed tasks in these patients can be attributed, in large part, to visual and motor deficits.[9] Where possible, interventions to improve functioning in these areas may potentially contribute to better cognitive functioning as well as better HRQOL.

We only investigated the association between HRQOL and cognitive functioning in this study; it is likely that this association is confounded by other patient-related factors like fatigue, sleep quality, anxiety, depression, and instrumental activities of daily living (IADL), which have been reported to affect the daily lives of patients as well.[12, 13, 122, 134] Although it is not yet available as a validated instrument, a brain-tumor specific measure of IADL is currently being developed at our institution. Because this test includes adapted items based on IADL assessment in patients with dementia and focuses on their everyday functional impairment resulting from cognitive deficits, it could prove to be a highly relevant tool in the future in clinical practice and the research setting.

In conclusion, our results indicate that when cognitive functioning is worse, LGG patients who are in a stable phase of their disease experience worse physical and mental HRQOL. Furthermore, LGG patients who experience more cognitive deficits also report more issues with disease-specific HRQOL, which is most pronounced in the scales future uncertainty, motor dysfunction, visual disorders, and seizures. Future longitudinal studies should include measures of anxiety and depression, fatigue, IADL, demographic characteristics and clinical variables in order to assess which other factors have an effect on these associations. While beyond the scope of the present study, examining associations between cognitive functioning and subscales, rather than summary scales of generic HRQOL could provide additional information in future studies. Maintaining or even improving HRQOL by preventing long-term cognitive sequelae, or rehabilitation of cognitive deficits if prevention is not feasible, is an important goal in the treatment of glioma patients. It is important to understand the functional significance of cognitive impairments in the everyday lives of LGG patients. Cognitive assessment of patients with gliomas cannot – or rather, should not – be performed in isolation from assessment of its impact on psychosocial functioning and HRQOL.

Acknowledgments

This data has been previously presented at the 2013 Mid-Year Meeting of the International Neuropsychological Society, Amsterdam (the Netherlands), and at the 4th quadrennial meeting of the World Federation of Neuro-Oncology held in conjunction with the 18th scientific meeting of the Society for Neuro-Oncology, San Francisco (United States).

Chapter 2.2

Health-related quality of life in stable, long-term survivors of low-grade glioma

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ABSTRACT

Purpose: Patients with low-grade glioma (LGG) often experience long periods of stable disease, emphasizing the importance of maintaining good health-related quality of life (HRQOL). We assessed the changes in HRQOL in long-term survivors of WHO grade I or II astrocytoma, oligodendroglioma, or oligoastrocytoma with clinically and radiologically stable disease.

Patients and methods: Patients completed self-report measures of generic HRQOL (SF-36) and disease-specific HRQOL (EORTC QLQ-BN20). Assessments took place at midterm and long-term follow-up, on average six and 12 years after histological diagnosis and initial treatment, respectively. Comparisons between patients with LGG and individually matched healthy controls were made, change within the patients with LGG was calculated, as was minimal detectable change.

Results: Although no statistically significant differences between patients with LGG and healthy matched controls were found at midterm follow-up, patients with LGG had worse physical role functioning (p=0.004) and general health perceptions (p=0.004) than controls at long-term follow-up. Within patients with stable LGG (N=65), physical HRQOL (the SF-36 physical component summary and the physical functioning subscale) was significantly worse at long-term than at midterm follow-up (both p<0.001). Although 48% of patients improved or remained stable on all HRQOL scales, 38.5% of patients experienced only detectable decline on one or more scales.

Conclusion: Although HRQOL remains mostly preserved in the majority of patients with LGG, a subset of patients experience detectable decline on one or more HRQOL scales despite long-term stable disease. For this subgroup, further research is recommended to better aid patients in dealing with the consequences of a LGG.

INTRODUCTION

With an incidence of six per 100,000,[26] gliomas are the most common primary malignant brain tumors. Treatment decisions and prognosis are primarily based on the malignancy grade of the tumor. Although many low-grade gliomas (LGGs; WHO grade I or II) eventually evolve into more aggressive high-grade gliomas, LGGs have a relatively favorable prognosis.[119] Patients often experience extensive periods of stable disease.[119, 135] Therefore, especially in this patient population, maintaining good health-related quality of life (HRQOL) is important.

Although literature focusing on HRQOL in patients with LGG is relatively sparse, studies demonstrate HRQOL of these patients to be poorer than the HRQOL of healthy controls[136] and, surprisingly, sometimes also worse than the HRQOL of patients with high-grade gliomas.[137, 138] Before receiving the definite diagnosis,[139] as well as after tumor resection,[140] patients with LGG report mildly reduced HRQOL compared with normative controls. After this initial phase, limitations in HRQOL reported by patients with LGG are generally subtle in nature, if present at all.[140-143] However, during stable disease, patients' HRQOL may be different from that during active treatment, as priorities may shift and patients may have had more time to psychologically adapt to their diagnosis and prognosis. Contrary to what one might expect, affective disturbances were present in the majority of patients with stable LGG at three and a half years after diagnosis in a pilot study.[122] Compared with healthy controls, we found compromised HRQOL in a large cohort of patients with LGG on average six years after diagnosis.[31] Therefore, it seems likely that HRQOL of patients with LGG remains vulnerable throughout the period of stable disease.

To our knowledge, there are no reports on the HRQOL of patients with LGG with stable disease, extending six years after diagnosis. With preservation of HRQOL becoming ever more important as a measure of prolonged well-being in clinical trials aimed at improving survival,[25] we presently describe changes in HRQOL in a unique sample of patients with LGG who have been radiologically and clinically stable for, on average, 12 years. First, to evaluate the severity of a possible HRQOL compromise, we compare HRQOL of patients with LGG over the midterm (on average, six years after diagnosis) and long-term (on average, 12 years after diagnosis) with HRQOL of a matched control group of individuals from the general population. Then, comparing midterm and long-term follow-up within our sample of patients with LGG, we describe 1) statistically significant changes at the group level; and 2) minimal detectable intraindividual changes. Subsequently, we describe sociodemographic and treatment-related factors of the patients in whom change in HRQOL did or did not occur. Knowledge of the HRQOL of this group of LGG patients and a description of those in whom HRQOL declines may provide leads for preventive actions or recommendations for maintaining the HRQOL of patients with LGG over time.

PATIENTS AND METHODS

Participants

The data reported here were collected during our previous multi-center studies on HRQOL and cognitive functioning in patients with clinically and radiologically stable LGG at midterm

and long-term follow-up (a mean of six and 12 years after diagnosis, respectively). The study design and methods have been described in detail elsewhere.[31, 144] Briefly, for the midterm assessment, which took place, on average, six years after diagnosis, we included patients with a histologically confirmed WHO grade I or grade II astrocytoma, oligodendroglioma or oligoastrocytoma. Patients were diagnosed at least one year before study entry and had to have been clinically stable for at least one year after primary treatment, as evaluated by the treating physician, as well as radiologically stable for at least three months before study entry, as judged by the local radiologist. Patients who received corticosteroids or who were not proficient in the Dutch language were excluded. For the long-term assessment, which took place, on average, six years after the midterm assessment, we traced all patients who had been clinically and radiologically stable since the midterm assessment, as evaluated by the treating physician and local radiologist. Patients who completed the long-term assessment were older at diagnosis (mean difference, 4.9 years) and had shorter disease duration (mean difference, 1.5 years), but were otherwise comparable to those lost to follow-up.[144]

Procedures

The outcome measures assessed at midterm and long-term follow-up were identical. Information on age, sex, and educational level was collected, and patients provided information about their background during a structured interview. Clinical data were obtained from their medical records. Participants completed the assessments either at home or at their treating hospital. The institutional review boards of the participating centers approved the research protocol, and all participants provided written informed consent.

Outcome measures

MOS Short-Form Health Survey (SF-36).[19, 145] The Dutch version of the SF-36 was used to assess generic HRQOL. With 36 items, the following eight multi-item scales with scores ranging from 0-100 were computed: 1) physical functioning; 2) physical role functioning; 3) emotional role functioning; 4) pain; 5) vitality; 6) social functioning; 7) mental health; and 8) general health perceptions. In addition, two higher order component scores were calculated, one for physical health (Physical Component Summary; PCS) and one for mental health (Mental Component Summary). Higher scores represent better levels of functioning. In a normative sample from the general population, PCS and MCS scores have a mean of 50, with a standard deviation (SD) of 10.

EORTC Brain Cancer Module (BN20).[22] This 20-item questionnaire assesses patients' disease-specific HRQOL. Multi-item scales that assess future uncertainty, visual disorders, motor dysfunctions and communication deficits were calculated. Seven single items were used to assess headaches, seizures, drowsiness, hair loss, itching skin, weakness in the legs, and difficulties with bladder control (range 1-4). Raw scores were converted linearly to scales ranging from 0-100, with higher scores indicating more symptoms.

Statistical analysis

Statistical analyses were carried out using SPSS version 20.0 for Windows (SPSS, Chicago, IL). Standard scoring rules were applied for the questionnaire data. With independent sample t-tests, we compared generic HRQOL of patients with LGG at midterm and long-term follow-up with HRQOL of a control group from the general population,[19] individually matched for age, sex and educational level. Wilcoxon signed rank tests were used to determine differences in generic and disease-specific HRQOL between the midterm and long-term follow-up assessments. $P<0.05$ was considered statistically significant, and all 10 scales of the SF-36 and 11 scales of the BN20 were adjusted for multiple testing using the false discovery rate technique.[146] Effect sizes were calculated as partial eta squared. Minimal detectable changes, defined as 1.96 * √2 * standard error of measurement (SEM),[147] were calculated for the multi-item scales. Test-retest reliability scores and SDs necessary to calculate the SEM were derived from other studies performed in comparable patient populations.[148-150]

Patients were divided into the following four groups: those who did not experience detectable change on any HRQOL scale, those who only experienced decline, those who only experienced improvement, and those who experienced both decline and improvement. Demographics (age at diagnosis, sex, educational level, and marital status) and clinical characteristics (time since diagnosis, tumor grade and type, surgery, radiotherapy, change in epilepsy, change in use of antiepileptics) of the four groups were described.

RESULTS

Demographics and clinical characteristics

In total, 67 patients participated in the long-term follow-up assessment. Of the 195 patients originally included at midterm follow-up,[31] 30% of patients were deceased (N=58), 23% had tumor recurrence or tumor treatment (N=45), 3% declined participation (N=6), and 10% could not be traced or had other reasons for nonparticipation (N=19). For the present analyses, only patients who participated in both the midterm and long-term follow-up were included. Furthermore, two patients were excluded due to incomplete HRQOL data, yielding a total sample of 65 patients.

On average, participants were 45 years old at long-term follow-up, see Table 1. The range of time since diagnosis was one to 16 years at midterm follow-up (M=6.6, SD=3.2) and six to 24 years at long-term follow-up (M=12.8, SD=3.5). Most participants (70.7%) were diagnosed with an astrocytoma. The majority of patients (78%) reported having a seizure in the year before assessment at midterm follow-up, but only 35.4% of patients reported a seizure in the year before the long-term follow-up assessment. Overall, epilepsy decreased in 43.1% of patients with LGG, whereas it remained stable in 56.9% of patients. The use of antiepileptic drugs (AEDs) did not differ much between the midterm and long-term follow-up assessments (55.4% vs. 44.6%, respectively). The majority of patients (81.5%) did not shift from using or not using AEDs. Seven patients (10.8%) used AEDs at the midterm but not at the long-term assessment, and four patients (6.2%) did not use AEDs at the midterm assessment, but did use them at the long-term assessment.

Table 1. Demographic and clinical characteristics of the participants.

	Participants (*N*= 65)
Time since diagnosis in years	
T1 range	1-16
T1 *M* (SD)	6.6 (3.2)
T2 range	6-24
T2 *M* (SD)	12.8 (3.5)
Age at diagnosis *M* (sd)	32.0 (13.6)
Range	8 – 62
Age at T2 in years *M* (SD)	44.5 (12.1)
Range	23-72
Sex *N* (%)	
Male	36 (55.4%)
Female	29 (44.6%)
Educational level *N* (%)	
Low	21 (32.3%)
Middle	22 (33.8%)
High	22 (33.8%)
Marital status *N* (%)	
Single	17 (26.2%)
Married or living together	38 (58.5%)
Divorced	7 (10.8%)
Widowed	3 (4.6%)
Tumor grade *N* (%)*	
WHO grade I	7 (10.8%)
WHO grade II	57 (87.7%)
Tumor type *N* (%)	
Astrocytoma	47 (72.3%)
Oligodendroglioma	11 (16.9%)
Oligoastrocytoma	7 (10.7%)
Tumor location *N* (%)	
Frontal	5 (7.7%)
Temporal	15 (23.1%)
Parietal	7 (10.8%)
Occipital	5 (7.7%)
Mixed	25 (38.5%)
Other	6 (9.2%)
Unknown	2 (3.1%)
Tumor lateralization *N* (%)	
Left	36 (55%)
Right	23 (35.4%)
Middle	6 (9.2%)

Table 1. Continued

	Participants (*N*= 65)
Epilepsy in the last year (T1) *N* (%)	
Yes	51 (78%)
No	14 (22%)
Epilepsy in the last year (T2) N (%)*	
Yes	23 (35.4%)
No	41 (63.1%)
Antiepileptic drug use in the last year (T1)	
Yes	36 (55.4%)
No	29 (44.6%)
Antiepileptic drug use in the last year (T2)*	
Yes	32 (49%)
No	32 (49%)
Neurosurgical intervention *N* (%)	
Resection	41 (63.1%)
Biopsy	19 (29.2%)
Unknown	5 (7.7%)
Radiotherapy (ever) *N* (%)	
Yes	32 (49%)
No	33 (51%)

T1: midterm follow-up; T2: long-term follow-up; *data from 1 participant missing

Differences in HRQOL at midterm and long-term follow-up between patients with LGG and matched healthy controls

At long-term follow-up, patients with LGG, compared with healthy controls, had lower physical role functioning (*M*=57.7, SD=42.6 vs. *M*=78.8, SD=37.1, *p*=0.004) and general health perceptions (*M*=63.8, SD=23.3 vs. *M*=74.5, SD=18.3, *p*=0.004). No other statistically significant differences were observed between healthy controls and patients with LGG, at midterm or long-term follow-up (data not shown).

Statistically significant change in HRQOL

Analyses at the group level revealed that physical health in patients with LGG, as assessed with the SF-36 PCS score, was significantly worse at the long-term assessment compared with the midterm assessment ($p<0.001$, partial $\eta^2 = 0.107$; see Table 2). Similarly, the score on the physical functioning subscale was significantly worse at long-term follow-up ($p<0.001$, partial $\eta^2 = 0.044$). No other statistically significant differences were observed between the midterm and long-term assessments for either generic or disease-specific HRQOL (see Figure 1).

Table 2. Means and SDs for generic HRQOL scores at midterm and long-term follow-up.

	Mid-term follow-up (*N*=65)	Long-term follow-up (*N*=65)	*p*-value	Partial η^2
Component scales				
Physical Component Summary M (sd)	49.46 (8.88)	46.91 (11.45)	<0.001*	0.107
Range	25.26-63.42	15.87-63.50		
Mental Component Summary M (sd)	49.45 (8.57)	47.87 (10.90)		
Range	30.84-61.73	26.15-69.53	0.350	0.113
SF-36 subscales				
Physical functioning	86.79 (20.36)	77.88 (26.95)	<0.001*	0.044
Physical role functioning	68.36 (39.40)	58.06 (42.89)	0.120	0.022
Bodily pain	80.00 (22.83)	76.56 (25.31)	0.197	0.042
Social functioning	80.86 (20.77)	76.54 (23.54)	0.222	0.046
Mental health	74.14 (15.70)	70.28 (18.68)	0.154	0.060
Emotional role functioning	79.69 (31.77)	71.43 (36.35)	0.140	0.028
Vitality	61.88 (18.48)	59.31 (20.19)	0.395	0.052
General health perceptions	68.70 (19.18)	64.97 (22.65)	0.079	0.049

Abbreviations: HRQOL, health-related quality of life; SF-36, Short-form 36 Health Survey. *level of statistical significance as determined with the False Discovery Rate technique.

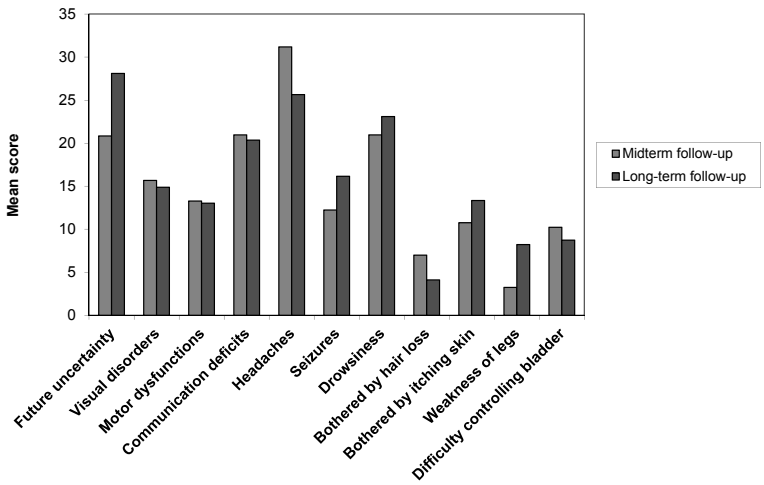

Figure 1. Disease-specific HRQOL at first (midterm) and second (long-term) assessment. Higher scores indicate more symptoms being present.

Minimal detectable change in health-related quality of life

In our cohort, 9.2% (*N*=6) of patients with LGG experienced detectable decline on the SF-36 PCS, whereas 3.1% of patients (*N*=2) had detectable improvement, see Table 3. On the SF-36

MCS, 12.3% (*N*=8) of patients experienced detectable decline, and 7.7% of patients (*N*=5) had detectable improvement. The majority of patients maintained a stable level of both physical (PCS) and mental (MCS) HRQOL, 87.7% (*N*=57) and 80% (*N*=50), respectively.

This pattern of results was similar on all other SF-36 scales and the BN20 multi-item scales. The majority of patients with LGG maintained a stable level of HRQOL (see Table 3), ranging from 63.1% of patients (*N*=41) on physical role functioning to 93.8% of patients (*N*=61) on general health perceptions and communication deficits. Detectable decline was present in a subgroup of patients, ranging from 3.1% of patients (*N*=2; for general health perceptions) to 23.1% of patients (*N*=15; physical role functioning). Detectable improvement was also found in some patients, ranging from 1.5% of patients (*N*=1; physical functioning, future uncertainty and communication deficits) to 13.8% of patients (*N*=9; physical role functioning).

In total, 21.5% of patients (*N*=14) did not experience detectable change on any of the scales assessed, 38.5% of patients (*N*=25) experienced only detectable decline on one or more scales, 26.2% of patients (*N*=17) experienced only detectable improvement on at least one scale, and 13.8% of patients (*N*=9) experienced both detectable decline and improvement. Table 4 lists the characteristics of patients in these four categories.

Table 3. Percentages of patients with LGG experiencing detectable change in HRQOL (multi-item scales only).

	LGG patients (*N*=65)
SF-36 Component scales	
Physical Component Summary* % (N)	
Decline (>13 points)	9.2% (6)
Stable	87.7% (57)
Improvement (>13 points)	3.1% (2)
Mental Component Summary % (N)	
Decline (>12.7 points)	12.3% (8)
Stable	80% (52)
Improvement (>12.7 points)	7.7% (5)
SF-36 subscales	
Physical functioning % (N)	
Decline (>28 points)	12.3% (8)
Stable	86.2% (56)
Improvement (>28 points)	1.5% (1)
Physical role functioning % (N)	
Decline (>45 points)	23.1% (15)
Stable	63.1% (41)
Improvement (>45 points)	13.8% (9)
Bodily pain % (N)	
Decline (>25 points)	15.4% (10)
Stable	75.4% (49)
Improvement (>25 points)	9.2% (6)

Table 3. Continued

	LGG patients (*N*=65)
Social functioning % (N)	
Decline (>29 points)	15.4% (10)
Stable	81.5% (53)
Improvement (>29 points)	3.1% (2)
Mental health % (N)	
Decline (>19 points)	18.5% (12)
Stable	72.3% (47)
Improvement (>19 points)	9.2% (6)
Emotional role functioning % (N)	
Decline (>45 points)	16.9% (11)
Stable	72.3% (47)
Improvement (>45 points)	10.8% (7)
Vitality % (N)	
Decline (>19 points)	12.3% (8)
Stable	73.8% (48)
Improvement (>19 points)	13.8% (9)
General health perceptions % (N)	
Decline (>28 points)	3.1% (2)
Stable	93.6% (61)
Improvement (>28 points)	3.1% (2)
BN20 multi-item scales	
Future uncertainty % (N)	
Decline (>36 points)	10.8% (7)
Stable	87.7% (57)
Improvement (>36 points)	1.5% (1)
Communication deficits % (N)	
Decline (>41 points)	4.6% (3)
Stable	93.8% (61)
Improvement (>41 points)	1.5% (1)
Motor dysfunction % (N)	
Decline (>28 points)	6.2% (4)
Stable	87.7% (57)
Improvement (>28 points)	6.2% (4)
Visual disorders % (N)	
Decline (>23 points)	9.2% (6)
Stable	84.6% (55)
Improvement (>23 points)	6.2% (4)

Table 4. Demographics and clinical characteristics of the patients in whom meaningful change was either present or absent.

	Patients with stable HRQOL (*N*=14)	Patients with declining HRQOL only (*N*=25)	Patients with improving HRQOL only (*N*=17)	Patients with both declining and improving HRQOL (*N*=9)
Time since diagnosis at T1 in years *M* (SD)	5.9 (3.9)	6.8 (3.4)	6.8 (2.5)	7.0 (3.6)
Age at diagnosis in years *M* (SD)	32.2 (12.9)	34.4 (13.1)	28.1 (14.4)	32.4 (15.3)
Gender (male) *N* (%)	8 (57.1%)	17 (68%)	7 (41.2%)	4 (44.4%)
Marital status *N* (%)				
Single	2 (14.3%)	4 (16%)	8 (47.1%)	3 (33.3%)
Married or living together	9 (64.3%)	16 (64%)	8 (47.1%)	5 (55.6%)
Divorced	2 (14.3%)	4 (16%)	0 (0%)	1 (11.1%)
Widowed	1 (7.1%)	1 (4%)	1 (5.9%)	0 (0%)
Tumor type *N* (%)				
Astrocytoma	11 (78.6%)	15 (60%)	15 (88.2%)	6 (66.7%)
Oligodendroglioma	2 (14.3%)	5 (20%)	2 (11.8%)	2 (22.2%)
Oligoastrocytoma	1 (7.1%)	5 (20%)	0 (0%)	1 (11.1%)
Tumor grade *N* (%)				
WHO grade I	2 (14.3%)	2 (8%)	2 (11.8%)	1 (11.1%)
WHO grade II	12 (85.7%)	23 (92%)	15 (88.2%)	8 (88.9%)
Change in epilepsy (yes/no) *N* (%)				
No change	10 (71.4%)	12 (48%)	10 (58.8%)	5 (55.6%)
Decrease in seizures	4 (28.6%)	13 (52%)	7 (41.2%)	4 (44.4%)
Change in AED use (yes/no) *N* (%)*				
No change	13 (92.9%)	20 (80%)	14 (82.4%)	6 (66.6%)
Decrease in AED use	0 (0%)	2 (8%)	2 (11.8%)	3 (33.3%)
Increase in AED use	1 (7.1%)	2 (8%)	1 (5.9%)	0 (0%)
Surgery (resection) N (%)	9 (64.3%)	16 (64%)	12 (70.6%)	4 (44.4%)
Radiotherapy (yes) N (%)	6 (42.9%)	14 (56%)	7 (41.2%)	5 (55.6%)

*data from 1 participant missing

DISCUSSION

This study is, to our knowledge, the first to examine HRQOL longitudinally in adult patients with LGG who have been stable for 12 years on average. In this prospective follow-up study, we found mild compromise in HRQOL, with patients with LGG scoring significantly lower on the subscales physical role functioning and general health perceptions compared with controls from the general population at long-term follow-up. In patients with LGG, we found a statistically significant decline in physical aspects of HRQOL. This is roughly reflected in the percentages of patients with detectable decline: 9-12% of patients experienced decline in these aspects of physical HRQOL. However, another 23% of patients experienced decline in

physical role functioning, while this is not reflected in a significant within group change. These seemingly discrepant results can reflect differences in scale score distributions and statistical methods. On the physical role functioning scale, there was greater score variability (23% decline, 14% improvement) than in the other physical scales mentioned above (9-12% decline, 2-3% improvement). A larger interindividual score range can make it more difficult to detect change at the group level – although this change may well be important to individual patients.

Conversely, the general health perceptions of patients with LGG did not appear to change over time, and we observed significant differences compared with healthy controls at long-term follow-up only. In patients with LGG, small, near-significant differences over time were observed at the group level. These observed differences are not likely to be clinically meaningful, but may nevertheless result in statistically significant differences with the healthy controls.

In general, our analysis of detectable change revealed that the majority of patients maintain a stable level of HRQOL, indicating that in our cohort of patients with stable LGG, HRQOL is not severely compromised. This is potentially reassuring news for patients with LGG, their families, and their clinicians. However, analyses at the individual level revealed that although HRQOL remained stable or improved in 48% of patients with LGG, decline on one or more scales was reported in 52% of patients – sometimes concurrently with improvement on a different scale. This and the fact that the different statistical approaches yield somewhat different results emphasize the complex nature of the concept of HRQOL, but our results also indicate that limitations in HRQOL in patients with LGG can be present throughout years of stable disease. This is consistent with results from other patient populations with (non-CNS) cancer, because symptoms including fatigue, pain, and depression can remain present for up to ten years after treatment in survivors of cancer.[151] Studies in patients with colorectal cancer yield similar results, describing mild limitations in HRQOL five years after treatment.[152] In this study, HRQOL compromise in patients with long-term stable LGG seems to be similarly subtle.

Another aim of our study was to describe the sociodemographic and treatment-related factors of patients in whom change in HRQOL did or did not occur. Although we could not formally compare the four subgroups due to a lack of statistical power, there is no clear indication that one or more characteristics are indicative of a more vulnerable HRQOL status within patients with stable LGG. The patient profile of those who are affected by decline in HRQOL appears similar to that of the whole cohort. This seems to contradict our previous cross-sectional report in which female gender and greater epilepsy burden were predictive of worse HRQOL.[31] However, the long-term follow-up assessment that we report on in this article was conducted six years later on average, which may make an important difference for patients' future perspective, life phase, and the experience of long-term sequelae of the LGG – the so-called response shift.[153] Other studies show that patients over 40 years old,[138] men, and those who fail to return to work more often report worse HRQOL.[154] Pain, fatigue,[134,155] and sleep disturbances[134] may be related to poorer HRQOL, although these variables may actually be part of the concept of HRQOL rather than separate factors influencing HRQOL. Relationships with disease duration,[154] tumor volume and lateralization,[156] have also been found. In this study, we did not find clear indications that these variables and HRQOL are related. Importantly, we identified detectable decline in HRQOL at the intraindividual level, which

is fundamentally different from assessment of HRQOL per se. Future studies, preferably including a larger number of participants to increase statistical power, are needed to assess which variables are predictive of poorer HRQOL, or of a decline in HRQOL over time.

It should be noted that in this article, we report on statistically significant differences between patients with LGG and matched controls, and statistically significant change and minimal detectable change within the LGG cohort. Our methods enabled us to evaluate whether HRQOL differed between patients and controls, as well as the probability that change occurred by random variation and if changes found are larger than the measurement error of the instrument. Although valuable, these approaches may not directly reflect meaningful changes as determined by patients themselves. With HRQOL being a self-reported measure by definition, it is vital that future studies incorporate a patient-reported anchor to assess meaningful change.

Another issue in this study is the serial nature of the measurements, which were not based on a fixed interval since diagnosis, but have been performed at least one year after diagnosis and initial treatment. This means that there was a wide variation in disease duration, and that some patients had longer disease duration at the first assessment than others at the second assessment, and vice versa. Moreover, results from our previous report on the same LGG cohort indicate that the patients who did not participate in the long-term follow-up (i.e. those without stable disease) had a longer disease duration (1.5 years on average) than the long-term stable patients. This limits to some degree the generalizability of our findings. However, with the unique prolonged follow-up in this patient population with stable LGG, our results are useful in better understanding the HRQOL of long-term, stable survivors of LGG.

Finally, the definition of radiologically and clinically stable disease could be disputed, because there is evidence that WHO grade II gliomas are rarely completely stable.[157] In a separate publication on cognitive functioning and radiologic changes between midterm and long-term follow-up, we found that white-matter hyperintensities and global cortical atrophy increased in between those two points in time.[144] This suggests that presumed radiologically stable patients might not be stable after all. To ascertain that we examined a representative group of patients with LGG, we compared this study sample with those lost to follow-up and found these groups to be comparable.[144]

In conclusion, HRQOL remained mostly preserved in patients with long-term, stable LGG, whereas subtle decline was observed in physical functioning on the group level. Although our outcomes are reassuring, we also found that 38.5% of patients experienced detectable decline in specific aspects of HRQOL. Future studies into meaningful change, as well as the associations of patient-, disease- or treatment-related variables with (decline in) HRQOL, are recommended to better aid patients with LGG in dealing with the possible mental and physical consequences of LGG.

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Chapter 2.3

The effect of modafinil on fatigue, cognitive functioning and mood in primary brain tumor patients: a multicenter randomized controlled trial

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ABSTRACT

Background: Fatigue, cognitive deficits, and depression are frequently reported but often undertreated symptoms that can profoundly affect daily life in patients with primary brain tumors (PBTs). To evaluate the effects of the psychostimulant modafinil on fatigue, depression, health-related quality of life (HRQOL) and cognitive functioning in PBT patients, we performed a multicenter, double-blind placebo-controlled crossover trial.

Methods: Patients randomly received either six weeks of treatment with modafinil (up to 400mg/day) or six weeks with placebo. After a one week washout period, the opposite treatment was provided. Assessments took place at baseline and immediately after the first and second condition. Patients completed self-reported questionnaires on fatigue (CIS), depression (CES-D), HRQOL (SF-36), and self-perceived cognitive functioning (MOS). They also underwent comprehensive neurocognitive testing.

Results: In total, 37 patients participated. Relative to baseline, patients reported lower fatigue severity (CIS) and better motivation (CIS) both in the modafinil (p=0.010 and p=0.021, respectively) and placebo condition (p<0.001 and p=0.027, respectively). The same held for physical health (SF-36 PCS score ; p=0.001 and p=0.008, respectively), working memory (p=0.040 and p=0.043, respectively) and information processing capacity (p=0.036 and p=0.040, respectively). No improvement in depressive symptoms was found in either condition.

Conclusions: Modafinil did not exceed the effects of placebo with respect to symptom management. Patient accrual was slow, and relatively many patients dropped out during the trial, due mostly to side-effects. Other, preferably nonpharmacological intervention studies should be considered to improve symptom management of PBT patients.

INTRODUCTION

Fatigue, cognitive deficits, and depression are frequently reported symptoms in patients with primary brain tumors (PBTs).[27, 158] Over 80% of PBT patients treated with cranial irradiation experience some degree of somnolence, defined as symptoms of drowsiness, lethargy and fatigue.[10, 11] Unrelated to radiation treatment, 39% of long-term survivors of low-grade glioma (LGG) report severe symptoms of fatigue.[12] In addition to fatigue, cognitive impairments are experienced by 80% of PBT patients.[7] The prevalence of depression in PBT patients ranges from 15% to 27%.[13] All of these symptoms have a large impact on the everyday life of patients and may lead to a significant decrease in health-related quality of life (HRQOL).[34] It is suggested that effective treatment of these symptoms may increase HRQOL,[69] although an optimal strategy to reach this goal has not been defined yet.

Modafinil (2-benzhydrylsulfinylethanamide) is a wakefulness-promoting agent that targets fatigue, cognitive functioning, and mood. Although categorized as a psychostimulant, it differs from amphetamine in both physiological and behavioral aspects. It is highly selective for the central nervous system, has a lower abuse potential, and poses a lower risk of adverse effects on organ systems.[159-163] The precise mechanism of action of modafinil is unknown, but it is theorized to act in a localized manner, utilizing hypocretin, histamine, epinephrine, γ-aminobutyric acid (GABA), and glutamate.[159] It enhances catecholaminergic signaling and decreases GABA release, primarily at level of the anterior hypothalamus and locus coeruleus.[161, 164] It has been shown to bind directly to dopamine and norepinephrine receptors.[162] Forty to sixty-five percent of modafinil is readily absorbed, with only 10% of the drug being excreted in the urine in unchanged form.[162, 165] Modafinil appears to target the sleep-wake centers of the brain more specifically than other psychostimulants.[160, 161] With a half-life of 12 to 15 hours,[162, 165] modafinil requires only a single daily dose for efficacy. Lower dosages (50-200 mg/day) are generally prescribed for fatigue and concentration problems, while higher dosages (up to 600 mg/day) are used for daytime sleepiness in narcolepsy.[166] Although originally marketed for the latter,[167, 168] modafinil has recently been found to be of use in improving fatigue,[169-176] mood[177-180] and overall HRQOL[181] in several study populations. Moreover, there is evidence that it may even enhance cognitive functioning.[162, 182-185] In healthy adults, working memory, recognition memory, sustained attention and cognitive control are improved after modafinil.[162, 182] In children and adolescents with attention deficit hyperactivity disorder (ADHD), improved attention and response inhibition have been reported, while in several adult psychiatric populations, modafinil appears to improve cognitive functions that depend on prefrontal structures.[162] In patients with schizophrenia, especially working memory and problem-solving abilities improved.[185]

Despite these potentially beneficial effects, notably little is known about the effects of modafinil on symptom management in PBT patients. Compared to modafinil, methylphenidate is more similar to amphetamine in its pharmacologic profile. It inhibits dopamine and norepinephrine uptake and increases concentrations of these neurotransmitters in the brain.[186] It targets primarily the prefrontal cortex.[187] Immediate-release methylphenidate has a relatively short half-life, which necessitates two or three doses a day, while sustained-release methylphenidate only requires a

single dose per day.[43] In an open label pilot study, 24 PBT patients were randomly assigned to four weeks of modafinil (200 mg q.d.), immediate-release methylphenidate (20 mg b.i.d.), or sustained-release methylphenidate (18 mg q.d.).[43] Comparison of combined immediate- and sustained-release methylphenidate with modafinil showed the latter to have significant positive effects on information processing speed and executive functioning requiring divided attention. Additionally, a general beneficial effect of both methylphenidate and modafinil on fatigue, mood and HRQOL was found.[43] Another pilot study, presented at the 2006 annual meeting of the American Society of Clinical Oncology, that had a double-blind dose-controlled randomization of 200 or 400 mg/day modafinil for three weeks, a washout period of one week, and an open label extension of eight weeks, also reported decreased fatigue and improvements in cognitive functioning and mood in PBT patients, although final results have not been published yet.[44] Presently, we performed a multicenter, double-blind placebo-controlled crossover trial to evaluate the effects of modafinil on fatigue in PBT patients. As fatigue may interact with functional activities and HRQOL, and considering the encouraging study results described above, the effects of modafinil on cognition, mood, and overall HRQOL were also evaluated.

2.3

METHODS

Participants

We identified patients who visited the outpatient departments of three tertiary referral centers for neuro-oncology (VU University Medical Center, Amsterdam; Academic Medical Center, Amsterdam; and Medical Center Haaglanden, the Hague) between January 2009 and December 2011. Participants were eligible if they: 1) were ≥ 18 years old, 2) had been diagnosed with a histologically confirmed glioma or meningioma (collectively called primary brain tumor (PBT) throughout this report); and 3) had no signs of tumor recurrence in the last six months. In addition, they were only invited to participate if they reported a heightened experience of fatigue (score >27 on the Checklist Individual Strength (CIS)[188], as this was our primary outcome measure. Patients were excluded if 1) they had a history of psychiatric disease or symptoms, including depressive disorders; 2) adverse interactions between modafinil and other prescribed medications were expected (e.g., decreased effectiveness of oral contraceptives, levonorgestrel-releasing intrauterine systems and anti-depressants, fluctuations in the effectiveness of anti-epileptic drugs acting on similar enzymes); 3) they were unable to communicate in Dutch. A priori sample size calculations based on statistical power (1-β) of 0.80, r=0.30 and α=0.05, yielded 64 patients to be included in the study. The study was approved by the institutional review boards of all participating centers and was registered at http://www.clinicaltrialsregister.eu/ with EudraCT number 2007-003102-10. All patients provided written informed consent.

Procedure

Eligible patients were introduced to the trial by their treating physician either in person or by mail. The researchers then contacted the patients by telephone to inquire if they were interested in

participation. As fatigue was our primary outcome measure, interested patients were asked to fill out the CIS to assess the severity of their complaints and their suitability for participation. After obtaining informed consent, sociodemographic and clinical data were collected from patients' medical records. A pharmacy randomisation system was used to assign participants to either the modafinil or the placebo condition, while patients, treating physicians and researchers were blind to treatment allocation. Patients received six weeks of treatment with either modafinil or placebo starting with a 100 mg dose upon waking and at lunch (200 mg/day in total). After the first week, the dose was doubled to 400 mg/day. After treatment period one, a washout period of one week was applied. Hereafter, the opposite treatment was provided during treatment period two (i.e., those who first received modafinil now received placebo and vice versa). During the trial, patients were asked not to take benzodiazepines as these might interfere with modafinil. Assessments took place at baseline (T1), immediately after treatment period one (after six weeks; T2) and immediately after treatment period two (after twelve weeks; T3). These assessments included self-report questionnaires and neuropsychological assessment, as well as physical and neurological examination carried out by a physician. If patients experienced adverse effects, they were allowed to decrease the medication to the lower dose (200 mg/day) or to stop participating in the trial after consulting the physician involved in the trial.

Patient-reported outcomes

Patients were asked to complete self-report questionnaires on measures of fatigue as the primary outcome measure and depression, HRQOL, and subjective cognitive functioning as secondary outcome measures.

Checklist Individual Strength (CIS).[188] Fatigue was assessed with this multidimensional scale, each item scored on a seven-point Likert scale. The CIS includes four aspects of fatigue (fatigue severity, concentration problems, reduced motivation and reduced activity) and a total score. High scores indicate a high level of fatigue, a high level of concentration problems, low motivation and a low activity level. Based on normative controls, a total score between 27 and 35 indicates a heightened experience of fatigue.

Center for Epidemiological Studies Depression Scale (CES-D).[189] This 20-item questionnaire was used to assess symptoms of depression. Participants were asked to indicate, on a four-point scale, how often they feel a statement was applicable to their situation during the last week. Scores range between 0-60, with higher scores indicating more feelings of depression. In the general population, respondents with a total score of ≥16 are considered depressed.

MOS Short-Form Health Survey (SF-36).[19] This HRQOL survey is composed of 36 items that are organized into eight multi-item scales assessing: (1) physical functioning; (2) limitations in role functioning due to physical problems; (3) limitations in role functioning due to emotional problems; (4) pain; (5) vitality; (6) social functioning; (7) mental health; and (8) general health perceptions. From these scales, two higher-order summary scores can be calculated: 1) Physical Component Summary (PCS), measuring physical health; 2) Mental Component Summary

(MCS), measuring mental health. In a normative sample from the general population, PCS and MCS scores had a mean of 50 with a standard deviation of 10.

MOS Subjective cognitive functioning scale.[190] This six-item scale assesses everyday problems in cognitive functioning, including difficulty with reasoning and problem solving, slowed reaction time, and problems with concentration (range 1-6).

Objective cognitive functioning

Using an extensive battery of neuropsychological tests, objective cognitive functioning was assessed. Tests included measures of verbal memory (auditory verbal learning test[191]), working memory (memory comparison test[131]), attentional functioning (Stroop color word test[127]), information processing (letter digit substitution test[192]), executive functioning (concept shifting test[130], categorical word fluency test[126]), and psychomotor speed (concept shifting test, letter digit substitution test).

Statistical analysis

All statistical analyses were performed with SPSS software version 20. Standard scoring rules were applied to convert the data from the questionnaires. Mean imputation was used to handle missing values within completed questionnaires or neuropsychological assessments. To assess a change in cognitive functioning as accurately as possible, cognitive test scores were converted to Z-scores using the means and standard deviations of the patients' scores at baseline. To achieve data reduction, six cognitive domains were formed (verbal memory; working memory; attentional functioning; information processing; executive functioning; psychomotor speed), see Table 3. Construction of these cognitive domains was based on a principal component analysis using Varimax rotation with Kaiser normalization performed on the Z-scores of an extensive study among healthy subjects into the biological predictors of cognitive aging.[193] To test whether the outcome measures were normally distributed, Kolmogorov-Smirnov tests were used. Since none of the outcome measures were normally distributed, Wilcoxon signed-rank tests were used to determine differences within patients in fatigue, depression, the PCS and MCS scales of the SF-36 (HRQOL), and subjective and objective cognitive functioning. Given the small sample size, no corrections for multiple statistical testing were applied. A p-value of ≤0.05 was considered statistically significant, a p-value of ≤ 0.10 was considered a trend.

RESULTS

Patient characteristics

Figure 1 shows details of the participant flow. In total, 155 PBT patients were assessed for eligibility. A total of 39 patients (25.2%) met the inclusion criteria, agreed to participate, and subsequently signed the informed consent form. Thirty-seven patients were assigned randomly to a treatment condition, whereas two patients dropped out before randomization because they were no longer willing to participate. During the trial, overall 12 patients dropped

out: seven participants dropped out between T1 and T2, and five patients dropped out between T2 and T3. Reasons for not completing the trial were discontinuation of medication due to side-effects (*N*=7; patients reported a tingling sensation, nausea, vertigo, anxiety, depression, and feeling fidgety), missed follow-up (*N*=4), and disease progression (*N*=1). Table 1 presents sociodemographic and clinical characteristics of the study sample. The mean age of participants was 42.2 years, and more women than men participated (62.2% vs 37.8%). Most participants had a low-grade glioma (37.8%) and the mean time since diagnosis was 49.5 months.

Patient-reported outcomes

Fatigue

As can be seen in Table 2, scores on the CIS scales fatigue severity and reduced motivation were significantly lower after both modafinil (p=0.010 and p=0.021, respectively) and placebo treatment (p<0.001 and p=0.027, respectively) compared with the baseline assessment. The extent of decrease in fatigue as measured by these scales, however, did not significantly differ between

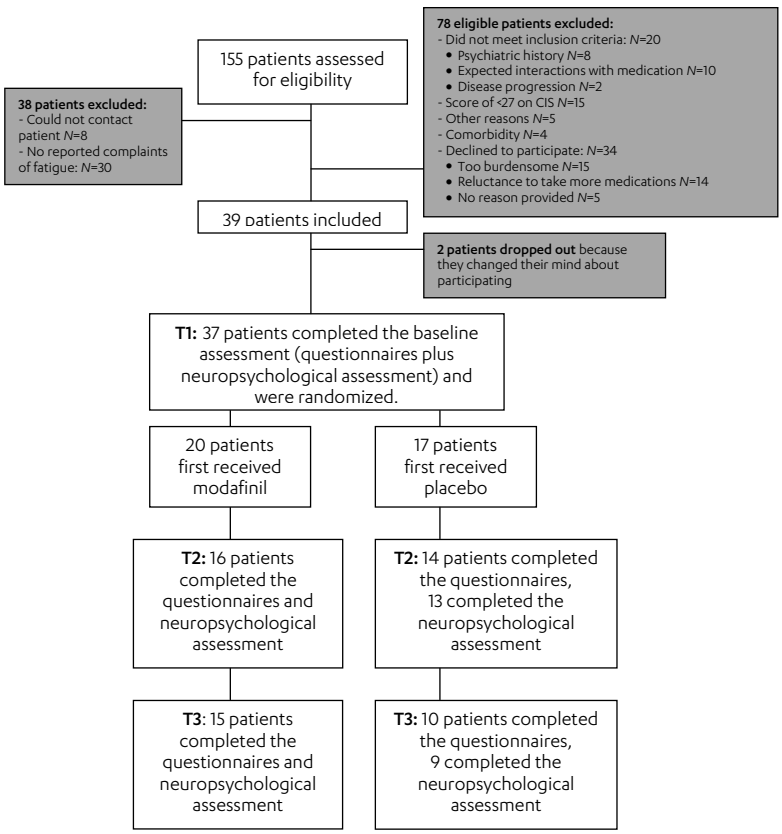

Figure 1. Participant flow.

Table 1. Demographic and clinical characteristics of the study sample.

	Participants (*N*= 37)
Age in years *M* (SD)	48.16 (12.02)
Gender *N* (%)	
Male	14 (37.8%)
Female	23 (62.2%)
Educational level *N (%)*	
Low	10 (27%)
Medium	15 (40.5%)
High	11 (29.7%)
Other	1 (2.7%)
Marital status *N* (%)	
Single	7 (18.9%)
Married or living together	25 (67.6%)
Divorced	2 (5.4%)
Widow(er)	3 (8.1%)
Tumor grade *N* (%)	
Grade I	15 (40.5%)
Grade II	10 (27.0%)
Grade III	7 (18.9%)
Grade IV	5 (13.5%)
Tumor type *N* (%)	
Meningioma	12 (32.4%)
Low-grade glioma	14 (37.8%)
High-grade glioma	11 (29.7%)
Tumor location *N* (%)	
Frontal	13 (35.1%)
Temporal	5 (13.5%)
Parietal	6 (16.2%)
Occipital	2 (5.4%)
Mixed	6 (16.2%)
Other	5 (13.5%)
Tumor lateralisation *N* (%)	
Left	15 (40.5%)
Right	20 (54.1%)
Bilateral	2 (5.4%)
Epilepsy *N* (%)	
Yes	12 (32.4%)
No	25 (67.6%)
Neurosurgical intervention *N* (%)	
Resection	33 (89.2%)
Biopsy	2 (5.4%)
None	2 (5.4%)

Table 1. Continued

	Participants (*N*= 37)
Months since time of diagnosis *M* (range)	49.46 (16-197)
< 36 months *N*(%)	18 (48,6%)
> 36 months *N*(%)	19 (51,4%)
Medication use, prior to trial *N* (%)	
Anti-epileptic drugs	20 (54.1%)
Anti-hypertensive drugs	8 (21.6%)
Cholesterol inhibitors	4 (10.8%)
Anticoagulants	3 (8.1%)
Analgesics (mild opioids)	2 (5.4%)
Analgesics (non-opioids)	1 (2.7%)
Anti-allergic drugs	2 (5.4%)
Bladder control drugs	2 (5.4%)
Stomach protectors	2 (5.4%)
Laxatives	2 (5.4%)
Benzodiazepines	2 (5.4%)
Anorexiants	1 (2.7%)
Progestagens	1 (2.7%)
Oral contraceptives	1 (2.7%)
Change in medication use during trial *N* (%)	
Analgesics (non-opioids)	4 (10.8%)
Antibiotics	3 (8.1%)
Flue vaccine	1 (2.7%)
Anti-diabetics	1 (2.7%)
Anti-emetics	1 (2.7%)
Radiotherapy (ever) *N* (%)	
Yes	16 (43.2%)*
No	21 (56.8%)
Chemotherapy (ever) *N* (%)	
Yes	8 (21.6%)*
No	29 (78.4%)
Progressive disease during intervention *N* (%)	
Yes	2 (5,4%)
No	35 (94,6%)

* One participant had received radiotherapy not involving the CNS and chemotherapy for breast cancer, not for PBT. The patient did not have brain metastases.

both conditions. Although not statistically significant, a trend can be seen for an improvement in reduced activity in the placebo condition (p=0.093) compared with baseline. On the total CIS-score, patients' symptoms were alleviated in both the modafinil and placebo condition (p=0.005 and p=0.001, respectively) while scores between the experimental conditions did not differ.

Table 2. Results of comparisons between the baseline assessment and the modafinil and placebo conditions for fatigue (CIS).

Bas *N*=36 *M* (sd)	Mod *N*=26 *M* (sd)	Pla *N*=29 *M* (sd)	Bas vs. Mod *Z (p)*	Bas vs. Pla *Z (p)*	Mod vs. Pla *Z (p)*
		Concentration problems			
20.75 (9.18)	18.85 (7.90)	19.91 (8.36)	-1.10 (0.270)	-1.15 (0.252)	-0.97 (0.331)
		Reduced motivation			
17.00 (5.40)	14.38 (5.72)	14.86 (6.72)	-2.31 (0.021*)	-2.22 (0.027*)	-0.383 (0.702)
		Reduced activity			
13.49 (4.87)	11.58 (5.34)	12.59 (5.17)	-1.37 (0.170)	-1.68 (0.093)	-0.43 (0.671)
		Fatigue severity			
41.72 (9.22)	34.92 (12.04)	35.14 (10.86)	-2.56 (0.010*)	-3.72 (<0.001*)	-0.75 (0.456)
		Total score			
93.80 (20.16)	79.73 (26.45)	82.48 (26.26)	-2.83 (0.005*)	-3.35 (0.001*)	-1.01 (0.313)

Abbreviations: Bas. baseline; Mod. modafinil; Pla. placebo.
* p<0.05

2.3

Depression

Scores on the CES-D did not differ significantly between treatment conditions. At baseline, reported scores were only slightly higher (*M*=15.86, sd=9.49) than in both the modafinil and placebo condition (*M*=14.16, sd=9.06 and *M*=13.97, sd=9.44, respectively; *p* = n.s.). All mean scores were within the non-depressed range (i.e. < 16).

Health-related quality of life

Patients' physical health as measured by the PCS scale improved significantly after both the modafinil (*M*=46.05, sd=7.96) and placebo condition (*M*=44.71, sd=9.13) compared with baseline (*M*=40.60, sd=7.58; *p*=0.001 and *p*=0.008, respectively). No other significant differences were observed for either physical or mental health scales.

Subjective cognitive complaints

A trend was observed where participants tended to report higher self-perceived cognitive functioning after the placebo condition compared with baseline (*p*=0.056), see Table 3.

Objective cognitive functioning

Table 3 shows that patients improved after both the modafinil and the placebo condition compared with baseline for both the working memory domain (*p*=0.040 and *p*=0.043, respectively) and the information processing domain (*p*=0.036 and *p*=0.040, respectively). Scores did not differ between the experimental conditions. For attentional functioning, scores improved significantly after the placebo condition compared with baseline (*p*=0.015) and after modafinil treatment (*p*=0.013).

Table 3. Overview of cognitive tests administered and results of comparisons between the baseline assessment and the modafinil and placebo conditions for cognitive functioning.

Baseline *N*=36 *M* (sd)	Modafinil *N*=25 *M* (sd)	Placebo *N*=28 *M* (sd)	Baseline vs. Modafinil *Z (p)*	Baseline vs. Placebo *Z (p)*	Modafinil vs. Placebo *Z (p)*
		Verbal memory			
		Auditory Verbal Learning Test[45]			
0.00 (0.71)	0.14 (0.86)	-0.12 (1.02)	-1.63 (0.104)	-0.29 (0.767)	-1.60 (0.110)
		Working memory			
		Memory Comparison Test[46]			
0.00 (0.86)	0.24 (0.93)	0.17 (0.90)	-2.06 (0.040*)	-2.03 (0.043*)	-1.26 (0.209)
		Attentional functioning			
		Stroop Color-Word Test[47]			
0.00 (1.04)	0.15 (0.94)	0.18 (0.75)	-1.28 (0.201)	-2.44 (0.015*)	-2.49 (0.013*)
		Information processing			
		Letter Digit Substitution Test[48]			
0.00 (0.94)	0.36 (1.18)	0.19 (1.12)	-2.01 (0.036*)	-2.05 (0.040*)	-0.24 (0.808)
		Executive functioning			
		Concept Shifting Test[49] Categorical Word Fluency Test[50]			
0.00 (0.80)	0.19 (0.78)	0.05 (0.94)	-1.17 (0.242)	-1.25 (0.210)	-0.03 (0.977)
		Psychomotor speed			
		Concept Shifting Test[40] Letter Digit Substitution Test[48]			
0.02 (0.61)	0.26 (0.56)	0.16 (0.53)	-1.60 (1.09)	-1.48 (0.139)	-0.54 (0.587)
		Subjective cognitive functioning			
31.79 (17.62)	29.11(16.04)	27.49 (18.11)	-0.79 (0.428)	-1.91 (0.056)	-1.33 (0.184)

The cognitive domains included the following assessments: Verbal memory: AVLT 1, AVLT recall, AVLT recognition, AVLT delta, AVLT total; Working memory: MCT %, MCT 1, MCT 2, MCT 3, MCT4; Attentional functioning: Stroop card 1, Stroop card 2, Stroop card 3; Information processing: LDMT reading, LDMT writing; Executive functioning: CST A, CST B, CST C, CWFT animals (60 seconds); Psychomotor speed: CST 0, LDMT delta.
* $p<0.05$

DISCUSSION

Contrary to our hypotheses, we did not find beneficial effects of modafinil on fatigue, depression, overall HRQOL, or cognitive functioning in comparison with placebo. Patients reported a decrease in fatigue severity, an improvement in reduced motivation, and a better overall fatigue score in both the modafinil and the placebo condition compared to baseline, indicating a placebo effect. Counterintuitively, a trend was found for an improvement in the reduced activity scale after the placebo condition, but not after the modafinil condition. For depression, overall HRQOL, and cognitive functioning, we found no difference between the treatment conditions.

In different study samples of patients with various neurological conditions (Charcot-Marie-Tooth disease, fibromyalgia, amyotrophic lateral sclerosis, multiple sclerosis, schizophrenia, narcolepsy), beneficial effects of modafinil for symptoms of fatigue, HRQOL, and cognitive functioning have been shown.[169, 170, 172-174, 176, 181, 183] However, the majority of these studies were not placebo-controlled, and study samples were often relatively small. Although the literature on modafinil for symptom management in PBT patients is scarce, two studies have been reported and both showed positive results. Gehring *et al*. reported beneficial effects of both modafinil and methylphenidate for patient-reported measures of fatigue, mood and HRQOL as well as for objective neuropsychological testing.[43] However, no differences between treatment arms over time were reported for fatigue, mood and HRQOL, and findings with regard to cognitive functioning were inconsistent, indicating that nonspecific treatment effects may have played a role. In an unpublished pilot study, Kaleita *et al*. mention improvement in fatigue, mood and cognitive functioning in PBT patients randomized to either a 200mg or a 400mg modafinil dose.[44] However, since the results of Kaleita *et al*. remain unpublished, we cannot properly compare their methodology to ours. Importantly, in both studies, no placebo condition was used. As psychological mechanisms such as the presence of expectations prove to be powerful aspects of the experienced effects of medication use,[194] it seems likely that the beneficial effects reported in these previous studies could at least, in part, be attributable to a placebo-effect.

Despite this methodological advantage of the present study, there are also significant limitations. In spite of great efforts in recruiting patients, accrual was difficult and ultimately, we did not reach the required sample size. As shown in Figure 1, almost half of the eligible patients declined participation for several reasons, such as expecting participation to be too burdensome or declining to take more drugs than was strictly necessary. Furthermore, during the trial, a considerable number of patients (32%) dropped out for various reasons, although the majority of these (58.3%) decided to discontinue medication because of side-effects. Interestingly, this also includes patients in the placebo condition who should not have experienced any side-effects. Although it is not uncommon to experience side-effects with placebo use,[195] the fact that these patients dropped out of the trial does suggest that possibly pharmaceutical trials for symptom management are less suitable for PBT patients. Another study limitation is the heterogeneity of the patient population. We included patients with meningiomas as well as gliomas, while these diseases are not equal in many respects (e.g., nature of the disease, symptoms and treatment, prognosis). Although there is no indication that modafinil would be more effective in one subgroup of PBT patients than in another, it would have been preferable to study the effects of modafinil in a larger, more homogenous group of patients.

Despite these limitations, we did find clear differences between the baseline assessment and outcome after both treatment conditions. This suggests that our lack of evidence for beneficial effects of modafinil for symptom management of PBT patients cannot be attributed to the small sample size. Rather, the participants in our sample did not experience better results from modafinil than from placebo. Given the apparent reluctance of a relatively large proportion of PBT patients to participate in pharmacological trials for symptom management, as is shown in the present study as well as in the study by Gehring *et al*.,[43] and given the high percentage of patients

suffering from fatigue, cognitive deficits and mood disorders, other intervention studies should be considered. Concerning fatigue, Armstrong and Gilbert[41] provided an interesting overview of the guidelines of the National Comprehensive Cancer Network in relation to PBT patients. Although many nonpharmacologic interventions to treat fatigue (e.g., activity enhancement, physically-based therapy, psychosocial interventions, nutritional consultation, cognitive behavioral therapy for sleep hygiene) have been proven to be effective in the general cancer patient population, randomized controlled trials in PBT patients have not yet been performed. Concerning cognitive deficits, a cognitive function training program has been proven to be effective in PBT patients.[65] For depressive symptoms, nonpharmacological intervention studies in this patient population are also still scarce, although many therapeutic interventions already exist for different cancer patient populations.[196] Because of their unique symptom pattern with neurological and cognitive sequelae, PBT patients are not easily comparable to other cancer patient groups. Therefore, the efficacy of the majority of interventions remains to be evaluated in this particular patient population. We recommend the development of nonpharmacologic interventions aimed specifically at symptom management in PBT patients, which may alleviate their symptom burden substantially and could improve their HRQOL significantly.

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Chapter 2.4

Internet-based guided self-help for glioma patients with depressive symptoms: design of a randomized controlled trial

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ABSTRACT

Background*:* Among glioma patients, depression is estimated to be more prevalent than in both the general population and the cancer patient population. This can have negative consequences for both patients and their primary informal caregivers (e.g., a spouse, family member or close friend). At present, there is no evidence from randomized controlled trials for the effectiveness of psychological treatment for depression in glioma patients. Furthermore, the possibility of delivering mental health care through the internet has not yet been explored in this population. Therefore, a randomized controlled trial is warranted to evaluate the effects of an internet-based, guided self-help intervention for depressive symptoms in glioma patients.

Methods/Design: The intervention is based on problem-solving therapy. An existing five-week course is adapted for use by adult glioma patients with mild to moderate depressive symptoms (Center for Epidemiology Studies Depression Scale score ≥12). Sample size calculations yield 126 glioma patients to be included, who are randomly assigned to either the intervention group or a waiting list control group. In addition, we aim to include 63 patients with hematological cancer in a non-central nervous system malignancy control group. Assessments take place at baseline, after six and 12 weeks, and after six and 12 months. Primary outcome measure is the change in depressive symptoms. Secondary outcome measures include health-related quality of life, fatigue, costs and patient satisfaction. In addition, all patients are asked to assign a primary informal caregiver, who does not participate in the intervention but who is asked to complete similar assessments. Their mood, health-related quality of life and fatigue is evaluated as well.

Discussion: This is the first study to evaluate the effects of problem-solving therapy delivered through the internet as treatment for depressive symptoms in glioma patients. If proven effective, this treatment will contribute to the mental health care of glioma patients in clinical practice.

BACKGROUND

Patients with gliomas, primary brain tumors originating from glial tissue, are not only faced with the diagnosis of a life-threatening disease, but also with various neurological symptoms.[7, 27] Glioma patients often suffer from headaches,[28-30] cognitive deficits, paresis, visual-perceptual deficits, sensory loss, and seizures.[7] In addition, depression is common in glioma patients. During the first eight months following the diagnosis, 15 to 20% of glioma patients become clinically depressed.[13, 77] Longitudinal studies show that the prevalence of depression among these patients keeps increasing up to one year after surgery.[78] Surprisingly, glioma patients not only seem to be at increased risk compared with the general population (12-month prevalence 6.6%), but also compared with other cancer patient populations.[80, 81] This may affect not only patients, but also their direct environment, including their spouses, family members, and close friends. In fact, glioma patients' neuropsychiatric status, including depressive symptoms, was found to influence the presence of depressive symptoms in significant others.[197] These mental health issues can contribute significantly to a decrease in significant others' health-related quality of life (HRQOL).[33, 198]

The precise cause of depression in glioma patients remains unclear. A number of mechanisms, including tumor location, elevated intracranial pressure, and biochemical changes may contribute to the development of depression.[199] Evidently, the patient's emotional reactions to the diagnosis can contribute. Patients can experience shock and disbelief, dysphoria, despair, anger and anxiety, and intrusive thoughts about their diagnosis.[200] These issues may cause an adjustment disorder to the situation, which if persistent, can become a major depressive episode.[201] However, evidence for this theory is inconclusive as awareness of the prognosis is not always associated with mood disorders.[202] Moreover, these mechanisms occur in other cancer patient populations as well, which only emphasizes the unexpectedly high prevalence of depression among glioma patients, specifically.

While the etiology of this problem is not fully known, it is clear that the above mentioned contributing factors may impede the diagnosis of depression in glioma patients.[73] For example, the mood problems can be interpreted by treating physicians as 'understandable' considering the circumstances, and this may complicate communication about these symptoms.[75] The depression is then less likely to be recognized, which can lead to an underdiagnosis, and subsequently to an undertreatment, of depression.[76] This process can have serious negative consequences for glioma patients as in this population, depression has been associated with increased morbidity and even with poorer survival.[203, 204] Moreover, depression is the most important independent predictor of HRQOL in patients with brain tumors.[34]

If this potentially treatable condition is recognized, the treatment usually consists of the combination of antidepressants and intensive psychological treatment, such as cognitive behavioral therapy (CBT).[84, 85] Both pharmacological and psychological treatment can encounter problems in glioma patients specifically. Glioma patients often take multiple medications concurrently, which increases the risk for drug interactions and may lead to a reluctance to try antidepressants. For example, one study shows that only 60% of patients in whom the treating physician recognized depression, actually received antidepressants,[90] and it is unclear if the remaining 40% of depressed

patients received an alternative treatment such as psychotherapy. Treatment with psychotherapy can encounter problems as well, as psychotherapy usually requires good cognitive functioning in order for a patient to benefit most while approximately 80% of brain tumor patients experience cognitive deficits to some degree.[7] Therefore, while treatment for depression has been shown effective in both the general population[205, 206] and in cancer patients,[207] it remains to be seen if either antidepressants or psychotherapy are equally effective in glioma patients.

Problem-solving therapy (PST), a form of CBT, may prove helpful in alleviating depressive symptoms especially in this patient population, as it is a brief and practical approach. Depression is linked with stressful life events, and when depressed, patients may be less able to actively cope with these stress inducing factors. In PST, it is assumed that depressive symptoms are caused by everyday problems that can be resolved with problem-solving techniques. Resolution of problems then leads to a reduction in depressive symptoms. By teaching more adequate coping strategies, and aiding in the acceptance of problems that cannot be solved,[208] PST can prove effective.[209, 210] Indeed, it has been suggested as the preferred treatment in depressive patients with somatic disease.[211]

During their disease trajectory, glioma patients frequently have to visit the hospital. In a subset of patients who suffer from neurological sequelae that affect their physical functioning and mobility (e.g. paresis, paralysis, epilepsy, fatigue), face-to-face treatment for depression may lead to additional burden. Alternative ways of delivering PST, such as through the internet, may therefore become more appealing. This may especially be the case in the Netherlands, where in 2013, approximately 95% of all households has internet access.[212] Internet-based psychological interventions, including PST, have already been found to be equally effective as face-to-face treatment.[205, 213] These internet-based programs make use of self-help, where patients work through a standardized psychological treatment independently, sometimes guided by a coach. This way, the interventions are thought to pose low thresholds for participation, as it is more anonymous, easily accessible as patients can work on the programs at a time of their choosing, and cost-effective as only minimal involvement of health-care professionals is necessary. As of yet, there is no scientific evidence from randomized controlled trials available for the effectiveness of psychotherapy, whether internet-based or face-to-face, in glioma patients.[91] Therefore, we presently present the design of a randomized, controlled trial aimed at alleviating depressive symptoms in glioma patients using an internet-based guided self-help course. A secondary aim is to evaluate the effect of the intervention on HRQOL of both patients and their significant others.

METHODS/DESIGN

Design

This study is a randomized controlled trial evaluating the effects of an internet-based guided self-help course for depressive symptoms in glioma patients. We compare a group of patients who receive the intervention with a three month waiting list control group and a non-central nervous system malignancy control group. The intervention, which takes approximately five weeks to complete, is aimed at patients with mild to moderate depressive symptoms.

Assessments include self-reported outcomes completed online. The assessments are scheduled at baseline (T0), after completion of the online course (approximately six weeks after baseline; T1), 12 weeks after baseline (T2), and 12 months after baseline, see Figure 1. Those in the waiting list control group receive the same assessments, but are also assessed after completion of the online course (T3; approximately six weeks after T2), and 12 weeks thereafter (T4). Furthermore, patients with a high-grade malignancy undergo an additional assessment at six months after baseline (T3 or T5), as is also depicted in Figure 1.

This study is performed in accordance with the Declaration of Helsinki. This study is approved by the institutional review board of the VU University Medical Center (IRB00002991). Due to the internet-based nature of the intervention and the assessments, this approval is deemed sufficient for nation-wide recruitment.

Study population

Adult (>18 years of age) WHO grade II, III or IV glioma patients with mild to moderate depressive symptoms (Center for Epidemiological Studies Depression Scale[189] (CES-D) score ≥12) are invited to participate. After screening, patients scoring above 16, the usual cut-off score for depression on the CES-D, subsequently receive the full study information. Those scoring between 12 and 16 are informed of their relatively low score and are given the option to receive the full study information or not.

For the non-central nervous system oncology control group, adult (>18 years of age) patients with non-Hodgkin lymphoma (NHL), chronic lymphatic leukemia (CLL), multiple myeloma (MM), or a myelodysplastic syndrome (MDS) who have mild to moderate depressive symptoms (CES-D score ≥12) are invited to participate. Here, too, those patients scoring between 12 and 16 on the CES-D at the time of screening are informed of their relatively low score and they are asked if they want to receive full information of the study or not.

Although not a strict requirement for participation, all patients are additionally asked to invite an informal caregiver to participate in the study. This refers to a significant other who provides the majority of mental and physical support to the patient. These informal caregivers do not participate in the intervention but are asked to complete the same assessments at the same time points concerning their own mood, HRQOL, fatigue, etc.

Potential participants are excluded if they have no access to the internet and/or no email address, if they have insufficient proficiency of the Dutch language, and if they express suicidal intent. Suicidal intent is screened for with the Beck Scale for Suicide Ideation (BSS).[214] If patients have a score higher than 0 on the BSS, a board certified psychologist (MK) conducts an interview through telephone to assess the severity of symptoms. If a patient is excluded due to suicidal intent, the general practitioner is always contacted to assure proper referral to health care professionals.

Recruitment and inclusion procedure

Patients are recruited through advertisements and news items on websites frequently visited by glioma patients and hematological patients. Patient associations are asked for help in spreading study information through their websites, newsletters and meetings. Treating physicians

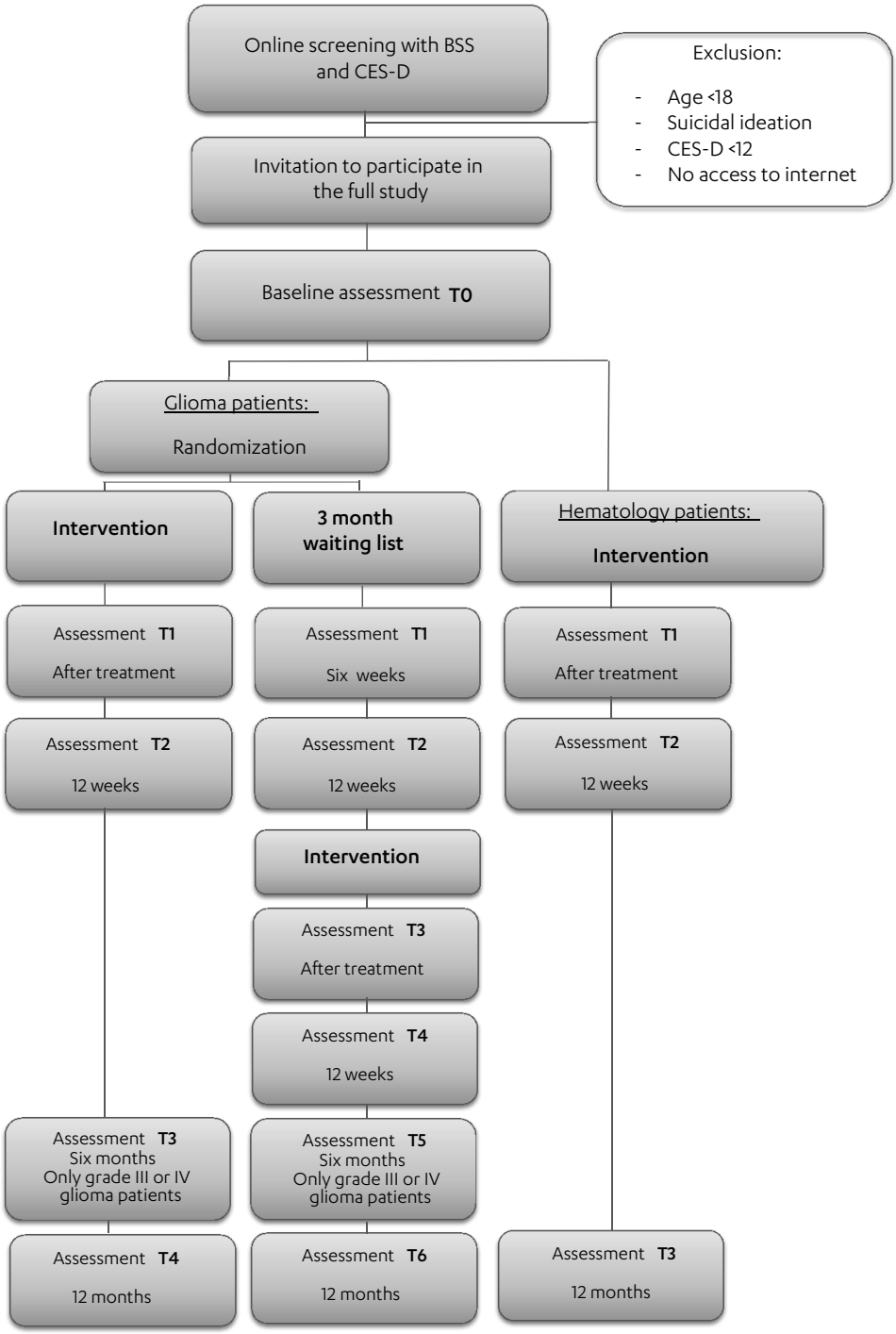


Figure 1. Participant flow

and nurse practitioners throughout the Netherlands collaborate in this study by providing information brochures to their patients. These professionals are contacted through the intermediary of the Dutch Society for Neuro-Oncology and the Dutch Neurology Association, as well as through the authors' personal networks.

The advertisements, news items and information brochures contain a link to a website with an online screening procedure. If interested, patients complete this online questionnaire that contains questions on basic demographic information (age, gender, level of education), contact information, and the BSS and CES-D. On this website, it is explained that by completing the questionnaire, patients give permission to contact their general practitioner if the researchers deem this necessary. Furthermore, they are made aware that the personal information they provide will only be used if they later decide to take part in the study and sign informed consent forms.

Eligible patients receive an information letter. Within a week the study coordinator (FWB) contacts the eligible participants by telephone to answer possible questions. Subsequently, they are asked to sign the informed consent form they received with the information letter. They are also asked to sign a form enabling the researchers to request information on the patient's disease and treatment at their treating hospital. Figure 2 illustrates this recruitment

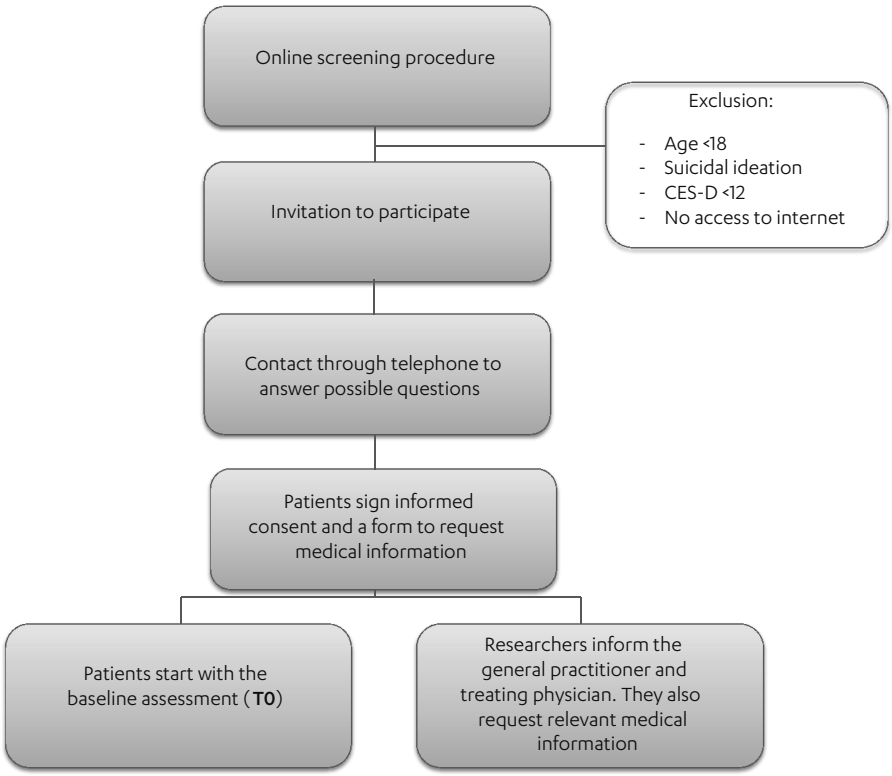


Figure 2. Recruitment procedure

procedure. After informed consent is obtained, both the general practitioner and the treating physician are informed about the patient's intent to participate in the trial.

Randomization

Glioma patients are randomly assigned to either the intervention group or the waiting list control group after completion of the baseline assessment (T0). An adaptive simple randomization technique is employed to minimize the chance of imbalanced group sizes.

Intervention

The internet-based guided self-help intervention is based on the principles of problem solving therapy. The original intervention, 'Everything under control' ("*Alles onder controle*") has been shown to have significant positive effects on depression, anxiety and stress/burnout in a randomized controlled trial with 215 adults from the general population.[215] With small changes, this online intervention is adapted for use by glioma patients and patients with hematological malignancies. Modifications concern additional information about the specific diseases and their treatment, and the psychological impact on everyday life. Examples of participants' assignments are made disease-specific.

The intervention consists of five modules with text and exercises. Patients are asked to complete one module a week and spend a minimum of two hours a week on their exercises. During the intervention, patients describe what they feel is important in their lives, make a list of their problems and concerns, and divide these into three categories: 1) unimportant problems (problems that are not related to what is important in their life), 2) important and solvable, and 3) important but unsolvable. For each of these problems the patient makes a plan on how to cope with this, guided by methods explained in the modules. The participants receive feedback on the exercises from a personal coach within three working days after completion of the assignment. The coach is not a therapist, but only supports the patient in working through the intervention. Participants can always contact their coach for additional support through the website. The coaching is provided by one of the researchers (FWB), by trained and supervised students in the final phase of a Master's program in Psychology or by specialists from Prezens. In collaboration with the VU University medical center, Prezens provides psychological care and support.

The glioma patients in the waiting list control group are offered the same intervention after completion of the 12 weeks follow-up (T2).

Outcome measures

Self-report measures of depressive symptoms, HRQOL, fatigue, costs and patient satisfaction are presented online in a fixed order. Patients are allowed to return to any of the measures for review or changes during an assessment.

Primary outcome measure

The primary outcome measure is the change in depressive symptoms as measured with the CES-D.[189] This questionnaire is designed to measure depressive symptoms in the general population (i.e., persons older than 18, without psychiatric disease). The 20-item scale measures the major components of depressive symptomatology, including depressive mood, feelings of guilt and worthlessness, psychomotor retardation, loss of appetite, and sleep disturbance. Participants are asked to indicate if they feel a particular item is applicable to their situation of the past week, on a four-point scale. Scores range between 0 and 60, with higher scores indicating more depressive symptoms. In the general population, the usual cut-off score for depression is ≥16. Within cancer patients, the CES-D has yielded good psychometric properties, with good construct validity, good internal consistency and proper test-retest reliability.[216]

Secondary outcome measures

Suicidal intent (BSS). The Beck Scale for Suicide Ideation (BSS)[214] is a 21-item self-report instrument for detecting and measuring the current intensity of the patients' specific attitudes, behaviors, and plans to commit suicide during the past week. The first 19 items consist of three options graded according to the intensity of the suicidal intent and rated on a three-point scale ranging from 0 to 2. These ratings are then summed to yield a total score, which ranges from 0 to 38. The last two items assess the number of previous suicide attempts and the seriousness of the intent to die associated with the last attempt. In this study, only the first 19 items are administered. The BSS consists of five screening items. If the patient reports any active or passive desire to commit suicide, then the additional 14 items are administered as well.

Health-related quality of life (SF-36 and EQ-5D). HRQOL is assessed by means of the Short-Form Health Survey (SF-36).[19] The SF-36 is composed of 36 items, organized into eight multi-item scales assessing: (1) physical functioning; (2) role functioning-physical; (3) role functioning-emotional; (4) pain; (5) vitality; (6) social functioning; (7) mental health; and (8) general health perceptions. Scores range from 0-100. Furthermore, two higher-order summary scores can be computed – one for physical health (Physical Component Summary) and one for mental health (Mental Component Summary). On these scales, scores have a mean of 50 and a standard deviation of 10 based on data from the general population.

In addition, the EuroQol (EQ-5D)[217] is administered. This is a standardized, non-disease specific instrument assessing HRQOL. With five items scored on a three-point Likert type scale, the EQ-5D measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Brain tumor-specific HRQOL (EORTC BN20). For glioma patients, a supplementary questionnaire module is employed to assess additional health problems associated specifically with brain tumors and their treatment. The EORTC Brain Cancer Module (BN20)[22] is organized into multi-item subscales assessing future uncertainty, visual disorders, motor dysfunctions, and communication deficits. The remaining seven items assess other disease symptoms and side-effects of treatment found to be prevalent among patients with brain tumors, including

headaches, seizures, drowsiness, hair loss, itching, weakness in the legs, and lack of bladder control. The scores range from 0-100, with higher scores indicating more symptoms.

Fatigue (CIS). Fatigue and fatigue related symptoms are measured with the Checklist Individual Strength (CIS).[188] The CIS is a multidimensional fatigue scale; it measures fatigue severity (eight items), concentration problems (five items), reduced motivation (four items), and reduced activity (three items). Each item is scored on a seven-point Likert scale. Total scores of every subscale are obtained by adding the individual items, with high scores indicating a high level of fatigue, a high level of concentration problems, low motivation, and a low level of activity. Based on data from patients with chronic fatigue syndrome, patients with a score of >35 on the fatigue severity subscale are considered to be severely fatigued.

Cognitive functioning. Patient's self-reported cognitive functioning is rated by the scale developed for use in the Medical Outcomes Study.[190] This six-item scale assesses day-to-day problems in cognitive functioning including difficulty with reasoning and problem solving, slowed reaction time, forgetfulness, and problems with concentration (range 1-6).

Costs (TIC-P). Costs in terms of health care utilization and production loss is assessed with the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TIC-P).[218] This questionnaire consists of two parts; part one covers the direct costs of care utilization of participants (15 items), and part two is used to determine indirect costs that result from production loss associated with the psychiatric symptoms. Here, the Short Form Health and Labor Questionnaire[219] is incorporated. This questionnaire contains three modules that assess the absence from paid employment, production loss without absence from paid employment, and impediments to paid or unpaid employment.

Patient satisfaction. During the post-intervention assessment (T1 or T3), the patients' experience with the online course is evaluated. A short study-specific questionnaire evaluating the usability, readability, course content, and self-perceived usefulness of both the online course and the feedback provided by the coach is presented along the other questionnaires. Room for remarks is provided as well.

Statistical analyses

Appropriate parametric and non-parametric statistical tests will be employed to examine differences between the groups in terms of all relevant demographic and clinical variables at baseline. Missing observations at follow-up will be imputed using the multiple imputation procedure.[220] Following the CONSORT guidelines, the intention-to-treat principle will be applied. All randomized participants will be included in the analyses, regardless of how many treatment modules or sessions they complete. Within-group and between-group differences (e.g., patients with or without epileptic seizures, pain, neurological deficits, or self-reported cognitive deficits) in dependent variable scores will be analyzed using both univariate and multivariate statistical techniques. For between-group statistical comparisons, sociodemographic variables (age, gender, and education) will be used as covariates, where necessary. The effects of the interventions will be tested by means of Helmert contrasts. Relative improvements in depressive

symptoms (CES-D score) in the experimental group compared with pre-treatment assessment as well as both control groups will be calculated using Cohen's d. If the primary outcome measure is non-normally distributed, the test and the 95% confidence intervals will be based on robust standard errors and/or on non-parametric bootstrap techniques. This will help to correctly ascertain the relative effectiveness of the treatment over the control conditions.

Sample size

The effect of the intervention on symptoms of depression is the primary outcome measure and this is used as starting point for the sample size calculations. Based on previous experience with this intervention in adults, we expect a Cohen's d of 0.50. Assuming an alpha of 0.05 and a statistical power (1-beta) of 0.80, we need 50 patients in each condition. Allowing for a dropout percentage of 25% once included, we aim to recruit 126 glioma patients (63 per group) and 63 patients with hematological malignancies in total.

DISCUSSION

In this paper, we describe the study design of a randomized controlled trial aimed at evaluating the effects of an internet-based, guided self-help intervention for depressive symptoms in glioma patients. This study is innovative in two ways: 1) as of yet, there is no evidence from RCTs for the effectiveness of psychotherapy in glioma patients with depressive symptoms; and 2) to our knowledge, providing psychosocial care through the internet has not been explored in the depressed glioma patient population until now.

We expect the external validity of this study to be high, as we employ only few exclusion criteria. Any adult WHO grade II, III or IV glioma patient at any disease stage with mild depressive symptoms is invited to participate in the trial to try and relief these symptoms. Furthermore, as the intervention is administered through the internet and patient inclusion is organized nation-wide, we should be able to reach a large group of potential participants. Using the internet also evidently has its downsides. For certain patients, such as those unaccustomed to using the computer in their everyday lives or those with more severe cognitive impairment, using the internet may prove more difficult and could possibly result in non-participation or dropout of the study. We aim to construct the website in a very straightforward and easy-to-use way, in order to minimize this possibly negative effect. In addition, both interventions using the internet and self-help interventions are prone to high dropout rates,[221] suggesting that this problem could occur in our trial as well. Therefore we present the online questionnaires separately from the intervention website, and email reminders are sent for both the assessments and the course assignments separately. Moreover, if participants do not respond to these reminders, we try and contact them through telephone instead. This should strengthen the relationship between the participants and the researchers substantially, thereby possibly improving patient participation throughout the trial.[222]

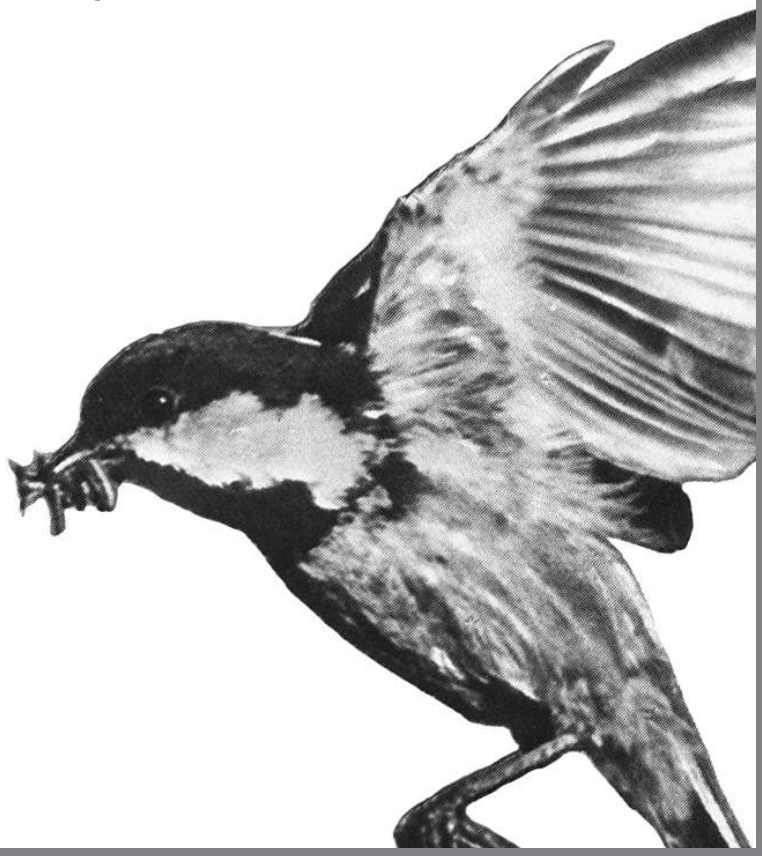
Our frequent follow-up assessments, up until 12 months after the guided self-help course, enable evaluation of both short- and long-term effects of the intervention. However, frequent

evaluation of mental well-being through self-reported questionnaires may also lead to patients' increased awareness of their depressive symptoms. To minimize this possible effect we keep track of the patients' suicidal ideation and depressive symptoms throughout follow-up and we will contact both the participant and their general practitioner in case symptoms worsen significantly.

Due to its nationwide design, our study could raise awareness of depressive symptoms among both physicians and patients. Whereas this is favorable for patients, it may lead to a risk for contamination in this randomized controlled trial, as more psychological help may be offered outside of the intervention offered in our study. However, the TIC-P assessment records all contact with health-care professionals, so with adequate power we will be able to correct for this in the analyses.

In conclusion, we currently present the design of our study aimed at improving symptoms of depression in glioma patients using a brief internet-based guided self-help intervention based on the principles of PST. This can provide methodological clarity and can aid and encourage further research efforts to improve mood and HRQOL in glioma patients. Our randomized controlled trial is expected to contribute substantially to the existing literature as there is a hiatus in both studies evaluating the effectiveness of different treatments for depression, as well as interventions delivered by means of the internet in this patient population. Furthermore, implementation in clinical practice should be relatively easy to accomplish if our intervention proves to be effective, as it only requires minimal involvement of health care professionals. Currently, this trial is in the recruitment phase.

Section 3:
Towards improving health-related quality of life in informal caregivers of glioma patients



Chapter 3.1

Health-related quality of life of significant others of patients with malignant CNS versus non-CNS tumors: a comparative study

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ABSTRACT

Background*:* It is often assumed that brain tumor patients' significant others (SOs: partners, other family members or close friends) may face greater stress than those of patients with malignancies not involving the central nervous system (CNS), due to progressive changes in neurological and cognitive functioning. We compared health-related quality of life (HRQOL) of SOs of patients with high-grade glioma (HGG) and low-grade glioma (LGG) with that of SOs of patients with non-CNS tumors with similar prognosis and at a similar phase in the disease trajectory (i.e. non-small cell lung cancer (NSCLC) and low-grade hematological malignancies (NHL/CLL), respectively).

Methods*:* HRQOL of SOs and patients was assessed using the Short Form-36 (SF-36) Health Survey. Patients' neurological functioning was indexed and they underwent comprehensive neurocognitive testing.

Results: SOs of 213 LGG patients, 99 NHL/CLL patients, 55 HGG patients and 29 NSCLC patients participated. The SOs of LGG and NHL/CLL patients reported similar levels of HRQOL. SOs of HGG patients reported significantly lower mental health scores (MCS; p=0.041) and social functioning (p=0.028) than those of NSCLC patients. Mental health scores (MCS) of HGG and NSCLC patients were associated significantly with the mental health of their SOs (p=0.013 and p<0.001, respectively). Surprisingly, HGG patients' cognitive and neurological functioning were not predictive of SOs' mental health at the multivariate level.

Conclusion*:* SOs of patients with highly malignant CNS tumors in the acute phase are at increased risk of compromised HRQOL compared to those of patients with systemic tumors without CNS involvement and a comparable life expectancy.

INTRODUCTION

The diagnosis, disease trajectory, and treatment of a malignant tumor have a profound impact on the lives of both patients and their significant others (SOs: including partners, family members or close friends). Across different stages of the disease trajectory, SOs may experience considerable stress and caregiver burden, fatigue, and financial strain.[223, 224] They often experience levels of psychological distress equal to or even greater than that of the patients themselves.[224, 225] In particular, previous studies have indicated that the mental health aspects of the health-related quality of life (HRQOL) of SOs of cancer patients may be particularly affected.[226, 227]

With an incidence of five to seven per 100,000,[228] gliomas are the most common primary brain tumors. The median survival for glioma patients depends on the malignancy grade of the tumor. Patients with glioblastoma multiforme (GBM; WHO grade IV) have a median survival of one to two years,[6] whereas patients with low-grade glioma (LGG) can live substantially longer, with a median survival of approximately 16 years for low-grade oligodendroglioma.[119] Yet, even within relatively homogeneous patient groups, the survival range can vary considerably at the individual patient level and is largely unpredictable.[229]

Because SOs of brain tumor patients not only have to deal with the diagnosis of cancer in their loved one, but are also confronted with the neurological sequelae associated with the disease and progressive changes in neurological and cognitive functioning, it is assumed that these SOs experience greater levels of distress than SOs of patients with tumors not involving the central nervous system (CNS).[15, 27, 158] However, this assumption has, to our knowledge, not been examined empirically. Because identifying vulnerable SO groups is an important step in developing possible interventions aimed at improving their well-being, we performed a cross-sectional, observational study to compare the HRQOL of the SOs of glioma patients with that of SOs of patients with non-CNS malignancies. As we expected that mental health of SOs in particular is a potential target in future intervention studies, an additional aim of the study was to identify patient-related variables (e.g., HRQOL, neurological and cognitive functioning) associated with the mental health of those SOs suffering from a deterioration in HRQOL.

MATERIALS AND METHODS

Participants

The data reported here were derived from a larger, nationwide, multicenter study of the neurocognitive functioning and HRQOL of glioma patients and their SOs (here defined as a spouse or partner, family member or good friend of the patient). The study design and methods have been reported in more detail elsewhere.[9, 31, 121] Briefly, glioma patients were recruited from 11 neurosurgical centers throughout the Netherlands (see the acknowledgements for a complete list of participating centers). LGG patients were included in the study if they had: (1) been diagnosed with a histologically confirmed low-grade astrocytoma, oligodendroglioma, or oligoastrocytoma at least one year prior to study entry; (2) no clinical signs of tumor recurrence for at least one year after diagnosis and primary treatment; (3) no radiological signs

of recurrence within three months before the first assessments were performed, (4) no current treatment with corticosteroids, and (5) basic proficiency in the Dutch language. On average, patients were diagnosed six years prior to data collection.

HGG patients were recruited into the study if they: (1) had histologically confirmed anaplastic glioma or GBM; (2) had a life expectancy of three months or more; (3) were eligible for postoperative radiotherapy; and (4) had basic proficiency of the Dutch language. They were recruited after initial diagnosis but prior to receiving post-operative treatment.

Two comparison groups were formed simultaneously, one for the LGG and one for the HGG patient-SO samples. As a comparator for the LGG sample, we included patients with non-Hodgkin's lymphoma or chronic lymphatic leukemia (NHL/CLL) and their SOs. The NHL/CLL patients had to have no radiological signs of recurrence within three months before the first assessment, no clinical signs of CNS involvement, and they had to have completed treatment at least one year earlier. The second comparison group was composed of patients with non-small cell lung cancer (NSCLC, stage IIIa/IIIb/IV) and their SOs. The NSCLC patients had to have (1) a life expectancy of three months or more; (2) a basic proficiency of the Dutch language; and (3) no clinical evidence of brain metastases. The NHL/CLL and the NSCLC comparison groups were chosen because of similarities in terms of disease stage, expected disease course and prognosis with that of the LGG and the HGG patient groups, respectively. For the interpretation of the neuropsychological data, healthy control groups, matched for age, sex, and educational level were formed. These controls were selected from a large cohort of healthy participants of the Maastricht Aging Study.[125]

All patients were asked to identify a SO who could be invited to take part in the study. The current analysis was restricted to the available patient-partner dyads, i.e., those patients whom had a SO who was willing to participate in the study.

Procedures

After inclusion procedures, SOs were asked to complete the Short Form-36 (SF-36) Health Survey[19] once. The SF-36 is composed of 36 items, organized into eight multi-item scales assessing: (1) physical functioning; (2) limitations in role functioning due to physical problems; (3) limitations in role functioning due to emotional problems; (4) pain; (5) vitality; (6) social functioning; (7) mental health; and (8) general health perceptions. Raw scores are converted linearly to 0 to 100 scales, with higher scores indicating better levels of functioning. From these scales, two higher-order summary scores can be calculated: (1) Physical Component Summary (PCS), measuring physical health; and (2) Mental Component Summary (MCS), measuring mental health. The SOs also were asked to provide sociodemographic information, including their age, gender and level of education.

The patients underwent objective neuropsychological testing and completed a series of self-report questionnaires. Details of the neuropsychological test battery are reported in more detail elsewhere.[9, 31, 121] Briefly, it included a broad range of tests assessing perception and psychomotor speed, memory, attention, and executive function. Self-report questionnaires included measures of performance status (Karnofsky Performance Status[230]), activities of daily living (ADL; Barthel Index[231]), HRQOL (SF-36), neurological functioning (EORTC QLQ-BN20[22]) and subjective cognitive functioning (MOS subjective cognitive functioning scale[190]).

The study was approved by the institutional review boards of all participating centers. All patients and SOs provided written, informed consent.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0.[232] Standard scoring rules were used to convert the data from the questionnaires. The SF-36 PCS and MCS scores were calculated based on normative data of 2,393 Americans from the general population. Sociodemographic characteristics of the LGG and NHL/CLL groups as well as of the HGG and NSCLC groups were compared using univariate analysis of variance (ANOVA) and the chi-square statistic. Multivariate analysis of covariance (MANCOVA) adjusting for age (for the low-grade malignancy groups) and educational level (for the high-grade malignancy groups) was performed to compare the HRQOL of the SOs of the LGG patients with that of the SOs of the NHL/CLL patients, and the HRQOL of the SOs of the HGG patients with that of the SOs of the NSCLC patients. Effect sizes were calculated using Cohen's d statistic. Cohen's d of 0.20 is considered a small effect size, of 0.50 a moderate effect size, and 0.80 a large effect size.[233] If differences between the groups were found, univariate linear regression analyses were conducted to assess the association between patient-related factors (age, gender, performance status, ADL, HRQOL, neurological functioning, subjective and objective cognitive functioning) and the mental health of the SOs. Neuropsychological test scores were dichotomized to represent either normal or impaired scores (i.e., two standard deviations below the mean of healthy matched controls). The total number of deviant test scores was used as a measure of overall objective cognitive functioning. Those variables that were significantly associated with the SO's SF-36 scores at the 0.10 level were subsequently entered in a backward multivariate linear regression analysis. Here, a two-sided *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic characteristics

Approximately 70% of the patients identified a SO who could be invited to participate in the study. For the original study, 281 LGG patients, 68 HGG patients, 143 NHL/CLL patients, and 50 NSCLC patients signed written, informed consent. The current study sample included 213 LGG patient-SO dyads, 55 HGG patient-SO dyads, 99 NHL/CLL patient-SO dyads, and 29 NSCLC patient-SO dyads (see Table 1). Primary reasons for SO non-participation included perceived burden of the study (37.0%), and insufficient mastery of the Dutch language or visual or mental disability (14.8%). 48.2% of non-participants did not provide a reason.

The SOs of the NHL/CLL patients were significantly older than those of the LGG patients ($p<0.001$) while the educational level of the SOs of the HGG patients was significantly higher than that of the SOs of the NSCLC patients ($p=0.004$). From the patient report forms we learned that the large majority of SOs were partners of the patients, although it should be noted that this information was not available for 36 dyads in total (9.1% of all participants), see Table 1.

Table 1. Characteristics of SOs of LGG, NHL/CLL, HGG and NSCLC patients.

	LGG SOs (*N*=213)	NHL/CLL SOs (*N*=99)	*p*-value	HGG SOs (*N*=55)	NSCLC SOs (*N*=29)	*p*-value
Age in years *M* (sd)	45.27 (11.94)	52.96 (11.94)	< 0.001*	53.31 (11.43)	57.32 (11.75)	0.133
Gender N (%)			0.898			0.918
Male	78 (36.6%)	37 (37.4%)		9 (16.4%)	5 (17.2%)	
Female	135 (63.4%)	62 (62.2%)		46 (83.6%)	24 (82.8%)	
Educational level N (%)			0.440			0.004*
Low	62 (29.1%)	31 (31.3%)		14 (25.5%)	14 (48.3%)	
Middle	89 (41.8%)	46 (46.5%)		16 (29.1%)	12 (41.4%)	
High	62 (29.1%)	22 (22.2%)		25 (45.4%)	3 (10.3%)	
Marital status N (%)			0.268			0.527
Single	9 (4.2%)	7 (7.1%)		2 (3.6%)	0 (0.0%)	
Married or living together	195 (91.5%)	91 (91.9%)		50 (90.9%)	28 (96.6%)	
Divorced	3 (1.4%)	1 (1.0%)		3 (5.4%)	1 (3.4%)	
Widow(er)	6 (2.8%)	0 (0.0%)		0 (0%)	0 (0%)	
Relationship to patient N (%)			0.002*			0.129
Husband, wife or partner	152 (71.4%)	90 (90.9%)		43 (78.2%)	25 (86.2%)	
Parent	24 (11.3%)	1 (1.0%)		2 (3.6%)	0 (0.0%)	
Sibling	3 (1.4%)	2 (2.0%)		1 (1.8%)	1 (3.4%)	
Child	5 (2.3%)	1 (1.0%)		0 (0.0%)	2 (6.9%)	
Friend	2 (0.9%)	1 (1.0%)		6 (10.9%)	0 (0.0%)	
Unknown	27 (12.7%)	5 (5.1%)		3 (5.4%)	1 (3.4%)	

Abbreviations: SO, significant other; LGG, low-grade glioma; NHL/CLL, non-Hodgkin lymphoma/chronic lymphatic leukemia; HGG, high-grade glioma; NSCLC, non-small cell lung cancer
*p<0.05

HRQOL (SF-36)

SOs of LGG patients versus NHL/CLL patients

Corrected for age, we found no statistically significant differences in HRQOL, as measured by the SF-36, between the SOs of the LGG patients and those of the NHL/CLL patients (Table 2).

HGG patient partners versus NSCLC patient partners

As shown in Table 3, corrected for differences in educational level, the SOs of the HGG patients reported significantly worse mental health as assessed by the SF-36 mental component summary (MCS) than the SOs of the NSCLC patients (p=0.041, d=0.48). The SOs of the HGG patients also reported significantly lower social functioning than those of the NSCLC patients (p=0.028, d=0.495). No other statistically significant group differences in SF-36 scores were observed.

Table 2. Means and standard deviations for HRQOL scores for SOs of LGG and NHL/CLL patients.

	LGG SOs (*N*=213)	NHL/CLL SOs (*N*=99)	*p*-value
Component scales			
Physical Component Summary M (sd)	51.54 (8.40)	50.01 (9.76)	0.385
Range	23.24–67.89	21.65–66.15	
Mental Component Summary M (sd)	48.94 (10.67)	50.39 (10.96)	0.203
Range	16.11-64.58	18.94–68.09	
SF-36 subscales			
Physical functioning	89.31 (17.11)	85.03 (20.97)	0.254
Physical role functioning	77.54 (34.34)	78.03 (36.47)	0.782
Bodily pain	80.47 (22.81)	76.98 (24.40)	0.398
Social functioning	82.86 (20.99)	84.22 (21.99)	0.329
Mental health	72.19 (18.94)	73.49 (18.78)	0.348
Emotional role functioning	80.13 (34.36)	81.14 (35.37)	0.599
Vitality	65.03 (19.66)	67.14 (20.24)	0.477
General health perceptions	71.48 (21.02)	70.39 (16.66)	0.707

Abbreviations: HRQOL, health-related quality of life; SO, significant other; LGG, low-grade glioma; NHL/CLL, non-Hodgkin lymphoma/chronic lymphatic leukemia; SF-36, Short-form 36 Health Survey.

Table 3. Means and standard deviations for HRQOL scores for SOs of HGG and NSCLC patients.

	HGG SOs (*N*=55)	NSCLC SOs (*N*=29)	*p*-value
Component scales			
Physical Component Summary M (sd)	52.61 (9.99)	49.39 (9.04)	0.370
Range	27.64–68.59	32.87-63.22	
Mental Component Summary M (sd)	36.37 (12.45)	42.56 (12.69)	0.041*
Range	9.90-60.20	14.66-64.43	
SF-36 subscales M(sd)			
Physical functioning	85.75 (17.69)	82.76 (15.27)	0.803
Physical role functioning	60.91 (46.59)	54.02 (38.87)	0.774
Bodily pain	77.85 (24.46)	76.69 (23.77)	0.963
Social functioning	60.68 (28.61)	74.14 (22.14)	0.028*
Mental health	54.80 (21.56)	60.28 (21.55)	0.168
Emotional role functioning	41.21 (42.05)	55.17 (37.03)	0.219
Vitality	54.36 (20.53)	60.00 (16.37)	0.123
General health perceptions	67.40 (21.88)	64.59 (18.40)	0.993

Abbreviations: HRQOL, health-related quality of life; SO, significant other; HGG, high-grade glioma; NSCLC, non-small cell lung cancer; SF-36, Short-form 36 Health Survey.
*$p<0.05$

Patient-related factors associated with SO's mental health

Several patient-related variables were found to be associated significantly with the SF-36 MCS scores of the SOs of both the HGG and the NSCLC patients at the univariate level (Table 4 and Table 5).

The mental health (MCS) of the SOs of the HGG patients exhibited a significant, positive association with the mental health (MCS) of the patients (r^2 = 0.098, p=0.020), and a significant negative association with patients' subjective cognitive functioning (r^2 = 0.050, p=0.090), as well as with three aspects of the patients' brain cancer-specific HRQOL: uncertainty about the future (r^2 = 0.086, p=0.030); drowsiness (r^2 = 0.091, p=0.021); and motor dysfunction (r^2 = 0.062, p=0.062) (Table 4).

The mental health (MCS) of the SOs of the NSCLC patients exhibited a very similar pattern of association with the patients' mental health (r^2 = 0.327, p<0.001) and the patients' sense of uncertainty about the future (r^2 = 0.129, p=0.034). In addition, patients' age was associated positively (r^2 = 0.080, p=0.100), and objective measures of cognition were associated negatively (r^2 = 0.080, p=0.099) with SOs' mental health (Table 5).

In the multivariate regression analyses, the patients' mental health status (MCS) was associated significantly with the SOs mental health (r^2 = 0.301, p=0.034 and r^2 = 0.464, p=0.002, for the HGG and the NSCLC patient SOs, respectively) (Tables 4 and 5). Furthermore, patients' cognitive functioning was associated significantly with NSCLC SOs' mental health (r^2 = -0.363, p=0.019).

DISCUSSION

The present study clearly shows that not all partners of all cancer patient groups experience the same limitations in HRQOL. The most prominent finding of our study is that the SOs of recently diagnosed HGG patients suffer from significantly lower levels of mental health and social functioning than SOs of recently diagnosed NSCLC patients, while both partner groups experienced similar burden in term of the dismal prognosis and the disease phase of their loved one. Contrary to what one might expect given the nature of the different diseases, the HRQOL of SOs of stable LGG and NHL/CLL patients did not differ. It appears that the added burden of neurological and cognitive deficits associated with being the SO of a glioma patient does not necessarily impact on the SO's HRQOL, at least not as measured by the SF-36 and objective neuropsychological assessment.

When the prognosis is poorer and the diagnosis is more recently established, as was the case in our HGG patient cohort, having a glioma appears to impact negatively on the SO's mental health. This is consistent with a study by Janda *et al.*, who described that, in a diverse group of brain tumor patients and their informal caregivers (relatives and friends), there was a trend for lower HRQOL among those taking care of patients with a glioblastoma multiforme compared to lower-grade CNS tumors.[198] Consistent with our findings in the univariate analyses of patient-related factors, previous studies have found that patients with more rapidly progressive malignant tumors report more uncertainty concerning the future than patients with less rapidly progressive malignant tumors,[9, 31] and that fear of tumor recurrence can have a profound impact on the HRQOL of patient and partners alike.[234] A different study on caregivers of patients with malignant gliomas

Table 4. Backward linear regression analysis for mental health (MCS) of SOs of HGG patients.

				95% Confidence Interval	
Model	**B**	**R^2**	***p*-value**	**Lower bound**	**Upper bound**
Univariate analyses					
Age patient	0.090	0.009	0.472	-0.158	0.337
Gender patient	2.971	0.011	0.439	-4.654	10.595
Tumor grade patient	-0.146	<0.001	0.970	-7.811	7.519
Lateralisation tumor patient	-2.371	0.009	0.471	-8.909	4.167
Cognition patient	-0.168	0.003	0.668	-0.947	0.612
Subjective cognition patient	-0.157	0.050	0.090*	-0.339	0.025
Barthel patient	-0.238	0.003	0.688	-1.418	0.943
Karnofsky patient	-0.053	0.005	0.580	-0.242	0.137
PCS patient (SF36)	0.004	<0.001	0.982	-0.340	0.348
MCS patient (SF36)	0.368	0.098	0.020**	0.060	0.676
Future uncertainty (BN20)	-0.126	0.086	0.030**	-0.239	-0.013
Visual disorder (BN20)	-0.043	0.003	0.673	-0.246	0.160
Motor dysfunction (BN20)	-0.136	0.062	0.060*	-0.278	0.006
Communication deficit (BN20)	-0.091	0.039	0.137	-0.211	0.030
Headaches (BN20)	-0.024	0.004	0.645	-0.126	0.079
Seizures (BN20)	-0.008	<0.001	0.886	-0.118	0.102
Drowsiness (BN20)	-0.165	0.091	0.021**	-0.306	-0.025
Multivariate analyses					
MCS patient	0.348	0.301	0.034**	0.028	0.669

Abbreviations: SO, significant other; HGG, high-grade glioma; SF36, Short-form 36 Health Survey; BN20, brain cancer module.
*p<0.10; **p<0.05

reported that declining health and fear that the loved one would die was negatively associated with the HRQOL of caregivers of glioma patients.[235] In our study however, uncertainty concerning the future, a scale that takes this fear into account, was not predictive of the SOs' HRQOL at the multivariate level (although a significant association was observed at the univariate level). Unexpectedly, glioma patients' cognitive and neurological functioning proved to be less important to glioma patient SOs' mental health than is commonly assumed. Moreover, contrary to a study on caregivers of a diverse group of cancer patients,[225] we did not find a significant association between the physical functioning of the patient and the SOs' HRQOL. Mental health, however, was associated significantly with the HRQOL of the SOs of both the HGG and the NSCLC patients. We would note, however, that the amount of variance in SOs' mental health scores explained by the mental health of the patients was relatively modest, particularly for the HGG sample.

Several limitations of the study should be noted. Due to the nature of this multi-center study described previously, mental well-being of SOs of cancer patients was not the primary objective of the study. As a consequence, we could not compare SOs of the low- and high-grade malignancy groups because the time since diagnosis of the patients differs by a number

Table 5. Backward linear regression analysis for mental health (MCS) of SOs of NSCLC patients.

				95% Confidence Interval	
Model	**B**	**R^2**	***p*-value**	**Lower bound**	**Upper bound**
Univariate analyses					
Age patient	0.422	0.080	0.100*	-0.085	0.930
Gender patient	-3.934	0.012	0.531	-16.573	8.705
Cognition patient	-0.915	0.080	0.099*	-2.011	0.181
Subjective cognition patient	-0.134	0.014	0.493	-0.527	0.259
Barthel patient	-0.438	0.002	0.795	-3.839	2.964
Karnofsky patient	-0.003	<0.001	0.985	-0.297	0.291
PCS patient (SF36)	-0.263	0.047	0.212	-0.684	0.157
MCS patient (SF36)	0.608	0.327	<0.001**	0.299	0.917
Future uncertainty (BN20)	-0.184	0.129	0.034**	-0.353	0.015
Visual disorder (BN20)	0.085	0.012	0.538	-0.193	0.364
Motor dysfunction (BN20)	-0.047	0.003	0.771	-0.373	0.279
Communication deficit (BN20)	-0.038	0.002	0.789	-0.320	0.245
Headaches (BN20)	0.006	<0.001	0.948	-0.177	0.188
Drowsiness (BN20)	-0.020	0.001	0.835	-0.214	0.174
Multivariate analyses					
MCS patient	0.494	0.464	0.002**	-0.190	0.797
Cognition patient	-1.171	-0.363	0.019**	-2.138	-0.205
Age patient	0.457	0.306	0.052	-0.003	0.918

Abbreviations: SO, significant other; NSCLC, non-small cell lung cancer; SF36, Short-form 36 Health Survey; BN20, brain cancer module.
*p<0.10; **p<0.05

of years. Therefore we cannot determine at what point in time these SOs might benefit most from psychological interventions. Furthermore, only data on HRQOL of SOs were collected. Since the amount of variance in SOs' mental health explained by our model was quite modest, it seems plausible that there are other factors that may be associated with SOs' mental health.

Future studies should also include other assessments such as caregiver burden, depression and anxiety. Using a qualitative approach may add valuable information, as this may provide data that is not covered by questionnaires. In addition, while we evaluated HRQOL of SOs of four different groups of cancer patients, it would be valuable to compare these with a group of SOs of non-cancer patients undergoing neurosurgery per se to determine its relative contribution. As HRQOL is diminished in, for example, patients with subarachnoid hemorrhage and patients treated for unruptured intracranial aneurysms,[236, 237] exploring their SOs' HRQOL in comparison to our cancer patient SO groups seems worthwhile.

Despite these imperfections and our recommendations for future studies, the present cross-sectional analysis of multi-center data adds valuable information regarding HRQOL in SOs of cancer patients to the existing body of literature. In this relatively large dataset we show that SOs of recently diagnosed HGG patients experience worse mental health and that they are

an especially vulnerable group compared to SOs of patients with a recently diagnosed non-CNS high-grade malignancy. Better mental health of the patient proved to be modestly predictive of better mental health of HGG SOs. This knowledge provides new insight in potential areas that can be addressed in supportive interventions. We recommend that targeted psychological interventions be developed which include support in coping with impaired mental health of the patient in order to enhance HRQOL of significant others of HGG patients.

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Chapter 3.2

Enhancing quality of life and mastery of informal caregivers of high-grade glioma patients: A randomized controlled trial

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ABSTRACT

Background: High-grade gliomas (HGG) are serious primary brain tumors that may prevent the patient from functioning normally in social, emotional and cognitive respect. Often the partner's role will convert to that of informal caregiver. Consequently, they may experience significant stress and reductions in caregiver mastery, negatively affecting their health-related quality of life (HRQOL). We aimed at 1) determining factors that impact HRQOL and mastery of caregivers of HGG patients, and 2) investigating if a structured intervention consisting of psychoeducation and cognitive behavioral therapy leads to improvements in the mental component of HRQOL and mastery of caregivers.

Methods: Fifty-six patient-caregiver dyads were randomly assigned to the intervention group or the care as usual group. The intervention program consisted of six one-hour sessions with a psychologist. Participants completed questionnaires concerning their perceptions of the patients' HRQOL (SF-36), neurological functioning (BN20), and cognitive functioning (MOS), and concerning their own HRQOL (SF-36) and feelings of caregiver mastery (CMS) both at baseline (i.e. before randomization) and every two months thereafter until eight months later, five times in total.

Results: Patients' HRQOL and neurological functioning were found to be related to HRQOL and feelings of mastery of the informal caregiver at baseline. The intervention helped caregivers in maintaining a stable level of HRQOL and improved feelings of mastery over an eight month period.

Conclusions: Our findings suggest that informal caregivers can benefit from a psychological intervention as it is a helpful tool in maintaining a stable level of mental functioning and caregiver mastery.

INTRODUCTION

Primary brain tumors, as opposed to types of cancer not involving the central nervous system, have a direct effect on brain functioning. Primary brain tumor patients may be confronted with significant changes in cognitive functioning, mood, and personality.[27, 158] As a result, these patients tend to be more dependent on relatives than patients with other types of cancer.[238] In most cases, the partner is the person most involved and thus becomes the primary informal caregiver. In response to this new role and the grave disease of their loved one, informal caregivers of brain tumor patients may experience considerable stress and caregiver burden.[15, 239]

Informal caregivers of high-grade glioma (HGG) patients particularly may face stressful demands due to the behavioral problems associated with patient's cognitive deficits that may already be present early in the disease trajectory.[27] Health-related quality of life (HRQOL) of informal caregivers is further associated with HRQOL of the brain tumor patient, tumor grade, and neurological and neuropsychiatric symptoms experienced by the patient.[198, 235] As patient behavior becomes more problematic in the course of the disease, reductions in perceived caregiver mastery (i.e. the combined effects of the caregiver's self-perception and actual ability to successfully perform the activities of providing care) may also negatively affect caregiver's HRQOL.[197, 240]

Although many informal caregivers enjoy a profound sense of privilege and may derive deep satisfaction in this role, sadness, guilt, anger, resentment, and a sense of inadequacy are also common and understandable reactions. Furthermore, exhaustion, financial strain, disrupted daily activities, and continuous caregiving contribute to significant mental health morbidity, including anxiety and depression.[241] Caregiving is not only associated with poor sleep[242] but approximately half of all caregivers experience clinical depression, with intense caregivers (those providing at least 21 hours of care per week) having the highest incidence (61%) of depressed mood.[243, 244]

Given that caregiving has negative mental and physical sequelae for partners in general and for partners of brain tumor patients in particular, surprisingly few rigorous studies of supportive care interventions have been performed.[245-248] Research to date indicates that, while continuing to face significant caregiving stress, caregivers of cancer patients can benefit greatly from supportive psychological interventions based on cognitive behavioral therapy (CBT) and psychoeducational principles[246, 247] leading to clinically significant improvements in the caregiver's well-being.

In line with the studies described, our study aimed at determining whether apart from tumor characteristics, HRQOL and neurological symptoms of the patient as perceived by caregivers are indeed related to the informal caregiver's HRQOL and feelings of mastery. Furthermore, we developed a supportive intervention based on CBT and psychoeducation in order to determine, in a randomized controlled setting, whether this intervention enhances HRQOL and feelings of mastery of informal caregivers of HGG patients.

MATERIALS AND METHODS

Participants

From 2008 to 2010, eligible patient-caregiver dyads were identified through three tertiary referral centers for neuro-oncological patients: VU University Medical Center (Amsterdam), Academic Medical Center (Amsterdam), and Medical Center Haaglanden (The Hague), the Netherlands. Participants were included if they: 1) were informal caregivers (i.e. a spouse or significant other providing at least 21 hours of care per week) of high-grade glioma (grade III or IV) patients; 2) were ≥ 18 years old, and 3) gave written informed consent. Caregiver-patient dyads were excluded if 1) the patient had a life expectancy of less than three months; 2) the caregiver was unable to complete questionnaires due to insufficient mastery of the Dutch language or severe visual impairments and 3) the caregiver was unable to understand or apply the skills taught in the intervention due to (a) physical or mental condition(s). The physician or nurse practitioner of the patients introduced informal caregivers to the study. Local ethics committees of the participating medical centers approved the study protocol.

Outcome measures

Informal caregivers completed questionnaires concerning their HRQOL and feelings of caregiver mastery (caregiver measures). Furthermore, informal caregivers completed questionnaires concerning their view on the patient's HRQOL, cognitive and neurological functioning explicitly without consulting the patient (patient by proxy measures). This method was based on the assumption that the subjective perception of the patients' functioning rather than the patients' actual condition affects HRQOL and feelings of mastery of informal caregivers most.[249]

MOS 36-item short-form health survey (SF-36) (caregiver + patient by proxy).[250] This HRQOL survey is composed of 36 items, organized into eight multi-item scales assessing: (1) physical functioning; (2) limitations in role functioning due to physical problems; (3) limitations in role functioning due to emotional problems; (4) pain; (5) vitality; (6) social functioning; (7) mental health; and (8) general health perceptions. From these scales, two higher-order summary scores are composed: 1) Physical Component Summary (PCS), measuring physical functioning; 2) Mental Component Summary (MCS), measuring mental functioning.

Caregiver Mastery Scale (CMS) (caregiver).[251] General caregiver mastery was assessed with a seven-item scale. Caregivers were asked whether they agreed or disagreed with seven statements such as 'You believe you are mastering most of the challenges in caregiving', to indicate their perceptions of how well they were able to provide the necessary care (range 1-4). Higher scores on this scale indicate less feelings of mastery.

MOS subjective cognitive functioning scale (patient by proxy).[190] This six-item scale assesses day-to-day problems in cognitive functioning including difficulty with reasoning and problem solving, slowed reaction time, forgetfulness, and problems with concentration (range 1-6).

Brain Cancer Module (BN20) (patient by proxy).[22, 149] This module, assessing patients' neurological functioning, consists of 20 items of which 13 are organized into five scales assessing future uncertainty, visual disorder, motor dysfunction, communication deficit, and emotional distress. The remaining seven items assess other disease symptoms and side-effects of treatment, including headaches, seizures, drowsiness, and weakness in the legs (range 1-4).

Procedure

After obtaining both patient's and caregiver's informed consent, sociodemographic and clinical data were obtained from the patients' medical records. Informal caregivers received questionnaires for the baseline assessment (i.e. before randomization) by mail. Upon filling in and returning these questionnaires, caregivers were randomly assigned to either the control group or the intervention group. Informal caregivers in both study arms were asked to complete questionnaires every two months, five times in total.

Intervention group

Starting at baseline, individual and completely protocolized sessions of a psychologist with caregivers were held every other week for a maximum of six one-hour sessions. The intervention is designed to empower caregivers by providing psychoeducation regarding disease-specific symptoms and the resulting everyday problems, as well as offering CBT to increase their ability to cope with the demands of managing and providing care to the HGG patient. First, the caregiver and psychologist reviewed the symptoms experienced by the patient and the caregiver's involvement, and then, based on a prioritization of the need for help to assist with the patient symptoms, the psychologist and caregiver drew upon a pre-defined set of strategies. During the first session, patient and caregiver history and current functioning was documented. During the second session, an introduction of the intervention and rationale of CBT was given. For the next four sessions, informal caregivers could make a selection of topics they wanted to discuss. The options were: 1), contact with the patient, 2) the direct environment (contact with family, friends and others), 3) epilepsy, 4) changes in behavior, character and cognition, 5) time for yourself, 6) children (what and how to tell them), 7) practical and emotional care in the patient's end-of-life phase.

Control group

Patient-caregiver dyads in the control group received care as usual, which includes interactions with specialized neuro-oncology nurses, general practitioners and other professional caregivers, referrals to specialists when indicated, and opportunities for receiving support through a range of outside agencies such as the Dutch Cancer Society support group.

Statistical analysis

Statistical analyses were performed using SPSS version 15.0.[232] Standard scoring rules were used to convert the data from the questionnaires. A group of controls from the general population

matched for age, gender and educational level was used as a reference group in calculating higher-order scores for the SF-36. Differences in demographic characteristics and baseline levels of both outcome measures (mental functioning, caregiver mastery) and possible confounding factors (cognitive functioning, HRQOL of the patient, neurological functioning) between the groups were assessed using independent sample t-tests and chi-square tests. Exploratory Spearman rank correlations and chi-square tests were computed to explore if cognitive functioning (MOS), HRQOL of the patient (SF-36), neurological functioning (BN20) and tumor grade were associated with caregiver's mental functioning and caregiver mastery at baseline. To be able to analyze follow-up data, the Last Observation Carried Forward (LOCF) method was applied to deal with missing values. This technique, that replaces the caregiver's missing values after dropout with the last available assessment, assumes that the caregiver's benefit from the intervention is stable from the point of dropout to trial completion, rather than declining or improving further.[252] This is consistent with our null hypothesis (i.e. neither the intervention group nor the control group changes over time regarding the outcome variables). Missing data from within completed questionnaires were not imputed. Following the intention to treat principle we included all participants in the analysis. Delta scores (last minus baseline assessment) were calculated and univariate linear regression was used to asses the long-term effect (i.e. eight months after the baseline assessment) of the intervention on mental functioning and caregiver mastery. In a multiple linear regression analysis we determined whether patient's HRQOL (SF-36 by proxy), cognitive functioning (MOS) and neurological functioning (BN20) have a confounding effect (i.e. $\Delta\beta$ >10%) on the effects of the intervention. A two-sided *p*-value of < .05 was considered significant.

RESULTS

Patient-caregiver characteristics

3.2

Fifty-six patient-caregiver dyads enrolled in this study. Of these, 31 patient-caregiver dyads were randomly assigned to the intervention group and 25 patient-caregiver dyads were assigned to the control group (see Figure 1). Frequently selected and consequently addressed topics for the sessions were 'contact with the patient', 'the direct environment (contact with family, friends and others)' and 'time for yourself'. Eight informal caregivers (25.8%) in the control group only completed the baseline assessment, indicating that they did not complete all intervention sessions. Fifteen informal caregivers (48.4%) in the intervention group and 17 caregivers (68.0%) in the control group completed all five planned follow-up assessments. The primary reasons for not completing all assessments were lack of time to complete or return the questionnaires due to various reasons (50%) and death of the patient (50%). No differences between the experimental group and control group were found in terms of age, gender, educational level of both the informal caregivers and the patients, and clinical variables of the patients (see Table 1).

At baseline (i.e. prior to the start of the intervention) caregivers in the control group reported better physical functioning (PCS) of the patient (M=38.652, sd=10.047; $t(53) = 2.293$, p= 0.026) and less visual disorders of the patient (M=9.333, sd=11.863; $t(43)= -2.651$, p= 0.011) than did

Table 1. Characteristics of the patient-caregiver dyads of the intervention and control groups.

	Intervention group (*N*= 31)	Control group (*N*= 25)	*p*-value
Age in years (caregiver) *M* (sd)	50.77 (11.47)	50.56 (10.36)	0.830
Gender (caregiver) *N* (%)			0.101
Male	8 (26%)	12 (48%)	
Female	23 (74%)	13 (52%)	
Educational level (caregiver) *N (%)*			0.415
Low	2 (6.5%)	3 (12%)	
Medium	10 (32.3%)	11 (44%)	
High	19 (61.3)	11 (44%)	
Age in years (patients) *M* (sd)	53.16 (11.25)	52.12 (8.92)	0.708
Gender (patients) *N* (%)			0.389
Male	22 (71%)	15 (60%)	
Female	9 (29%)	10 (40%)	
Educational level (patients) *N* (%)			0.388
Low	4 (12.9%)	7 (28%)	
Medium	12 (38.7%)	9 (36%)	
High	14 (45.2%)	9 (36%)	
Tumor grade (patients) *N* (%)			0.410
Grade III	8 (25.8%)	9 (36%)	
Grade IV	23 (74.2%)	16 (64%)	
Tumor location (patients) *N* (%)			0.177
Frontal	9 (29%)	8 (32%)	
Temporal	4 (12.9%)	8 (32%)	
Parietal	4 (12.9%)	3 (12%)	
Occipital	0 (0%)	1 (4%)	
Mixed	10 (32.3%)	5 (20%)	
Other	4 (12.9%)	0 (0%)	
Tumor lateralisation (patients) *N* (%)			0.330
Left	13 (41.9%)	11 (44%)	
Right	13 (41.9%)	13 (52%)	
Bilateral	5 (16.1%)	1 (4%)	
Epilepsy (patients) *N* (%)			0.123
Yes	22 (71%)	22 (88%)	
No	9 (29%)	3 (12%)	
Neurosurgical intervention (patients) *N* (%)			0.140
Resection	24 (77.4%)	23 (92%)	
Biopsy	7 (22.6%)	2 (8%)	
Months since time of diagnosis (patients) *M* (range)	*19.7* (0-136)	*25.7* (0-89)	0.472
< 12 months *N*(%)	20 (65.5%)	12 (48%)	0.214
> 12 months *N*(%)	11 (35.5%)	13 (52%)	
Anti-tumor treatment received during intervention or follow-up (patients) *N* (%)	20 (64.5%)	12 (48%)	0.279
Progressive disease during intervention or follow-up (patients) *N* (%)	15 (48.4%)	12 (48%)	0.906
Deceased during intervention or follow-up (patients) *N* (%)	7 (22.6%)	5 (20%)	0.876

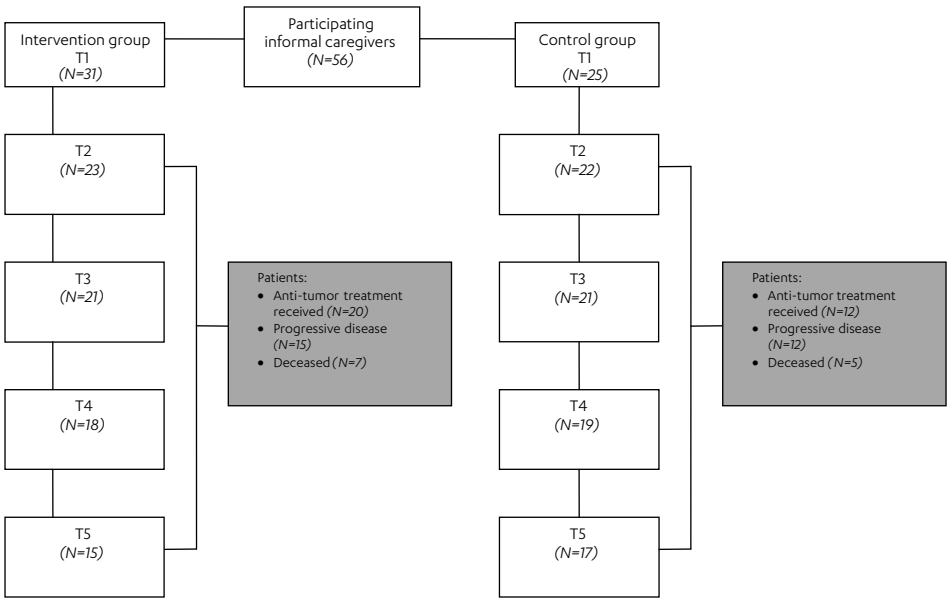

Figure 1. Flow chart depicting the number of participants in both study arms across the different assessments.

caregivers in the intervention group (*M*=31.798, sd=11.793 and *M*=23.656, sd=27.026 respectively). No differences between the groups were found in perceived patient's cognitive complaints, mental functioning, future uncertainty, motor dysfunction, communication deficits, emotional distress, and items assessing disease symptoms and side-effects of treatment (data not shown).

3.2 Predictors of informal caregivers' health-related quality of life and mastery at baseline

We found caregiver's HRQOL and caregiver mastery to be associated with patient-related factors at baseline. Caregiver's mental functioning as indexed by the SF-36 Mental Component Summary (MCS) was positively correlated with mental functioning (MCS) of the patient (r= 0.355, p= 0.008). This indicates that caregivers who perceive mental functioning of the patient to be good rate their own mental functioning accordingly. Additionally, patient's increased uncertainty concerning the future (BN20) and increments in communication deficits (BN20) were negatively associated with mental functioning (MCS) of the caregiver (r = -0.380, p= 0.004 and r = -0.272, p= 0.043, respectively). Tumor histology was not related to mental functioning (MCS) of caregivers.

Caregiver mastery was positively related to patient's visual disorders (BN20) (r = 0.299, p= 0.031) and communication deficits (BN20) (r = 0.385, p= 0.005). Higher scores on caregiver mastery indicate less feelings of mastery, suggesting that more visual disorders and more difficulty with communication are related to decreased feelings of mastery. Negative correlations were found between caregiver mastery and patient's physical functioning (PCS) (r = -0.362, p= 0.009) and the BN20 bothered by hair loss scale (r = -0.303, p= 0.029). This indicates that more feelings of mastery

are related to worse physical functioning of the patient, and less feelings of being bothered by hair loss, respectively. Again, tumor histology was not associated with caregiver mastery.

Effects of the intervention on caregivers' health-related quality of life and mastery

As is illustrated in Table 2 and Table 3, changes in mental functioning (MCS delta scores) differed significantly between the intervention and control group ($F(1,54)=4.188$, $p= 0.046$). Mental functioning of the intervention group stays relatively stable while that of the caregivers in the control group declines over time. Table 2 shows the mean scores for caregiver mastery. Caregiver mastery delta scores (last minus baseline assessment) also differed significantly between the two groups ($F(1,50)=7.730$, $p= 0.008$). Feelings of mastery in the intervention group increased over time while feelings of mastery in the control group showed the opposite pattern.

The influence of confounding factors on the effects of the intervention

Changes in patient's communication deficits (BN20), cognitive functioning (MOS) and physical functioning (PCS) are identified as confounders ($\Delta\beta$ >10%) for the changes in mental functioning (MCS) of the informal caregiver. Changes in patient's communication deficits (BN20), cognitive functioning (MOS) and mental functioning (MCS) are associated ($\Delta\beta$ >10%) with changes in caregiver mastery. After adding these variables to the model, the effect of the intervention on mental functioning (MCS) was no longer significant (ΔR^2 = 0.035, $p= 0.113$). The effect of the intervention on caregiver mastery, however, remains significant even after adding these variables to the model (ΔR^2=.055, $p= 0.021$), see Table 3.

Table 2. Means, standard deviations and ranges for mental functioning (MCS) and caregiver mastery for the intervention group and the control group.

	Intervention group	Control group
Mental functioning (MCS) (*N*)	*31*	*25*
T1 (M (sd); *range*)	42.59 (12.09); *6.46-57.65*	47.12 (11.35); *17.18-59.14*
T2 (M (sd); *range*)	44.04 (11.98); *5.20-60.57*	44.03 (11.06); *17.18-57.39*
T3 (M (sd); *range*)	42.60 (11.58); *11.76-56.47*	44.76 (11.87); *17.18-60.53*
T4 (M (sd); *range*)	43.33 (11.38); *20.32-57.16*	44.22 (11.87); *17.18-60.50*
T5 (M (sd); *range*)	42.93 (11.68); *19.14-57.67*	41.03 (13.96); *12.87-59.89*
Caregiver Mastery (*N*)	*31*	*24*
T1 (M (sd); *range*)	27.01 (11.84); *5.00-46.43*	21.15 (12.03); *0.00-42.86* Ψ
T2 (M (sd); *range*)	24.21 (11.66); *0.00-46.43*	22.72 (12.41); *0.00-42.86* Ψ Ψ
T3 (M (sd); *range*)	26.02 (12.29); *0.00-50.00*	23.97 (11.14); *4.17-42.86* Ψ Ψ
T4 (M (sd); *range*)	25.85 (11.49); *3.57-46.43*	24.77 (8.69); *7.14-42.86* Ψ Ψ
T5 (M (sd); *range*)	25.02 (13.53); *0.00-50.00*	24.61 (12.82); *5.00-53.57*

Ψ data not complete: caregiver mastery for the control group at T1 consists of 21 participants.
Ψ Ψ data not complete: caregiver mastery for the control group at T2, T3 and T4 consists of 23 participants.

Table 3. Effects of the intervention on mental functioning (MCS) and caregiver mastery.

	B	SE B	Beta	R^2	*p*-value
Model (mental functioning (MCS))					
Step 1					
Group	6.016	2.940	0.271*	0.073	0.046*
Step 2					
Group	7.405	2.812	0.333*	0.194	0.011*
Communication deficits (proxy)	-0.172	0.062	-0.353*		0.007*
Step 3					
Group	5.508	3.063	0.248	0.227	0.078
Communication deficits (proxy)	-0.080	0.087	-0.165		0.359
Cognitive functioning (proxy)	-0.193	0.131	-0.264	0.262	0.146
Step 4					
Group	4.911	3.048	0.221		0.113
Communication deficits (proxy)	-0.056	0.087	-0.115		0.524
Cognitive functioning (proxy)	-0.153	0.132	-0.210		0.251
Physical functioning (proxy)	0.225	0.146	0.212		0.131
Model (caregiver mastery)					
Step 1					
Group	-7.798	2.805	-0.369*	0.136	0.008*
Step 2					
Group	-6.003	2.782	-0.284*	0.228	0.036*
Cognitive functioning (proxy)	0.223	0.093	0.315*		0.021*
Step 3					
Group	-7.288	3.022	-0.345*	0.247	0.020*
Cognitive functioning (proxy)	0.135	0.124	0.190		0.284
Communication deficit (proxy)	0.098	0.090	0.184		0.286
Step 4					
Group	-7.044	2.943	-0.333*	0.302	0.021*
Cognitive functioning (proxy)	0.066	0.126	0.093		0.605
Communication deficit (proxy)	0.069	0.089	0.130		0.446
Mental functioning (proxy)	-0.265	0.139	-0.273		0.063

* $p<0.05$

DISCUSSION

According to our expectations, HRQOL of the patient and several aspects of neurological functioning at baseline are indeed related to HRQOL and feelings of mastery of the informal caregiver. However, we did not find a relationship with tumor grade, in contrast with Janda and colleagues.[198] This may be explained by the fact that we included caregivers of a more homogeneous group of patients (only high-grade glioma (grade III or IV) as opposed to also including grade I or II glioma).

Caregivers who received the intervention maintained a more stable level of mental functioning (MCS) and even showed a modest improvement in feelings of mastery in contrast to the caregivers in the control group. However, after correcting for communication deficits, cognitive functioning and HRQOL of the patient, the effect on mental functioning (MCS) lost statistical significance. This demonstrates that, irrespective of the effects of the intervention, the caregiver's perception of deterioration in the patient's communicative ability, cognitive functioning, and HRQOL negatively affects mental functioning of the caregiver. A previous study showed that both a higher age of the patient and a lower income and educational level of the informal caregiver can render informal caregivers of cancer patients more vulnerable to burden and depression.[253] Another study found that insecure attachment styles and the level of support experienced from the direct environment predict depression and anxiety of informal caregivers.[254] Our findings suggest that mental functioning (MCS) of informal caregivers of HGG patients is at increased risk when caregivers perceive changes in neurological symptoms in the patient.

Our study evidently has its limitations. In the first place, there was a relatively large percentage of patient-caregiver dyads dropping out of the study or follow-up assessments (42.9% in total, see Figure 1). This includes participants in both study arms (51.6% in the intervention group and 32% in the control group) and entails both caregivers who completed the intervention and those who did not. High attrition rates such as the ones found in this RCT may imply that participation in the study was too burdensome for some caregivers. Six sessions with a psychologist and/or filling in relatively extensive questionnaires about their own and their ill partners' wellbeing may be too taxing in this tumultuous and highly demanding period in their lives. Moreover, informal caregivers who lost their partner during follow-up may be fundamentally different from those who dropped out for other reasons. However, separating these participants in analyses would not be desirable, since owing to the dismal prognosis many informal caregivers of HGG patients will eventually experience the loss of their loved one. Nevertheless, cautious interpretation of the present study results certainly is warranted as the positive effects we found may not hold for all informal caregivers. Future studies should therefore focus on developing the least demanding way to improve informal caregivers' mental health, in terms of time invested by both the informal caregiver and the health care professional.

Unfortunately, in supportive care interventions for HGG patients dropout rates are usually high.[255] In a study by Meyers *et al.*, exploring the effects of a psychological intervention on quality of life of cancer patients and their caregivers, approximately 65% of patient-caregiver dyads withdrew before the end of the study.[256] In the palliative setting, intervention studies focussing on improving mental health in informal caregivers of cancer patients have roughly similar attrition rates, varying between approximately 31% and 57%.[257-259] Reasons for attrition mentioned in these studies, if any, were death or decline of the patient or decline of the caregivers (for example, because they felt overwhelmed). Reasons for attrition were similar in the present study. Taking this into consideration, it seems that the number and the reasons of patient-caregiver dyads dropping out of the present study is within expectations. Despite the number of participants dropping out, we included all caregivers who completed the baseline assessment in the analysis of the intervention using intention to treat analysis and the last observation carried forward (LOCF) method. Although imputation of data certainly has its methodological drawbacks, the LOCF method is suggested to consistently

underestimate within-group changes in efficacy.[260] As we did not expect HRQOL of either group to decline or improve, this method suggests that the relatively modest efficacy of the present intervention may actually be larger than shown with our rather conservative approach.

Caregivers of HGG patients differ from caregivers of patients with many other types of cancer in that they may experience rapid changes in functioning and therefore need immediate information and support.[261] Furthermore, caregivers of patients with cognitive and neuropsychiatric symptoms are at higher risk for increased levels of distress.[262, 263] Therefore, we consider our study of great importance to this specific group of informal caregivers. Our results should, however, at the same time be interpreted with some caution since we used questionnaires completed by caregivers at frequent time intervals. As self-evaluation is a complex process,[264] frequent evaluation of mental well-being may have caused participants to notice small changes in their own and the patient's functioning they otherwise would not have observed. For example, having subjective memory complaints can lead to an attentional bias toward everyday forgetfulness.[265] Moreover, Higginson and colleagues found that caregivers experiencing higher burden are more prone to rate specifically the psychological aspects of HRQOL of patients as worse than patients would report themselves. Concordance between patient's and caregiver's ratings improved when caregivers reported more positive feelings associated with caregiving.[266] Furthermore, there are indications that relatively severe symptoms of depression in cancer patients with persistent fatigue can hinder improvements in HRQOL in both patients and partners.[267] In the palliative cancer setting, caregivers aged 45 to 54 report the highest levels of depressive symptoms[268] and antidepressants can aid in improving symptoms of depression, burden and HRQOL.[269] Therefore it seems worthwhile to evaluate not only HRQOL and mastery but also caregiver burden and mood of both patient and caregiver in future studies.

To our knowledge, this is the first RCT to examine the effects of a psychological intervention on HRQOL and feelings of mastery of informal caregivers of HGG patients. Our study demonstrates that HRQOL of the patients and several aspects of neurological functioning are indeed related to HRQOL and feelings of mastery of the informal caregiver. The supportive intervention based on CBT and psychoeducational principles we offered showed modest effectiveness in improving feelings of mastery, even after correcting for changes in communication deficits, cognitive functioning and HRQOL of the patient. Caregivers' mental functioning proved to be more susceptible to changes in neurological symptoms of the patient as perceived by the informal caregiver, irrespective of the effect of the intervention. More research should be done to support and improve our findings, preferably including assessments of caregiver burden as well as mood and antidepressant use of both caregiver and patient. Meanwhile, however, since our findings were encouraging we highly recommend that supportive interventions be offered systematically to this vulnerable group of informal caregivers.

Acknowledgments

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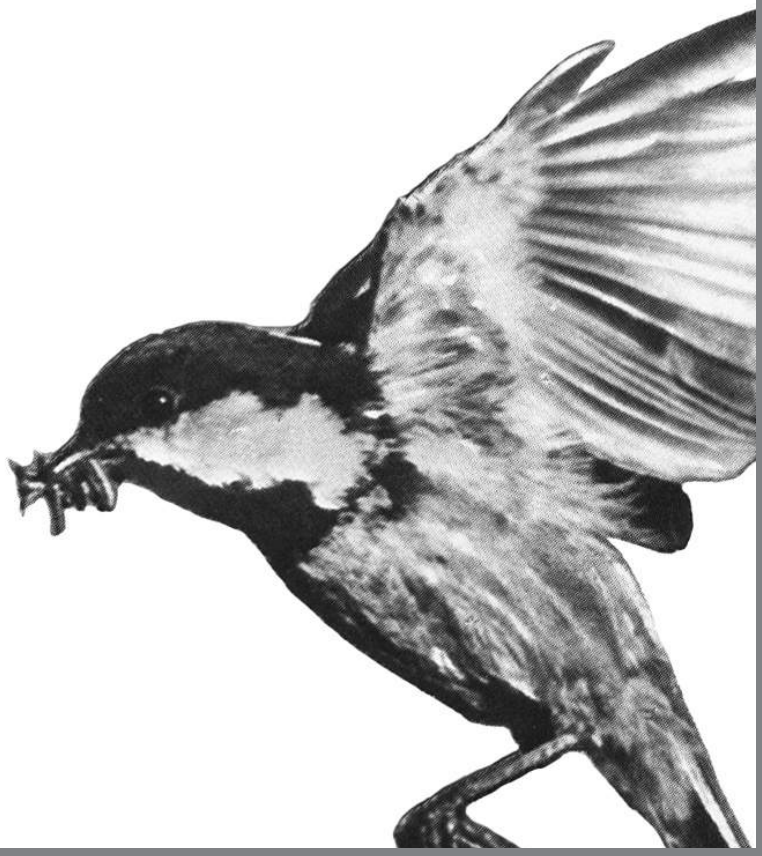
Section 4:
Summary, general discussion, future perspectives and conclusions



4.1 SUMMARY

The general aim of the studies described in this dissertation was to work towards an improvement in HRQOL for both glioma patients and their informal caregivers. Symptoms of fatigue,[12, 42] cognitive deficits,[27, 270] depression[13] and changes in personality and behavior[14, 98] are frequently reported in glioma patients and all these symptoms can affect their HRQOL to a great extent.[34, 271, 272] To improve the HRQOL of both glioma patients and their significant others, it is important to obtain a clearer view of the contribution of these tumor and treatment-related symptoms.

Therefore, in **chapter 1.4,** symptoms such as fatigue, cognitive deficits, depression and changes in personality and behavior, and the impact of these symptoms on the everyday lives of patients and their significant others were described in more detail. Unfortunately, the current practice guidelines that are available for managing these symptoms in a general (cancer) population are often not directly applicable to glioma patients, who have distinct problems and needs. Obtaining more evidence on the effectiveness of existing and new interventions targeting fatigue, cognitive deficits, depression, and changes in personality and behavior in this specific population is therefore advised.

Section 2: Towards improving health-related quality of life in glioma patients

Chapters 2.1 and **2.2** focused on identifying various aspects of functioning that affect HRQOL in low-grade glioma (LGG) patients. As LGG patients are not only confronted with the diagnosis and treatment of a brain tumor, but also with changes in cognitive and neurological functioning that can profoundly affect their daily functioning,[7, 27] it is often assumed that this diminished cognitive functioning is associated with poorer HRQOL. However, to our knowledge, this was never investigated as a primary research question. Therefore, the association between cognitive functioning and HRQOL in LGG patients (*N*=190) with stable disease at an average of six years after diagnosis was examined in **chapter 2.1**. In this cross-sectional study, poorer cognitive functioning appeared to be related to worse generic and disease-specific HRQOL.

LGG patients often experience long periods of stable disease. In the patient sample described in **chapter 2.1.**, HRQOL was re-evaluated six years after the first evaluation (i.e., 12 years after diagnosis on average, also described as long-term follow-up) in those patients with ongoing stable disease (*N*=65). Compared with healthy matched controls, LGG patients had worse scores on the subscales 'physical role functioning' and 'general health perceptions' at long-term follow-up. Within LGG patients, physical aspects of HRQOL proved to be significantly worse at long-term follow-up in comparison to the first assessment. Although 48% of patients improved or remained stable on all HRQOL scales, 38.5% of patients experienced solely decline on one or more scales (**chapter 2.2**). Although this compromise in HRQOL remains mild, the results indicated that certain limitations in HRQOL in LGG patients can be present throughout years of stable disease.

In **chapters 2.3** and **2.4** two interventions aiming at improving symptom management and HRQOL of glioma patients were presented.

To evaluate the effects of the psychostimulant modafinil on fatigue, depression, HRQOL, and cognitive functioning in primary brain tumor patients, a multicenter, double-blind placebo-

controlled crossover trial has been performed. Patients (*N*=37) randomly received either six weeks of treatment with modafinil (up to 400 mg/day) or placebo. After a one-week washout period, the opposite treatment was provided for another six weeks. The results showed that modafinil does not exceed the effects of placebo with respect to symptom burden. In this study, patient accrual was slow, and relatively many patients dropped out during the trial, due mostly to experienced side effects. Therefore, other, preferably nonpharmacologic intervention studies should be considered to improve symptom management in these patients (**chapter 2.3**).

The second intervention study described is such a nonpharmacologic intervention (**chapter 2.4**). The standard treatment of depression (antidepressants and/or cognitive behavioral therapy) may encounter specific problems in glioma patients. Glioma patients often take many medications concurrently, which increases the risk of drug interactions. Psychotherapy usually requires adequate cognitive functioning in order for the patient to benefit most. However, many glioma patients experience cognitive deficits. At present, there are, to our knowledge, no reports of randomized controlled trials on the effectiveness of psychological treatment for depression in glioma patients.[73] Therefore, a randomized controlled trial to evaluate the effects of an internet-based, guided self-help intervention for depressive symptoms in glioma patients has been initiated. This intervention, based on problem-solving therapy, consists of a five-week course adapted for use by adult glioma patients with depressive symptoms. Sample size calculations yield 126 glioma patients to be included, who will be randomly assigned to either the intervention group or a waiting list control group. Additionally, 63 patients with hematological cancer will be included in a non-central nervous system malignancy control group (**chapter 2.4**). This trial is currently in the recruitment phase, and the end of the inclusion process is scheduled in May 2015. If proven effective, this treatment will contribute to the mental health care of glioma patients in clinical practice.

Section 3: Towards improving health-related quality of life in informal caregivers of glioma patients

4.1

In **chapter 3.1** the HRQOL of significant others of glioma patients was described. As neurological and cognitive symptoms of glioma patients are assumed to have a large impact on patient behavior, it is often assumed that partners of glioma patients may face greater stress than partners of patients with malignancies not involving the central nervous system (CNS).[15] Although HRQOL has already been found to be worse in informal caregivers of glioma patients than in the normative population,[198] it was still unknown if this is also the case in comparison to informal caregivers of other oncological populations. In a cross-sectional study, the HRQOL of significant others of high- and low-grade glioma patients (*N*=55 and *N*=213) was compared with the HRQOL of significant others of non-small cell lung cancer (NSCLC) patients (*N*=29) and non-Hodgkin lymphoma or chronic lymphatic leukemia patients (NHL/CLL; *N*=99), respectively. The significant others of LGG and NHL/CLL patients, both assessed in a period of stable disease, had similar levels of HRQOL. Significant others of recently diagnosed HGG patients experienced worse mental health and worse social functioning compared with significant others of recently diagnosed NSCLC patients. The

mental health of the partners was associated with the mental health of the patients. Significant others of patients with high-grade CNS tumors in the acute phase are therefore at increased risk of compromised HRQOL compared to significant others of patients with systemic tumors without CNS involvement and with a comparable life expectancy (**chapter 3.1**).

In **chapter 3.2** a randomized controlled trial was described in which the effects of a structured psychological intervention on the HRQOL and mastery of informal caregivers of HGG patients were investigated. Factors that may determine HRQOL and mastery of informal caregivers of HGG patients at baseline were also investigated. Patients' HRQOL and neurological functioning were related to the HRQOL and feelings of mastery of informal caregivers (*N*=56) at baseline. Informal caregivers were randomly assigned to the intervention group or the care-as-usual group. The intervention, consisting of six one-hour sessions with a psychologist, was designed to empower informal caregivers through providing psycho-education and cognitive behavioral therapy. Results indicated that the intervention helps informal caregivers in maintaining a stable level of HRQOL and improves feelings of mastery over an eight month period compared to usual care.

4.2 DISCUSSION OF THE MAIN FINDINGS

Discussion of the main findings of this dissertation is presented below, separately for the patient studies and for the informal caregiver studies.

Towards improving health-related quality of life in glioma patients

Cognitive functioning and HRQOL were found to be highly correlated in LGG patients (**chapter 2.1**), a notion that is supported by a recent publication in which global neuropsychological functioning was related to subjective well-being in a heterogeneous sample of brain tumor patients.[273] Moreover, in preoperatively assessed brain tumor patients, a better score on a cognitive screening instrument (Mini Mental State Examination) was associated with better HRQOL, although other variables such as anxiety and depression explained a larger proportion of the variance.[271] Through these studies, a causal relationship between cognitive functioning and HRQOL can neither be confirmed nor denied. However, given the associations found it seems worthwhile to explore the effect of successful cognitive rehabilitation on the HRQOL of glioma patients. To date, one cognitive rehabilitation program for brain tumor patients was tested in a RCT.[65] Here, no significant effect on HRQOL or community integration was found at six months follow-up, despite the program's beneficial effects on cognitive functioning. An explanation for this counterintuitive result could be, that cognitive functioning does not directly affect HRQOL, but is influenced by mediating factors such as the awareness of cognitive deficits, participation in society, or possibly disease phase or disease severity. To better understand the potentially complex relationship between cognitive functioning and HRQOL in this patient population, further longitudinal studies are necessary.

Longitudinal assessments of HRQOL and possible determinants can be worthwhile both in research and in a clinical context. This is illustrated in **chapter 2.2,** where mild compromise in HRQOL was found in LGG patients with stable disease, on average 12 years after diagnosis. Ever more frequently, efforts are directed towards monitoring HRQOL and supportive care needs throughout the patient's disease trajectory, in order to provide referral to other health care specialists whenever necessary.[113] In this context, the findings of **chapter 2.2** may be particularly valuable. Statistically significant differences between LGG patients and healthy controls, statistically significant change within LGG patients specifically, and minimal detectable change per scale yielded different results. This emphasizes the complex nature of the concept of HRQOL and underlines the importance of combining different methods in determining what constitutes *meaningful* change in HRQOL.[147, 274] The combination of both anchor-based and distribution-based approaches has been investigated in different cancer patient populations,[e.g. 275-286] for various HRQOL questionnaires such as the Functional Assessment of Cancer Therapy,[e.g. 275, 276, 278, 283-285] the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30,[e.g. 276, 281] the Short Form-36,[e.g. 280] and others.[e.g. 277, 279, 282, 286] However, these studies seldom focus on brain tumor patients. This is important as glioma patients may differ dramatically from other cancer patient populations in terms of their perception of meaningful change in HRQOL because of their unique symptom pattern and neurological or cognitive compromise. Before

implementing patient reported measures in clinical practice to monitor HRQOL issues and supportive care needs to provide referral to health care specialists as necessary, the concept of meaningful change in a brain tumor patient context should be clarified further.

Furthermore, to reduce symptom burden and improve HRQOL in glioma patients, efforts should be directed towards obtaining more evidence for the effectiveness of existing and new interventions targeting fatigue, cognitive deficits, depression, and changes in personality and behavior (**chapter 1.4**). In **chapter 2.3**, the effectiveness of prescribing modafinil for fatigue was investigated. The results were not as anticipated as modafinil proved no better than placebo at decreasing symptoms of fatigue. A recent publication on a large, placebo-controlled study in patients with NSCLC similarly concluded that the effects on fatigue did not exceed the effects of placebo.[287] However, an interim-analysis of a study on armodafinil (a drug that is the R-enantiomer of modafinil) shows modest positive effects in brain tumor patients after cranial irradiation, in those patients who are most fatigued at baseline.[288] These results mirror those of a large trial, in which it was found that only those cancer patients who were severely fatigued, benefited from modafinil.[289] It seems that psychostimulants may help reduce fatigue in those who are very severely fatigued, and that patients with less severe symptoms may benefit more from other interventions.

Examples of other types of interventions aimed at decreasing symptom burden and/or increasing HRQOL in brain tumor patients have recently been reported on. An individualized, intensive multidisciplinary rehabilitation program improved physical activity levels (i.e. self-care, mobility, and continence) and psychosocial outcomes (i.e. psychosocial interactions, communication, and cognitive functioning) in brain tumor patients in the intervention group compared with a waitlist control group.[290] However, participants were not allocated to the groups randomly but based on their clinical need, and HRQOL did not improve significantly. In addition, a non-controlled, retrospective study on inpatient rehabilitation showed that functional status, mobility in particular, improved from admission to discharge in newly diagnosed glioblastoma patients.[291] Moreover, an Australian RCT on the 'Making Sense of Brain Tumor Program', a home-based therapy program for brain tumor patients and their family members, showed beneficial effects for patients' well-being.[292] After the intervention, patients had lower levels of depression, higher levels of existential and functional well-being, and better HRQOL than patients in the waitlist control group. In the Netherlands, Gehring *et al*. have recently initiated a RCT aimed at improving cognitive functioning through physical activity, and the first patients have been included. The results of this intervention, as well as of our own internet-based intervention aimed at reducing depressive symptoms in glioma patients (**chapter 2.4**) are eagerly anticipated.

Towards improving health-related quality of life in informal caregivers of glioma patients

From **chapter 3.1**, it becomes clear that informal caregivers of HGG patients, in particular, seem vulnerable for compromised HRQOL. However, the cross-sectional design of the study and the focus on two distinct groups of glioma patient caregivers make it difficult to determine

whether the vulnerability is mainly related to the patient's disease phase (i.e., shortly after diagnosis versus months to years thereafter) or the patient's disease severity (i.e., the diagnosis of HGG versus a lower-grade malignancy). This hinders identification of vulnerable (sub)groups of informal caregivers. Therefore, longitudinal assessments of caregiver burden and HRQOL in samples representative of the informal caregiver population in neuro-oncology are needed.

Findings from a large, longitudinal study of mind-body interactions in neuro-oncology caregivers performed in Pittsburgh are especially relevant in this respect. This study focused on examining the psycho-behavioral responses (i.e. depressive symptoms and sleep), biologic responses (i.e. blood pressure and interleukins) and overall physical health of family members of persons with a primary brain tumor at the time of diagnosis, and how the relationships between these variables vary over time in response to changes in the patient's disease trajectory. As part of this large project, different psychological distress patterns in family caregivers were identified with group-based trajectory modeling, linking high depressive symptoms with more anxiety and burden, lower age, income, and social support, and worse functioning of the patient. This indicates that there are subgroups of caregivers who are more likely to benefit from interventions.[293] Other factors that can be used to identify vulnerable subgroups of caregivers include spirituality,[294] positive aspects of care,[295] and marital adjustment.[296] Furthermore, when patients experience more physical problems, family caregivers are more likely to report lost hours from work,[297] which may cause financial burden. Experienced economic hardship in neuro-oncology was studied which showed its subsequent effect on emotional health.[298] Studies into sleep characteristics showed that sleep deprivation was commonly found in family caregivers,[299] and sleep quality was positively associated with quality of life.[300]

In addition, in Denmark, a longitudinal study on the quality of life of informal caregivers of HGG patients[301] has recently started. This study should shed additional light on informal caregivers' HRQOL issues along the course of the patients' disease trajectory. In addition to longitudinal research efforts, it would be valuable to monitor supportive care needs and HRQOL of informal caregivers throughout the patient's disease trajectory in clinical practice, as tailored advise and referral to health care services can then be routinely provided as necessary. Alternatively, if the need for supportive care proves low despite the presence of HRQOL issues, self-management tools such as 'Oncokompas'[302] could be useful.

In **chapter 3.2**, a first effort towards evidence-based psychological care for informal caregivers in neuro-oncology was made. In this trial, the attrition rate was high and the effects were modest, suggesting that perhaps other methods to improve psychological care should be employed in this unique group of informal caregivers. Therefore, attention should continue to be paid to testing the effectiveness of existing and new interventions in informal caregivers in neuro-oncology. At present, the possibilities of internet-based interventions for caregivers are under investigation. An Australian pilot study in cancer caregivers yielded promising results for those who completed the intervention, (a self-guided cognitive behavior therapy), as improvements in negative affect and emotional functioning were found, but the researchers experienced great difficulty with recruitment and retention.[303] In addition to the study mentioned above, from personal communication we know of two ongoing randomized controlled trials focusing on

internet-based supportive care for cancer caregivers. Although results are not yet available, a study focusing on informal caregivers in neuro-oncology ('SmartCare') is presently conducted in the United States (principal investigators: Sherwood and Donovan) and a study targeted at cancer caregivers in general ('Houvast, voor elkaar') is conducted in the Netherlands.[304]

4.3 METHODOLOGICAL LIMITATIONS

While the studies presented in this dissertation certainly add to the existing literature, there remain some important limitations with regard to the methodologies applied.

Difficulties in observational studies

Cross-sectional design

In an effort to shed more light on the associations between cognitive functioning and HRQOL in LGG patients (**chapter 2.1**), a cross-sectional study design was applied. HRQOL in significant others of patients with brain tumors versus partners of patients with tumors outside the central nervous system (**chapter 3.1**) was also investigated cross-sectionally. Therefore, it was not possible to assess changes over time in the outcome measures; cognitive performance and HRQOL. In addition, causal relationships could not be examined. Applying a longitudinal study design in future efforts is therefore recommended.

Selected group of participants

The participants included in the study described in **chapter 2.1** were all in a stable disease phase as defined by radiological and clinical observations. The selection of a specific subgroup of glioma patients hinders the generalizability of results. It is unclear if these findings apply to LGG patients in general, or if this is specific for patients who are in a stable disease phase. Moreover, the associations between cognitive functioning and HRQOL may be very different in HGG patients, as these patients seldom experience prolonged periods of stable disease.

A similar methodological limitation plays a role in **chapter 3.1**. The LGG and HGG patients of whom the significant others participated in this study, were in a stable disease phase or recently diagnosed, respectively. These groups are again selected and therefore, it is difficult to make any statement on the HRQOL of significant others per se. Therefore, it is advised that future studies aim to include study participants that represent a less selected group of glioma patients and/or their significant others.

Comparability of study populations

In the study on HRQOL in informal caregivers (**chapter 3.1**), there remain some issues regarding the comparability of the study populations. Although two groups of significant others of glioma patients (i.e., LGG and HGG partner samples) were presented in **chapter 3.1,** no statistical comparisons between these groups were made. The considerations for making this choice were that – because statistical comparison of the neuro-oncology partner samples was not appropriate – providing information on both samples in one chapter would lead to a greater understanding of the underlying concept, i.e., HRQOL in glioma patients' informal caregivers. If **chapter 3.1** had been restricted to a report on solely LGG and NHL/CLL caregivers, the conclusions would have been different, which does not do justice to the underlying problems. However, presenting the unrelated groups together in one report might be confusing to readers scanning **chapter 3.1** for the main findings. The data used in **chapter 3.1** were collected as part of a larger study, which

focused on two distinct groups of glioma patients (stable LGG patients and HGG patients in the acute disease phase) and their significant others. This contributes to the restricted comparability of the different study samples included in the chapter. In future studies, focus on informal caregiver's HRQOL throughout the disease course of the patient is therefore recommended.

Defining change in HRQOL

In **chapter 2.2**, differences in HRQOL between LGG patients and healthy controls were presented alongside statistically significant change in HRQOL at group level and minimal detectable change in HRQOL at the individual patient level in a longitudinal sample. This makes it possible to evaluate whether HRQOL differs between patients and controls, as well as to evaluate the probability that change within the group occurred by random variation, and if changes found are larger than the measurement error of the instrument. Although valuable, these approaches may not directly reflect meaningful change (i.e., "change that results in a meaningful reduction of symptoms or improvement in function"[274]). Therefore, the methods applied in **chapter 2.2** may not adequately reflect participants' own view of whether their HRQOL has changed over time. A combination of distribution-based and anchor-based methods is therefore usually recommended.[147, 274] Furthermore, when interpreting results from studies focusing on change in HRQOL, it is important to keep in mind the methods applied to determine change over time, as this can lead to different cut-off points and conclusions.

Difficulties in intervention studies

Participation and retention rates

Chapters 2.3, **2.4** and **3.2** are reports of randomized controlled trials. The study on the effect of modafinil on symptoms of fatigue (**chapter 2.3**) and the informal caregiver intervention study (**chapter 3.2**) both yielded relatively small sample sizes (*N*=37 and *N*=56, respectively). Although the internet-based intervention described in **chapter 2.4** is still a work in progress, the recruitment of participants is slower than anticipated. After 32 months of patient inclusion, the glioma patient sample consists of two thirds the required sample size in this nation-wide study. Moreover, the informal caregiver intervention study (**chapter 3.2**) in particular had a high attrition rate (43%) which may be related to the longer period of follow-up: eight months in this intervention versus twelve weeks in the modafinil study (attrition 32%) (**chapter 2.3**).

These relatively small sample sizes and high attrition rates, given the high prevalence of symptoms of fatigue, anxiety and depression and high caregiver burden, were surprising and indicate that the identification of barriers and facilitators of patient and informal caregiver participation is essential. A previous report on informal caregiving in the palliative care setting indicated that those caregivers experiencing relatively low levels of distress are less inclined to participate in interventions.[305] In addition, those who were younger, more familiar with social and professional support, or whose loved one was treated at the same facility where the intervention took place, were more likely to participate.[305] In an observational longitudinal study among brain tumor patients and their caregivers, demographic characteristics (e.g. age, gender, educational

level, marital status) and patient characteristics (cognitive status, severity of symptoms, tumor type) did not appear to influence participation in the study.[222] Throughout the study, younger caregivers, with a higher educational level, of whom the patients had better cognitive functioning were less likely to drop out,[222] indicating that higher burden can influence the willingness to continue participation in observational studies. Furthermore, recruiting brain tumor patients and their informal caregivers shortly after diagnosis can hamper participation rates, as the most frequently reported reasons for non-participation were that eligible participants felt overwhelmed and stressed.[222] Instead of focusing on barriers to and facilitators of participation, the needs and preferences in support opportunities can also be investigated, as was recently done in a North-American study.[306] On group level, most interest was expressed in education about the disease and the potential negative cognitive effects of treatment, whereas subgroups of patients and informal caregivers showed very high interest in specific brief supportive interventions.[306] Means to identify members of these subgroups remain, however, undetermined.

As often suggested, it seems worthwhile to routinely screen both patients and informal caregivers for HRQOL issues and distress, as well as the wish for supportive care. Patients or informal caregivers at risk can then be identified (**chapter 1.2**). When initiating intervention studies in these vulnerable groups, it is pivotal to prepare a randomized controlled trial by first performing a pilot study. This will provide insight into the prevalence and magnitude of the problems experienced by patients or informal caregivers, the experienced need for an intervention, and the barriers to and facilitators of participation. After pilot testing, realistic power calculations can be performed and a tailored recruitment procedure can be started.

Dealing with missing data and dropout

In the informal caregiver intervention study (**chapter 3.2**), an eight month follow-up period was scheduled, but not all participants completed all assessments due to dropout (43%). In order to analyze the follow-up data, we used the last observation carried forward technique. With this technique, the value of the last available assessment is used for each missing value afterwards (it is therefore 'carried forward'), which implies the assumption that the score remains stable from the point of dropout until trial completion.[252] As this is consistent with our null hypothesis, we felt confident in using this method. However, this technique evidently has its downsides, especially when missing values are unevenly distributed across the intervention group and the control group. It could lead to an overestimation of the effect of the intervention, for example, if the outcome measure is expected to show regression towards the mean with multiple assessments and if there are more missing values in the control group than in the intervention group.[307] In the caregiver intervention study, there were more missing data in the intervention group, leading us to conclude that in this case, last observation carried forward was indeed a conservative approach.

In those who retain in the intervention studies, not all assessments were completed throughout follow-up (**chapters 2.3 and 3.2**). Given the high symptom and caregiver burden of our target population, this is not surprising. Various methods for dealing with missing data are available.[308] However, all these methods have implications for the interpretation of the results. In **chapter 3.2**, we chose not to impute missing data from incomplete assessments. In

chapter 2.3, we used mean imputation, replacing missing values from incomplete self-reported assessments and neuropsychological assessments with the mean of observed values for that variable. Although not changing the mean for that variable, using this method can distort the variables' distribution, leading to an underestimation of the standard deviation. Moreover, mean imputation can have consequences for correlations between variables, as in those cases with imputation, there will be no relationship between the imputed variable (which is not as reported by the participant) and other measured variables (which *are* reported by the participant).[307]

To summarize, each method for dealing with missing values has its advantages and disadvantages. Imputed data are never as good as fully completed assessments. The participants, whether they be patients or caregivers, suffer from high burden, and much of the attrition and missing data can be attributed to the additional burden of participating in (intervention) studies. Therefore, it is worthwhile to decrease this burden - after all, these intervention studies were initiated to help the participants, rather than to cause further burden. It is recommended to reduce the length of assessments as much as possible. If short versions of questionnaires are available and have adequate psychometric properties, these should always be chosen over the longer version. Moreover, a member of the research team could help complete the questionnaires during a routine visit to the clinic or through a telephone interview. This way, participants are supported during the completion of the assessment, and missing values can be avoided as much as possible.

4.4 FUTURE PROSPECTS AND CONCLUSIONS

Below, recommendations for both clinical practice and future research are provided, as well as general conclusions from this dissertation.

Clinical implications

The studies described in this dissertation have contributed to a better understanding of the HRQOL issues of glioma patients and their informal caregivers. From the observational studies we now know that cognitive functioning and HRQOL are highly correlated in stable LGG patients, and that throughout long periods of stable disease, specific limitations in HRQOL may persist. Moreover, significant others of HGG patients in the acute disease phase were identified as having vulnerable HRQOL. In addition, a start was made to improve HRQOL in both glioma patients and their informal caregivers through intervention studies.

This knowledge is valuable in clinical practice, as it emphasizes that attention should be paid to HRQOL of both glioma patients and their informal caregivers throughout the disease trajectory. The findings from studies described in this dissertation suggest that it would be valuable to routinely screen both patients and informal caregivers for HRQOL issues and distress, as well as the wish for supportive care, to identify patients or caregivers with unmet needs for supportive care. Tailored advise and referral to health care services, including self-management tools and self-help interventions can then be provided as necessary.

Recommendations for further research

In order to accurately monitor HRQOL and supportive care needs, it is important to further clarify the concept of meaningful change in HRQOL in both neuro-oncology patient and informal caregiver populations. Moreover, obtaining knowledge on what constitutes a meaningful change can aid the interpretation of outcomes in clinical studies. Physicians, patients and family caregivers can then make better informed decisions on treatment options.

In addition, the potentially complex relationships between HRQOL, fatigue, cognitive deficits, depression, changes in personality and behavior, and caregiver burden require further research. Incorporating longitudinal measures in samples representative of the entire glioma patient or informal caregiver population is therefore recommended. Obtaining knowledge on the relationships between these variables can facilitate the design of, and increase the effectiveness of interventions targeted at improving any of these outcomes. Developing new interventions is important, but obtaining scientific evidence for the effectiveness of existing interventions that aim to improve HRQOL or decrease symptom burden deserves more attention in the neuro-oncology patient and informal caregiver setting as well. When initiating intervention studies for either glioma patients or informal caregivers, it is important to first perform a pilot study. This will provide insight into the prevalence and magnitude of the problems experienced by patients or informal caregivers, the experienced need for an intervention, and the barriers to and facilitators of participation.

General conclusions

To conclude, the observational studies that are included in this dissertation have contributed to a better understanding of HRQOL in glioma patients and their informal caregivers. However, the potentially complex relationships between HRQOL and (factors influencing) symptom or caregiver burden require further research. In three randomized controlled trials, attempts were made to improve HRQOL by targeting symptoms of fatigue, depression, or caregiver mastery, respectively. These studies have contributed to the advancement of evidence-based supportive care for the neuro-oncology patient and caregiver population. However, more research in this area is necessary and here, identifying barriers to and facilitators of patient and caregiver participation and retention is essential. In clinical practice, monitoring supportive care needs and referring to health care specialists as necessary seems worthwhile. These efforts are expected to benefit glioma patients and their informal caregivers, because they may provide some relief of the mental and physical consequences of living with a life-threatening disease.

SUMMARY IN DUTCH

Naar het verbeteren van de gezondheidsgerelateerde kwaliteit van leven van glioompatiënten en hun naasten

De studies die worden beschreven in dit proefschrift hadden tot doel om bij te dragen aan verbetering van de gezondheidsgerelateerde kwaliteit van leven (hierna voor de leesbaarheid afgekort tot 'kwaliteit van leven') van patiënten met een glioom en hun naasten. Veel mensen met een glioom ervaren vermoeidheid,[12, 42] cognitieve stoornissen,[27, 270] depressie,[13] en/of veranderingen in gedrag en persoonlijkheid.[14, 98] Deze symptomen, die kunnen samenhangen met de tumor maar ook met de behandeling van de tumor, kunnen de kwaliteit van leven in negatieve zin beïnvloeden.[34, 271, 272] Het ontrafelen van de relatieve bijdrage van deze symptomen aan de kwaliteit van leven is belangrijk om kwaliteit van leven te kunnen verbeteren bij zowel patiënten als hun naasten.

Eerst worden daarom in **hoofdstuk 1.4** vermoeidheid, cognitieve stoornissen, depressie, veranderingen in gedrag en persoonlijkheid, en de invloed van deze symptomen op het alledaagse leven van patiënten en hun naasten in meer detail beschreven. Hoewel er richtlijnen zijn voor de behandeling van deze verschijnselen, zijn deze veelal ontwikkeld voor de algemene (oncologische) populatie, waardoor ze vaak niet direct toepasbaar zijn bij glioompatiënten met hun zeer specifieke problemen en behoeften. Het verkrijgen van wetenschappelijk bewijs voor de effectiviteit van bestaande en nieuwe interventies bij vermoeidheid, cognitieve stoornissen, depressie en veranderingen in persoonlijkheid en gedrag is daarom belangrijk.

Naar het verbeteren van kwaliteit van leven bij glioompatiënten

Hoofdstukken 2.1 en **2.2** richtten zich op het identificeren van verschillende aspecten van functioneren die de kwaliteit van leven van patiënten met een laaggradig glioom kunnen beïnvloeden. Omdat glioompatiënten niet alleen geconfronteerd worden met de diagnose en behandeling van een hersentumor, maar ook met veranderingen in cognitief en neurologisch functioneren die een grote invloed kunnen hebben op het dagelijks leven,[7, 27] wordt vaak aangenomen dat slechter cognitief functioneren samenhangt met een slechtere kwaliteit van leven. Dit was tot nog toe echter nooit als primaire onderzoeksvraag aan de orde geweest. Met name bij patiënten met een laaggradig glioom, die vaak een langere overleving hebben, kunnen deze verschijnselen diep ingrijpen op het dagelijks leven. Daarom is in **hoofdstuk 2.1** de associatie tussen cognitief functioneren en kwaliteit van leven onderzocht bij 190 laaggradig glioompatiënten met stabiele ziekte, gemiddeld zes jaar na de diagnose. In deze cross-sectionele studie bleek een slechter cognitief functioneren inderdaad geassocieerd te zijn met slechtere algemene en ziekte-specifieke kwaliteit van leven.

Bij patiënten met een laaggradig glioom kan de ziekte gedurende een lange periode stabiel blijven. Daarom hebben wij zes jaar later wederom de kwaliteit van leven van dezelfde patiënten als beschreven in **hoofdstuk 2.1** onderzocht, met dien verstande dat we ons daarbij beperkten tot de patiënten bij wie de ziekte (inmiddels gemiddeld 12 jaar na de diagnose) stabiel was. Dat bleek bij 65 patiënten het geval te zijn. Uit de follow-up meting bleek dat deze patiënten slechtere

scores haalden op de schalen die fysiek rolfunctioneren en de algemene gezondheidsperceptie beogen te meten dan gezonde controles. Deze groep van 65 patiënten bleek op fysieke aspecten van kwaliteit van leven bij follow-up na 12 jaar slechter te scoren dan bij de eerste meting (die na gemiddeld zes jaar plaats had gevonden). Hoewel 48% van de patiënten verbeterden of stabiel bleven op alle kwaliteit van leven schalen, ervoer 38,5% van de patiënten een verslechtering op één of meer schalen (**hoofdstuk 2.2**). Uit deze studies blijkt dat bepaalde (milde) beperkingen in kwaliteit van leven kunnen blijven bestaan ondanks jaren van stabiele ziekte.

In **hoofdstuk 2.3** en **2.4** worden twee interventiestudies beschreven die beide zijn gericht op het verbeteren van symptoombestrijding en de kwaliteit van leven van glioompatiënten.

In **hoofdstuk 2.3** werden de effecten van modafinil op vermoeidheid, depressie, kwaliteit van leven, en cognitief functioneren bij patiënten met een primaire hersentumor (glioom of meningeoom) onderzocht. Modafinil is een middel dat de waakzaamheid bevordert en alertheid vergroot. In deze multicenter, dubbelblinde placebo-gecontroleerde studie werden 37 patiënten op willekeurige basis ingedeeld in een groep, waarbij ze ofwel zes weken behandeling met modafinil (tot 400mg/dag) ofwel placebo ontvingen. Na een 'wash-out' periode van één week kregen vervolgens de patiënten uit de eerste groep zes weken placebobehandeling, terwijl de patiënten uit de tweede groep nu zes weken behandeld werden met modafinil. Voor het bestrijden van symptomen bleek modafinil niet effectiever dan placebo.

Bij deze studie bleek het werven van deelnemers zeer moeizaam te verlopen. Bovendien vielen er relatief veel patiënten uit gedurende de studie – veelal door de ervaren bijwerkingen. Kennelijk bestaat er bij hersentumorpatiënten weerstand tegen het innemen van symptoomgerichte medicatie. Het lijkt daarom zinvol om het effect van andere, niet-farmacologische, interventies die zijn gericht op symptoombestrijding bij deze patiënten te onderzoeken.

De tweede interventiestudie die wordt beschreven betreft zo'n niet-farmacologische interventie (**hoofdstuk 2.4**). De standaardbehandeling voor depressie, die bestaat uit antidepressiva en/of cognitieve gedragstherapie, kan op problemen stuiten bij patiënten met een glioom. Glioompatiënten gebruiken vaak meerdere medicijnen tegelijk, waardoor gebruik van antidepressiva kan leiden tot ongewenste interacties. Daarnaast bleek al uit **hoofdstuk 2.3** dat patiënten vaak terughoudend zijn bij hun beslissing extra medicijnen te nemen. Om optimaal van psychotherapie te kunnen profiteren, is een goed cognitief functioneren belangrijk. Veel glioompatiënten ervaren echter cognitieve beperkingen als gevolg van de ziekte of behandeling. Echter, of dit daadwerkelijk tot belemmering van de behandeling van depressie leidt is onduidelijk omdat er tot op heden geen gerandomiseerde, gecontroleerde studies zijn uitgevoerd om de effectiviteit van psychologische behandelingen op depressie bij glioompatiënten te onderzoeken.[73] Daarom is nu een gerandomiseerde, gecontroleerde studie naar de effectiviteit van een begeleide zelfhulpcursus via internet gestart (**hoofdstuk 2.4**). Deze interventie, die is gericht op vermindering van depressieve verschijnselen en die is gebaseerd op een vorm van cognitieve gedragstherapie (d.w.z. probleemoplossende therapie), bestaat uit een cursus van vijf weken die is aangepast voor gebruik door volwassen glioompatiënten met depressieve klachten. Uit de berekening voor de steekproefgrootte bleek dat er 126 deelnemers geïncludeerd dienen te worden. Zij worden op willekeurige basis ingedeeld in de interventiegroep

of in een wachtlijstgroep. Daarnaast wordt de cursus aangeboden aan 63 patiënten met een hematologische vorm van kanker, buiten het centraal zenuwstelsel. Voor deze studie worden nog deelnemers voor beide patiëntgroepen gezocht, en het einde van de inclusieperiode staat gepland voor mei 2015. Als deze interventie effectief blijkt te zijn, vormt deze nieuwe behandeling een waardevolle aanvulling op de het bestaande zorgaanbod voor glioompatiënten.

Naar het verbeteren van kwaliteit van leven bij naasten van glioompatiënten

In **hoofdstuk 3.1** wordt de kwaliteit van leven van naasten van glioompatiënten beschreven. Omdat neurologische en cognitieve symptomen een grote invloed kunnen hebben op het gedrag van glioompatiënten, wordt vaak aangenomen dat naasten van patiënten met een glioom meer stress ervaren dan naasten van patiënten met een andere vorm van kanker.[15] Uit een eerdere studie was reeds gebleken dat de kwaliteit van leven onder mantelzorgers van glioompatiënten slechter is dan onder de algemene bevolking,[198] maar het was nog onbekend of de kwaliteit van leven van deze naasten ook slechter zou zijn dan de kwaliteit van leven van naasten van patiënten met een andere vorm van kanker. In een cross-sectionele studie werd de kwaliteit van leven onder naasten van verschillende groepen patiënten vergeleken (**hoofdstuk 3.1**). Zo werden naasten van patiënten met een laaggradig glioom in een stabiele ziektefase (*N*=213) vergeleken met naasten van patiënten met een hematologische maligniteit met stabiele ziekte (*N*=99). Het bleek dat deze groepen globaal dezelfde niveaus van kwaliteit van leven hadden. Ook werden naasten van patiënten met een recentelijk gediagnosticeerd hooggradig glioom (*N*=55) vergeleken met naasten van patiënten met een recentelijk gediagnosticeerd niet-kleincellig longcarcinoom (*N*=29). De naasten van hooggradig glioompatiënten ervoeren een slechtere mentale gezondheid en slechter sociaal functioneren dan naasten van longkankerpatiënten. Bovendien bleek dat de mate van mentale gezondheid van naasten geassocieerd was met de mate van mentale gezondheid van de patiënten. Naasten van patiënten met een hooggradige tumor in het centraal zenuwstelsel in de acute fase van de ziekte lijken daarom een hoger risico op een slechtere kwaliteit van leven te hebben dan naasten van patiënten met kanker buiten het centraal zenuwstelsel met een vergelijkbare prognose.

In **hoofdstuk 3.2** wordt een gerandomiseerde, gecontroleerde studie beschreven waarin de effecten van een gestructureerde psychologische interventie op de kwaliteit van leven en gevoelens van 'mastery', d.w.z. de ervaren grip op de situatie, van mantelzorgers van hooggradig glioompatiënten werden onderzocht. Daarnaast werd onderzocht welke factoren van aanvang aan (dus bij de "baselinemeting") invloed kunnen hebben op de kwaliteit van leven en de mastery in deze groep. Het bleek dat de kwaliteit van leven en het neurologisch functioneren van patiënten samenhangen met de kwaliteit van leven en de mastery van mantelzorgers (*N*=56).

Ten behoeve van deze gerandomiseerde, gecontroleerde studie werden mantelzorgers op willekeurige basis ingedeeld in de interventiegroep of de controlegroep. Degenen die in de controlegroep werden ingedeeld ontvingen alleen standaardzorg. De interventie, die bestond uit zes sessies met een psycholoog van één uur per keer, was ontworpen om mantelzorgers door middel van psycho-educatie en cognitieve gedragstherapie beter te leren omgaan met de zorgtaken en

met de symptomen van de patiënt. Uit de resultaten bleek dat de interventie mantelzorgers kan helpen een stabieler niveau van kwaliteit van leven te behouden, en een verbeterd gevoel van mastery te krijgen, over een periode van acht maanden in vergelijking met de standaardzorg.

Conclusies

De observationele studies uit dit proefschrift dragen bij aan een beter begrip van kwaliteit van leven bij glioompatiënten en hun naasten. Deze kennis is van nut voor de klinische praktijk en benadrukt het belang van het meten van kwaliteit van leven van zowel patiënt als partner gedurende het hele ziekteproces, ook als de ziekte stabiel is. Er is meer onderzoek nodig om de betekenis van een verandering in kwaliteit van leven goed in te schatten. Ook moet verder onderzoek plaatsvinden naar de zeer complexe relatie tussen kwaliteit van leven en de ervaren last van symptomen of van het geven van mantelzorg. Onderzoek naar de factoren die deze relatie kunnen beïnvloeden moet daar een onderdeel van vormen.

Met de bovengenoemde drie gerandomiseerde gecontroleerde studies is een poging gedaan om kwaliteit van leven te verbeteren door vermoeidheid, depressieve klachten, en gevoelens van mastery aan te pakken. Deze studies dragen bij aan de bevordering van evidence-based zorg voor hersentumorpatiënten – zowel voor de patiënten zelf, als voor hun naasten. Ook hier is echter meer onderzoek noodzakelijk en daarbij is het vooral belangrijk om helder in kaart te brengen hoe groot de behoefte aan een interventie is, en wat de factoren zijn die bepalen of patiënten en hun naasten wel of niet deelnemen aan een interventie. Het verrichten van een pilot studie, voorafgaand aan een gerandomiseerde, gecontroleerde studie zou hier uitkomst kunnen bieden.

Tot slot is de conclusie dat het herhaaldelijk meten van de behoefte aan ondersteunende zorg zou kunnen leiden tot een betere afstemming met de patiënt en de naasten over praktijkgerichte oplossingen zoals doorverwijzing. Uiteindelijk zou dit moeten leiden tot verlichting van de mentale en fysieke gevolgen van deze ernstige ziekte voor zowel de patiënt zelf als voor de naasten.

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Florien Boele was born on September 10th, 1988 in Uithoorn. After secondary school at the Alkwin Kollege in Uithoorn, she studied Psychology at the VU University in Amsterdam.

In 2009 she obtained her Bachelor's degree, after which she started a Master's program in Clinical Neuropsychology. During her studies, she maintained part-time jobs as a teaching assistant, research assistant and as a domestic help in home care.

At the Division of Psychosocial Research and Epidemiology of the Netherlands Cancer Institute, she wrote her Master's thesis on cognitive functioning during long-term treatment with tamoxifen in postmenopausal breast cancer patients.

Following a six-month clinical internship at the Department of Medical Psychology of the VU University Medical Center in Amsterdam, she started her PhD-project at the same department in 2011. Her research, supervised by professor Jan Heimans, professor Irma Verdonck-de Leeuw, Dr. Martin Klein and Dr. Jaap Reijneveld, revolved around quality of life issues in brain tumor patients and their significant others, including the work described in this dissertation. She received two awards for her work on informal caregivers of glioma patients, as well as a travel scholarship which enabled her to work together with professor Paula Sherwood's research group at the University of Pittsburgh in the United States.

In 2014, she was granted a Niels Stensen Fellowship, which will enable her to continue her research as a post-doctoral researcher at the University of Pittsburgh (USA) and at the Western General Hospital in Edinburgh (UK) in 2015/2016. She is looking forward to embark on this adventure abroad with her husband Erik Veldkamp, and their cat Sjaak.