REVIEW

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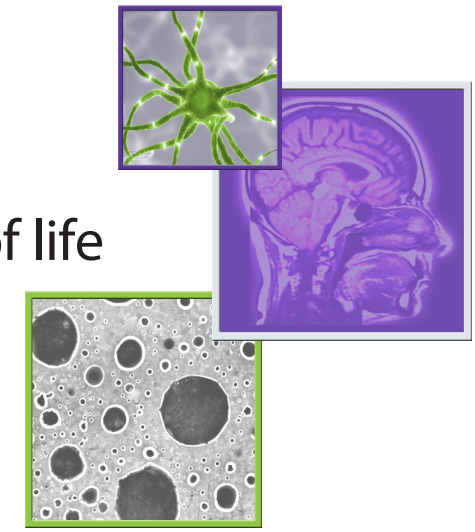

Symptom management and quality of life in glioma patients

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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 6 months following diagnosis.
- Changes in personality and behavior are often present and can heavily influence spousal relationships.
- These symptoms impact upon the 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.

Gliomas are relatively rare, with an incidence of only six per 100,000 individuals [1], 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

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cognitive symptoms [2]. Headaches are very common [3–5], as well as focal neurological symptoms, such as paresis, visual-perceptual deficits, sensory loss and seizures [6]. 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 [7–9]. 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 [10].

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 [11]. 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 patients and their partners [12].

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' [13]. 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 [14,15], persisting symptoms of fatigue are also typical symptoms of neurological disease, including traumatic brain injury [16]. 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 [17] 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 40–80% of patients report severe symptoms of fatigue [18–21], 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 [22] 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 [21], 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) [16,18,19,21,23].

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 guidelines for treatment of fatigue in the context of brain tumor patients is provided [22]. 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 [22]. 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 [24–26]. When using a placebo-controlled design, prophylactic methylphenidate failed to show a beneficial effect on fatigue in brain tumor patients [27]. In a study from our own group, we found no beneficial effects of modafinil on fatigue when compared with placebo [28]. 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 [29]. Some studies have shown positive results on fatigue using acupuncture, but scientific evidence is required before these interventions can be integrated into clinical practice [30].

The National Comprehensive Cancer Network 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 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 [6], 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 cutoff scores used [31]. However, it is clear that the majority of glioma patients experience deterioration in a broad array of cognitive domains [8,32].

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 [33]. In addition, psychological distress and the premorbid level of cognitive functioning can contribute to the level of deficits a patient exhibits [33]. In glioma patients, worse cognitive functioning has been associated with disease progression and poorer survival [34–38]. 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 [31]. Indeed, in long-term survivors even subtle cognitive deficits might hamper patients' autonomy and professional life [39]. 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 [31]. 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 [40], but they can achieve similar functional gains from participation in a neurorehabilitation program [41]. 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 [42]. Nevertheless, several interventions that show beneficial effects on cognitive functioning have been reported on in glioma patients, providing some support for its effectiveness [43–45]. However, these studies report on rather small groups (less than 20 patients) and all but one [44] 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 [46]. This study shows promising results, with improved attention and verbal memory and less mental fatigue after 6 months compared with a care-as-usual group. However, this program consists of six weekly home visits of 2 h 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 [47,48] 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 [24,27], modafinil [24,28], memantine [49] and donepezil [50]. Trials on the effects of armodafinil and liothyronine on cognitive functioning have also been reported on [31]. 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 [51,52]. 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 [53], MDD is defined as the presence of at least five of the following symptoms for a minimal duration of 2 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 [54]. For example, use of certain antiepileptic drugs is known to cause mood changes [55]. 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 [56]. In that case, MDD is less likely to be recognized and treated. This leads to an underdiagnosis of depression in cancer patients [57]. It is clear that MDD forms a serious problem in glioma patients with approximately 15–20% of the patient population becoming clinically depressed up to 8 months following diagnosis [58,59]. Furthermore, longitudinal data suggests that the proportion of depressed patients continues to increase up to 1 year after surgery [60]. To compare, the 1 year prevalence of depression in the general population is 6.6% [61]. There are even indications that glioma patients are at increased risk for developing MDD compared with other cancer patient populations [62,63].

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 [58]. 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) [58,60]. 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, Acquaye *et al.* examined predictors of mood disturbance in patients with brain tumors in several different phases of the disease [64]. 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 antidepressants were more prone to mood disturbance [64].

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 [65], 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 [66,67]. 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 [68]. Although it is now generally believed that depression and epilepsy share risk factors and that prescription of newer antidepressants does not evoke more seizures [69–71], physicians still seem reluctant to prescribe antidepressants to glioma patients. One study indicated that 6 months after surgery, only 60% of patients in whom the treating physician recognized depression, received antidepressants [72].

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 [73]. 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 [74], acceptance and commitment therapy [75], and mindfulness [76]. 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 & 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 [77] – meaning all behavior requiring an interaction. While various studies suggest that changes in personality and behavior are certainly not uncommon in glioma patients [78–81], including symptoms such as anger, loss of emotional control, indifference and maladaptive behaviors [82], 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 [83,84]. 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 [85]. Moreover, although uncommon, drug-induced behavioral problems, such as steroid psychosis, have also been reported on [86]. 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 [81]. When the patient exhibits a lack of insight into these changes, the distress of partners and others who are closely involved with the patient increases [87]. Indeed, awareness, recognition and communication are factors influencing whether couples share certain perceptions or drift apart [88]. 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 [89]. 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 [89].

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 [90]. 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 [91]. 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 time and cost restraints.

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.

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 [92]. 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 more 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 [93], 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 [94]. 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 & 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 [95]. To our knowledge, there are currently 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 [96–98]. 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 [99]. The researchers concluded that screening QoL in this manner is feasible and that monitoring QoL profiles over time can lead to improvements in healthcare 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 [100]. In this study, patients received information material with contact information of healthcare professionals or referral to a psychologist if they exceeded the cutoff 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 [100], results of screening were reported only to the physicians and not to the patients themselves. As physicians often have to cope with a lack of time and resources [95], providing feedback to professionals only limits the benefits of screening to patients. In the general cancer patient population, only 20–30% 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 [95].

Conclusion & 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 healthcare professionals and providing feedback to physicians and patients alike could be realized, disease burden of glioma patients and their partners could be substantially alleviated.

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