European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma

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Patients with glioma present with complex palliative care needs throughout their disease trajectory. The life-limiting nature of gliomas and the presence of specific symptoms related to neurological deterioration necessitate an appropriate and early palliative care approach. The multidisciplinary palliative care task force of the European Association of Neuro-Oncology did a systematic review of the available scientific literature to formulate the best possible evidence-based recommendations for the palliative care of adult patients with glioma, with the aim to reduce symptom burden and improve the quality of life of patients and their caregivers, particularly in the end-of-life phase. When recommendations could not be made because of the scarcity of evidence, the task force either used evidence from studies of patients with systemic cancer or formulated expert opinion. Areas of palliative care that currently lack evidence and thus deserve attention for further research are fatigue, disorders of behaviour and mood, interventions for the needs of caregivers, and timing of advance care planning.

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Introduction

Palliative care does not primarily aim to prolong life or cure disease but to relieve patient symptoms and to sustain or improve functioning and quality of life. Palliative care encompasses patients' symptoms and needs (physical, mental, social, and existential or spiritual) throughout the journey of a life-threatening disease. The WHO definition of palliative care states that it "is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life".[1] Early use of palliative care is supported by evidence showing that early intervention increases quality of life and duration of survival, and reduces the hospital care of patients with lung cancer.[2] Moreover, involvement of specialised and experienced palliative care teams in the care of patients with cancer might improve symptom management and caregiver satisfaction as well as reduce health costs,[3] underscoring the importance of early palliative care intervention. These findings have contributed to an increased interest in the integration of palliative care into current standards of care across oncology.

Awareness of the importance of palliative care is increasing, not only in the field of oncology but also in neurology and other branches of medicine. Patients with gliomas, which are primary brain tumours thought to originate from neuroglial precursor cells, suffer from both a progressive neurological disease and cancer. Because most patients with glioma cannot be cured, palliative care throughout the disease trajectory is particularly important in this patient group, including in the end-of-life phase. No uniform definition of the end-of-life phase exists. However, in this Review, we refer to the end-of-life phase as the last 3 months of life.[4]

In view of the increasing awareness for use of palliative care in patients with glioma, and despite the scarcity of evidence available about palliative care options from clinical studies, particularly about palliative care in the end-of-life phase of glioma, a systematic literature review was done by the European Association of Neuro-Oncology (EANO) palliative care task force (LD and JAFK) to identify relevant literature about palliative care in primary brain tumours.

This Review aims to summarise these research findings to provide evidence-based guidelines for palliative care in adult patients with glioma, with the aim of improving the quality of palliative care, particularly in the final stage of disease. When evidence was scarce, we either used evidence from studies of patients with systemic cancer or formulated expert opinion to provide more guidance for clinicians involved in the care of these patients. We designated three main areas of palliative care for adult patients with glioma: symptom management, patient and caregiver needs, and palliative care (including care in the end-of-life phase). For symptom management, we aimed to identify any intervention that could improve one of several symptoms: pain or headache, epilepsy, venous thromboembolism, fatigue, mood and behavioural disorders, neurological deficits for which rehabilitation is required, and cognition. All relevant articles related to patient and caregiver needs were included. For the topic of palliative care (including care in the end-of-life phase), we focused on delirium, nutrition, hydration, respiration, advance care planning, and organisation of the end-of-life phase.

The literature search yielded 6160 unique articles, of which 223 were classified as eligible and included in this Review (figure). In consensus with two task force members (LD and MJBT), the quality of evidence was classified according to guidelines by the European Federation of Neurological Societies.[5] Although subjective, this classification provided insight into the quality of evidence and hence the value of each recommendation. Table 1 shows evidence concerning treatment of the

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various symptoms of glioma, table 2 shows recommendations concerning the needs of patients and caregivers, and table 3 shows recommendations concerning care in the end-of-life phase.

Symptom management

Pain or headache

Headache is the main type of pain in patients with brain tumours, occurring in 23–90% of patients, with an increase in frequency and severity over time.[6,8,33,45–48] Headache pain mostly results from brain tumour growth or surrounding oedema and indicates an increased intracranial pressure. By contrast, bodily pain tends to have a more predominant role in systemic cancers (32–90% of patients) and is less frequently reported in patients with brain tumours (10–30%), although the prevalence increases in the last few weeks of life.[6,49]

The most frequent treatment for headache in patients with glioma is the use of corticosteroids (56–87% of patients[6,8]), usually dexamethasone in conjunction with gastric protection (in 81–86% of patients[8,13]). Dexamethasone is the preferred corticosteroid to use for the treatment of headache based on its side-effect profile, although its use has been associated with several side-effects, including the Cushing effect, muscle weakness, and diabetes mellitus, that worsen with increased dose and duration of treatment.[50,51] A randomised trial[7] of the use of dexamethasone in brain tumours showed that 4 mg/day dexamethasone resulted in the same degree of improvement as a dose of 16 mg/day dexamethasone after 1 week of treatment in patients without signs of impending herniation. However, non-steroidal anti-inflammatory drugs, analgesics, and co-analgesics should also be considered for the treatment of headache in patients with primary brain tumours.[8] Use of opioids for moderate and severe pain might involve oral, parenteral, or transdermal routes based on patient needs and the care setting. Near death, use of opioids (especially subcutaneous, transdermal) increases and predominates, and opioids are partly used pragmatically in case of respiratory discomfort.[52]

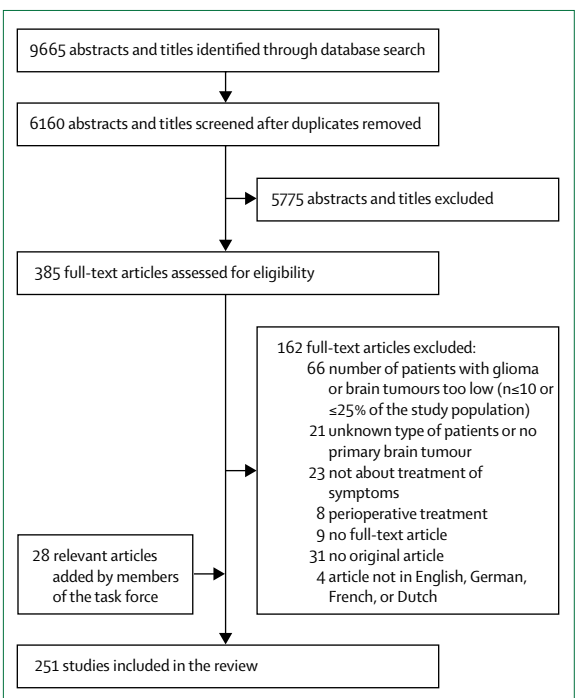

Figure: **Systematic literature selection procedure**

Epilepsy

Seizures occur in up to 90% of patients with glioma in the course of the disease, depending on the glioma subtype, tumour location, proximity to the brain cortex, and genetic factors.[53,54] Seizures often persist during the end-of-life phase and de novo seizures might develop during the last weeks before death. Uncontrolled seizures might lead to hospitalisation, which is typically not the desired option for patients in the end-of-life phase and might subsequently decrease their quality of life. The caregiver, who may already suffer from a heavy burden of care, might experience additional distress in the case of ongoing seizures. Therefore, adequate seizure management until death is essential in patients with glioma. 11 studies[55] showed that there was a 6–56% prevalence of seizures during the end-of-life phase in patients with glioma. During the last month before death, the seizure prevalence ranged from 30% to 37%, with one study[49] showing an increase in seizure prevalence towards death. Patients with a history of epilepsy, particularly those with a history of status epilepticus, have the highest risk of developing seizures at the end of life.

Seizure management during the end-of-life phase is often hampered by swallowing difficulties or impaired consciousness, which eventually occur in most patients during the last days before death. Because these patients are not able to swallow anti-epileptic drugs, they need alternative administrative routes to prevent sub-therapeutic serum concentrations of anti-epileptic drugs. To date, no data exist on the preferred drug of choice. In patients with non-brain-tumour-related epilepsy, intranasal midazolam and rectal diazepam have shown similar efficacy in the treatment of acute seizures.[56] In a prospective study[9] of 25 patients with glioma, intranasal midazolam appeared to be a feasible way to treat acute seizures and provided an important level of comfort among caregivers. In the same study,[9] use of buccal clonazepam was considered appropriate in the case of swallowing difficulties. Subcutaneous midazolam, levetiracetam, and phenobarbital are suitable alternatives to oral treatment. Intramuscular phenobarbital in patients assisted at home or intravenous levetiracetam in patients in hospital can also be an option. In patients with refractory epilepsy and a short life expectancy of up to 2 weeks, palliative sedation with subcutaneous midazolam might be considered.

Venous thromboembolism

Patients with cancer have an increased risk of venous thromboembolism compared with the general population. This complication worsens their prognosis and leads to increased morbidity and mortality. The observed incidence of venous thromboembolism in patients with gliomas, who have the highest risk of tumour-associated venous thromboembolism out of all cancers, was 8% in a large retrospective study[57] and 21–26% at 1 year and 32% at 2 years in prospective studies.[58,59] Several biomarkers have been identified that quantify the individual risk of developing venous thromboembolism in patients with glioma. Although the risk of venous thromboembolism peaks within the first 6 months after surgery, deep vein thrombosis, particularly in limbs with impaired mobility with and without pulmonary embolism, can occur at any time.

A randomised trial[10] comparing treatment with a sequential compression device, enoxaparin, or a combination of both, in 68 patients with brain tumours showed that initiation of enoxaparin at the time of anaesthesia increased the risk of intracranial haemorrhage. Venous thromboembolism prophylaxis with low molecular weight heparin should therefore only start within 24 h after surgery.[11] Venous thromboembolism prophylaxis after surgery is routinely done with low molecular weight heparin for 7–10 days. To date, no study has shown an advantage for prolonging prophylaxis beyond the perioperative period. In a phase 2 study[60] of 40 patients with brain tumours, two (5%) patients developed intracranial haemorrhage and four (10%) patients developed venous thromboembolism after prophylaxis with tinzaparin for 12 months. In another phase 2 study[61] of 45 patients, neither intracranial haemorrhage, venous thromboembolism, nor survival gain, were observed with use of dalteparin for a median duration of 6 months. A placebo-controlled trial[12] investigating the efficacy of long-term dalteparin in 186 patients with malignant glioma found that, during the first 6 months of treatment, nine (9%) of 99 patients in the dalteparin group developed venous thromboembolism compared with 13 (15%) of 87 patients in the placebo group, although this difference was not statistically significant. Moreover, during 12-month follow-up, five (5%) intracranial haemorrhages occurred in the dalteparin group versus one (1%) in the placebo group.[12]

Anticoagulation with low molecular weight heparin is safe in most patients with glioma, but should be avoided in patients with recent tumoural bleeding, thrombocytopenia (less than 50 000 platelets/mm³), and usual contraindications.[11] No data exist on the use of new oral anticoagulants in patients with brain tumours and their potential interactions with chemotherapy or seizure drugs. The duration of anticoagulant treatment as secondary prophylaxis in patients with glioma after venous thromboembolism should be planned individually, weighing the risk of intracranial haemorrhage against the risk of recurrence of venous thromboembolism in a patient whose tumour cannot be considered stable.[14] However, because of the

	Quality of evidence*
Pain or headache	
Corticosteroids (dexamethasone) should be the mainstay of treatment for headache in patients with gliomas[6,7]	++
Analgesics and co-analgesics could also be considered in the treatment of headache in patients with gliomas (also in accordance with the WHO cancer pain ladder)[8]	++
During care in the end-of-life phase, consideration needs to be given to the management of headache with corticosteroids; advantages of corticosteroids (alleviation of symptoms) should be weighed against side-effects (such as delirium)	Expert opinion
Epilepsy	
When the oral route is not an option, intranasal midazolam and buccal clonazepam are a feasible way to treat seizures in the end-of-life phase[9]	++
Alternative routes of anti-epileptic drug administration need to be considered when patients with glioma who have a history of epilepsy develop swallowing difficulties; the preferred route of administration depends on the local availability of anti-epileptic drugs and the place of care	Expert opinion
Venous thromboembolism	
Because the perioperative risk of intracranial haemorrhage increases when prophylaxis is started before induction of anaesthesia, venous thromboembolism prophylaxis with low molecular weight heparin in patients with brain tumours should be started within 24 h after surgery[10,11]	++++
No evidence supports extension of primary venous thromboembolism prophylaxis beyond the postoperative period in patients with glioma[12]	++++
The duration of secondary prophylaxis in patients with brain tumours after a venous thromboembolism event should be planned individually, but is lifelong in most patients[13,14]	+++
Fatigue	
There is to date no evidence of efficacy for pharmacological interventions against fatigue in patients with glioma[15]	++++
There is to date no evidence of efficacy for non-pharmacological interventions for fatigue in patients with glioma[15]	++++
Mood and behavioural disorders	
Evidence of several pharmacological interventions (eg, methylphenidate, donepezil) for mood disorders in patients with glioma is limited[16–21]	++
Multimodal psychosocial intervention might improve depressive symptoms in patients with brain tumours[22]	+++
Rehabilitation for neurological deficits	
Patients with brain tumours might benefit from early rehabilitation after surgery, as well as rehabilitation after tumour-specific treatment[23–25]	++
Cognition	
Medical treatment to prevent or treat cognitive decline in patients with brain tumours is not recommended[16–18,26–28]	+++
Cognitive rehabilitation has modest positive effects and should be considered especially in young patients with glioma who have a relatively favourable prognosis[29–31]	+++
Stable glioma patients with cognitive complaints, deficits, or both might benefit from cognitive rehabilitation	Expert opinion
Reduction of supportive medication should be considered in patients with glioma because they might be a potential cause of cognitive complaints or deficits	Expert opinion

++++=high quality. +++=moderate quality. ++=low quality. +=very low quality. *Expert opinion was formulated by task force members.

Table 1: **Quality of evidence for each recommendation concerning the treatment of the symptoms of glioma**

	Quality of evidence
Patient needs	
The need for ongoing support might best be served by having one dedicated point of contact for continuity of contact with a health-care professional (most likely a specialist nurse)[32]	+
Early referral to palliative care and psychosocial support should be implemented[32–34]	+
Caregiver needs	
Psychoeducation and cognitive behavioural therapy can increase feelings of mastery of caregivers and result in maintenance of their quality of life[35]	++
Medical professionals can mitigate caregiver stress by including the caregiver in medical consultations, requesting their feedback, and acknowledging their role[36]	+
Caregiver anxiety relating to the future death of the patient can be alleviated by more open communication[36]	+

++=low quality. +=very low quality.

Table 2: **Quality of evidence for each recommendation concerning needs of patients and caregivers**

	Quality of evidence*
Delirium	
Olanzapine, risperidone, aripiprazole, and haloperidol are equally effective in the treatment of delirium in patients with cancer[37]	+++
Risperidone and haloperidol (maximum dose up to 4 mg/day) are not more effective than placebo in the treatment of delirium in patients receiving palliative care and result in more adverse effects[38]	++++
In case of delirium, first the underlying causes must be identified and reacted on (eg, by adequate symptom control or changes in doses or type of medication)[39]	+++
If the underlying causes of delirium have been adequately identified and addressed but, despite this, delirium could not be relieved, low-dose haloperidol might be recommended as a treatment option in patients with glioma	Expert opinion
In case of refractory delirium, palliative sedation with benzodiazepines (eg, midazolam) might be used in patients with glioma	Expert opinion
Nutrition, hydration, and respiration	
No effective pharmacological treatment exists for noisy respiration (so-called death rattle) in the end-of-life phase of patients with glioma[40]	++++
Parenteral nutrition and hydration are unlikely to benefit patients with glioma in the end-of-life phase	Expert opinion
Advance care planning	
Medical decision-making might already be problematic for patients with glioma soon after the time of diagnosis because of cognitive deficits[41,42]	++
To improve dying with dignity in patients with glioma, caregiver's satisfaction with the care provided by the physician in the last week of life should be enhanced and transitions between health-care settings should be avoided[43]	+
Advance care planning and the use of advanced directives should be considered early in the disease trajectory	Expert opinion
Organisation of care in the end-of-life phase	
The quality of perceived care in the end-of-life phase is enhanced by effective symptom control, satisfaction with information received, and adherence to the preferred place of death; the quality is less dependent on the specific type of care in the end-of-life phase (eg, hospice, home care)[44]	+

++++=high quality. +++=moderate quality. ++=low quality. +=very low quality. *Expert opinion was formulated by task force members.

Table 3: **Quality of evidence for each recommendation concerning care in the end-of-life phase**

high risk of venous thromboembolism, lifelong use of prophylaxis is likely in most patients with brain tumours.[13]

Fatigue

Between 25% and 90% of all patients with primary brain tumours report fatigue, which can occur at any time during the disease course.[62] The biological mechanisms leading to cancer-related fatigue have not yet been fully elucidated, and most studies have been done in rodents. Human data have come from patients with solid tumours, such as breast cancer or lung cancer. The potential mechanisms involve increased blood concentrations of inflammatory cytokines, influencing neuroendocrine function, and decreased concentrations of glutamine and tryptophan in the brain, with or without disturbance of circadian rhythms.

Management of fatigue can be non-pharmacological (eg, physical exercise or cognitive behavioural therapies) or pharmacological. A 2016 Cochrane review[15] evaluating the effectiveness and safety of pharmacological and non-pharmacological interventions for adult patients with primary brain tumours and high levels of fatigue, in which only one (11%) of nine identified studies was eligible according to the inclusion criteria, did not find strong evidence to support the use of any pharmacological or non-pharmacological intervention in the management of cancer-related fatigue. A 6-week crossover study[26] of modafinil versus placebo in patients with stable brain tumours and moderate fatigue showed a reduction in fatigue severity in both arms, but no significant benefit from modafinil compared with placebo. Two randomised trials[63,64] have examined the effect of methylphenidate or armodafinil on fatigue in patients undergoing radiotherapy for brain metastases. These studies did not find a significant reduction in fatigue with pharmacological treatment, although a post-hoc analysis[63] noted an improvement at 4 weeks of follow-up in those patients with high baseline fatigue, and a trend towards improvement at 6 weeks of follow-up with armodafinil. Thus, there is no evidence to suggest that modafinil, armodafinil, methylphenidate, or donepezil confer a significant beneficial effect on fatigue in patients with stable brain tumours. However, one study[16] reported an improvement in fatigue, and post-hoc analyses suggested an improvement in fatigue when data on modafinil or methylphenidate study groups were combined versus placebo. Additionally, other studies reported an improvement in fatigue scores only at certain time-points: 8 or 12 weeks with methylphenidate,[65] or after 24 weeks with donepezil.[17]

Mood and behavioural disorders

Mood and behavioural disorders are major comorbidities for patients with brain tumours. The 6-month prevalence of clinical depression is in the order of 20%, whereas personality change might affect up to 60% of patients.[66]

Although the management of such disorders in patients with cancer has been reviewed,[67] guidance specific to those with brain tumours is required because patients with brain tumours are different from general patients with cancer in that they do not only have cancer but also a neurological disease.

No randomised trial has specifically examined the drug treatment of patients with primary brain tumours who are clinically depressed.[68] Studies of varying methodological quality, which used rating scales to measure depressive symptoms as secondary outcomes, have provided limited evidence for methylphenidate,[16,18] oxcarbazapine,[19] bupropion,[20] ginkgo biloba,[21] and donepezil.[17] It remains unknown whether these treatments are effective for clinically significant depression or whether they are better than placebo.

Regarding evidence for non-pharmacological interventions, a single-centre randomised trial[22] using a multimodal psychosocial intervention showed clinically significant benefit on depressive symptoms for patients with brain tumours. Evidence to suggest a possible beneficial role for massage therapy,[69] acceptance and commitment therapy,[70] or telephone-based support for anxiety[71] is limited and preliminary. Other studies[23,26,27,63,71] report no evidence of a benefit for non-pharmacological interventions on depressive symptoms. These negative results are invariably difficult to interpret when studies were neither focused on, nor were powered to, exclude an effect on depression.

Rehabilitation for neurological deficits

Neurorehabilitation aims to enable patients to reach and maintain their optimal levels of physical, sensory, intellectual, psychological, and social function. Patients with brain tumours commonly have multiple deficits in all of these areas.

No randomised controlled trial has examined the value of specialist rehabilitation after surgery in patients with primary brain tumours. Most studies of glioma are retrospective cohort studies investigating patients with neurological deficits that warrant specialised inpatient neurorehabilitation,[72–74] and only two studies[75,76] have examined outpatient rehabilitation. A review[25] of 11 retrospective studies suggested a mean improvement in functional independence of 36%, with a median length of inpatient stay of 1·5 months. Some studies[24,72] match controls with other conditions, such as stroke or traumatic brain injury, to compare functional outcomes (ie, functioning in daily living or ability to sit, stand, or walk). These two matched case-control studies suggested similar functional improvements in patients with brain tumours as in those patients seen after a stroke[24] or head injury.[72]

There is limited evidence to suggest that early physical training, massage therapy, and ambulatory rehabilitation can improve functional outcome, reduce stress, and improve quality of life in patients with glioma.[77] Importantly, performance of rehabilitation during radiotherapy does not appear to affect patient engagement with rehabilitation.[78] Rehabilitation after radiotherapy can lead to functional gains, some of which persist at 6 months.[23] There is no evidence to suggest that rehabilitation improves survival, however, although strenuous exercise was an independent prognostic factor for survival in patients with malignant glioma.[79]

Cognition

Intact cognitive abilities, such as executive functions, verbal fluency, memory and attention, and visuo-constructive skills, are a prerequisite for adequate communication, independent functioning, and active participation in daily life. In patients with brain tumours, cognitive abilities might be threatened by the disease in terms of disruption of local and distant neurocognitive networks, but also by patient characteristics, such as age and educational level, tumour characteristics, tumour treatment, supportive medication (eg, anti-epileptic drugs, corticosteroids), and psychological distress. Depending on the definition of cognitive disturbances, type of outcome measure used, and extent of cognitive functions examined, up to 91% of patients with brain tumours can have cognitive disturbances before treatment, which only moderately correlated with cognitive complaints.[80,81]

Medical treatment to prevent cognitive decline after radiotherapy in patients with brain tumours has been shown to be unsuccessful. Donepezil, an acetylcholinesterase inhibitor, had some significant positive effects on attention and memory in a non-randomised study of 24 patients.[17] However, this effect was not confirmed in a randomised placebo-controlled trial[28] of 198 brain tumour survivors (including 130 [66%] patients with primary brain tumours) at more than 6 months after the completion of cranial radiotherapy. Psychostimulants, such as methylphenidate and modafinil, are also not successful in terms of improved cognitive functions. Methylphenidate, which appeared promising in a non-randomised study[18] of 30 patients with glioma, with respect to both cognition and motor functioning, did not improve cognitive function in a randomised placebo-controlled trial[27] of 68 patients with brain tumours who were undergoing cranial radiotherapy. Additionally, no clear benefit for methylphenidate versus modafinil was found in a randomised, open-label, pilot study of 24 patients with brain tumours.[16] Modafinil, in a double-blind, placebo-controlled, crossover trial[26] of 37 patients with primary brain tumours, did not exceed the (positive) effects of placebo in terms of cognitive functioning. Three randomised studies[29–31] assessed the ability of cognitive rehabilitation to improve cognitive functioning. In one of these studies,[30] virtual reality training (ie, interactive rehabilitation and exercise training with virtual reality) was added to standard computer-based cognitive rehabilitation for 19 (50%) of 38 patients with brain tumours and significantly

improved several cognitive outcomes. The largest of those studies[29] included 140 patients with mainly low-grade glioma and both cognitive complaints and cognitive deficits. Immediate assessment after rehabilitation showed a significant and subjective improvement in the intervention group and, at 6 months after treatment, the intervention group had significantly improved attention and verbal memory, as well as reduced mental fatigue, compared with the waiting-list control group. Younger patients had the most benefit from cognitive rehabilitation. Another randomised study[31] of 58 patients with primary brain tumours showed significant improvement in the domains of visual attention and verbal memory in the treatment group immediately after 4 weeks of cognitive training.

Patient and caregiver needs

Palliative care and care in the end-of-life phase are often intertwined, but the care needs of patients with glioma and their caregivers vary considerably in the different stages of disease. In addition to the physical burdens and deficits, the deleterious psychosocial effect of glioma and its treatment is profound and affects both patients and their caregivers. A recent systematic review[82] reported that dealing with such changes can be overwhelming for both patients and caregivers, resulting in issues such as depression, anxiety, and isolation. Research continues to focus on describing the experiences of patients and caregivers rather than establishing the best methods to provide care or information or to develop and trial new supportive care interventions.

Patients

Continuous re-evaluation of the patient's support needs and need for information is required because patient needs change over time with disease progression.[83] A strong case exists for multidisciplinary support programmes to address patient problems, thus helping to reduce their burden.[84,85] Standards of care (including existential support) might be enhanced by moving towards a proactive approach, extending care goals beyond medical needs.[84] This ongoing support might best be served by having one dedicated and central point of contact for continuity of communication with a health-care professional most likely to be the specialist nurse.[32]

About half of distressed patients with cancer do not access psychosocial services, with some individuals refusing because they view it as a sign of personal weakness.[86] Patients with gliomas are often referred to these services late in their illness trajectory, with few patients participating in end-of-life decisions while they are cognitively and communicatively intact.[33,83] Early referral to palliative care and psychosocial support services is therefore essential.[32] Low referral to and use of psychosocial services might limit the ability of a patient to cope with their condition and the changes they experience through their disease trajectory.[33,34] Understanding glioma patients' use of these services, along with their physical and psychosocial experiences, is crucial to the development of service delivery models that help to meet their substantial needs.[34,83]

Caregivers

Because glioma is a highly disabling disease, substantial reliance is placed on the caregiver to support the patient, resulting in caregiver stress, anxiety, exhaustion, reduced quality of life, and various other negative effects. This distress has been reported as being related to the changing sense of identity, loss of a relationship with the patient (owing to the patient's personality changes), a sense of isolation and guilt, and fears regarding the eventual death of the patient (anticipatory grief). Medical professionals can mitigate these stresses by including the caregiver at medical appointments, requesting their feedback, and acknowledging their role.[36]

Anxiety associated with the future death of the patient has been widely reported in the literature, with some studies suggesting that this fear is intense and inescapable in the context of glioma.[87,88] This anxiety can be reduced through improving open communication between physicians or health-care professionals and caregivers, especially when cognitive and personality changes restrict the ability of the patient to speak for themselves.[36]

Caregivers have indicated that they want information about how to reduce stress and are interested in participating in stress-reduction programmes.[89] An effective and useful way to provide information to caregivers is through the appointment of a specialist nurse.[90] A randomised trial[35] showed that the quality of life of caregivers can be maintained and feelings of mastery can be enhanced with psychoeducation and cognitive behavioural therapy.

Care in the end-of-life phase

Delirium

Most patients with cancer have progressive decline in the level of consciousness in the last stage of disease (71% experience reduced consciousness in the last 3 months, and 81–95% in the last week before death).[39] Besides reduced consciousness due to progressive tumour growth leading to increased intracranial pressure, alterations in consciousness and reduced awareness and inattention might be part of the complex neuropsychiatric syndrome of delirium. Psychomotor subtypes of delirium include hyperactive (10–54% of cases), hypoactive (46–49% of cases), and mixed (41% of cases) subtypes.[39] The underlying causes and risk factors of delirium are multifactorial. For example, commonly prescribed agents in the palliative care setting, such as benzodiazepines, corticosteroids, or opioids, are associated with an increased risk of delirium. In patients receiving palliative care, delirium represents the third most frequent symptom near death and appears in up to 90% of patients in the dying phase.[39,49,91–93] Delirium was

described in eight (62%) of 13 patients with glioma, with an increasing incidence in the last week before death.[86] Few randomised or open-label trials have investigated the use of antipsychotics for in-hospital treatment of delirium in patients with cancer or who are terminally ill and, in those studies, only a few patients had brain tumours.[39] Olanzapine, risperidone, aripiprazole, and haloperidol were found to be equally effective for the treatment of delirium; extrapyramidal symptoms were most frequently reported in patients treated with haloperidol, whereas sedative effects predominately occurred during treatment with olanzapine.[37] A 2017 randomised trial[38] of 247 patients in palliative care (including 218 [88%] patients with cancer) compared risperidone and haloperidol (maximum dose up to 4 mg/day) with placebo and did not find a benefit for pharmacological treatment. Instead, pharmacological treatment was associated with significantly increased delirium symptom scores and extrapyramidal effects. To date, no non-pharmacological trials of delirium treatment in patients with cancer or in those who are terminally ill have been done. An article[39] reviewing the best available evidence for treatment of delirium in patients with cancer suggested that, in cases of delirium, the underlying cause must first be identified and treated.

In two studies, 33 (58%) of 57 patients[8] and 13 (45%) of 29 patients[49] with brain tumours were treated for delirium with various psychopharmacological drugs (eg, antipsychotics, antidepressants, benzodiazepines). Palliative sedation of patients with brain tumours to relieve delirium was reported in up to 30% of cases.[39] This treatment option is frequently required for refractory delirium during the end-of-life phase.[94]

Nutrition, hydration, and respiration

In the last weeks or days of life, patients with brain tumours often have difficulty swallowing because of dysphagia and decreased consciousness. Dysphagia is reported as one of the more frequent symptoms in the end-of-life phase of patients with brain tumours. However, the frequency of dysphagia in these patients ranges widely from 10% to 85% and increases towards death.[4,45] Losing the ability to swallow might induce pulmonary aspiration and hamper nutrition, hydration, and oral administration of drugs.

The difficulty in swallowing saliva in the oropharynx, particularly in terminally ill patients who are unconscious, might produce noisy and uncomfortable respiration, both during inspiration and expiration, which is called the death rattle. These respiratory symptoms have been reported in 12–23% of patients with brain tumours in the last weeks of life and might severely affect a peaceful process of dying, particularly disturbing caregivers and the patient's family.[6,48] Treatment to combat this issue might involve a change in posture to drain saliva or treatment with injectable hyoscine, an anticholinergic agent. However, a Cochrane review[40] assessing the evidence for the effectiveness of interventions used to treat the death rattle in terminally ill patients concluded that no evidence exists for the benefit of any pharmacological intervention, including treatment with hyoscine hydrobromide, atropine, hyoscine butylbromide, and octreotide. In that same Cochrane review,[40] glycopyrronium significantly reduced the sound of noisy breathing compared with hyoscine, although no placebo arm was used.

Treatment decisions about nutrition and hydration in the end-of-life phase are among the most important and ethically relevant issues in patients with brain tumours. No study has been done to investigate the effects of parenteral nutrition and hydration on terminally ill patients with brain tumours. Ethical and legal approaches to withdrawal and withholding of nutrition and hydration in terminally ill patients vary widely among different countries and cultures. However, there is consensus about the futility of artificial nutrition and hydration at the end of life in comatose patients with glioma.

Advance care planning

Advance care planning is a process by which patients and their physicians establish future goals for their care in the end-of-life phase, which offers patients the opportunity to define their goals and expectations. Advance care planning is concerned with, for example, preferences related to non-treatment decisions or preferred place of death. Advance care planning is most effective when it is started in a timely fashion, allowing patients, caregivers, and physicians to proactively address the challenges together during the course of the disease. Advance care planning can lead to an advance directive, which is a written statement about a person's preferences regarding future medical decisions.

Advance care planning is particularly important for patients with glioma because of their decreased decision-making capacities due to the presence of cognitive impairment, delirium, communication difficulties, loss of consciousness, and rapid evolution of neurological symptoms. About half of patients with glioma have problems understanding treatment situations, choices, and risks or benefits soon after diagnosis, and about half are unable to participate in decisions about care in the last weeks of life.[41,42] Even when theoretically competent, patients are rarely involved in decisions about their end-of-life care. Up to 40% of patients with brain tumours might not be aware of their prognosis, yet only a minority of patients are unwilling to discuss end-of-life care. Additionally, only half of physicians and nurses or health-care workers feel comfortable talking about end of life and symptoms with their patients.

Some data are available on advance care planning and advance directives specific to patients with glioma, but most studies have only small patient numbers. The occurrence of advance care planning ranged from 44% to 85% of patients in different studies.[33,41,86] The presence

Search strategy and selection criteria

A systematic literature search was done in the e-resources PubMed, Embase, CINAHL, PsychINFO, the Cochrane Library, Web of Science, Academic Search Premier, and ScienceDirect up to Jan 25, 2016. The search strategy consisted of a combination of two search strings: one relating to the three main areas of palliative care, and one relating to glioma. The full search strategy for PubMed is provided in the appendix. After screening of all retrieved titles and abstracts, the full texts of potentially relevant articles were checked for eligibility. Any uncertainty about the relevance of a specific study was resolved by consensus. Additionally, several relevant studies that were not identified by the literature search, but known to members of the task force, were added. Studies were included if they were original studies involving patients with glioma or brain tumours (n≥10 or ≥25% of the total study population); if they described symptom management, the palliative care needs of patients and caregivers, or care in the end-of-life phase; and if the full text was available in either English, German, French, or Dutch.

See Online for appendix

of advance directives ranged from 0% to 70% in different studies.[33,95] One study[96] found a positive association between recorded discussions about prognosis and those about life-sustaining treatments and the presence of a do-not-resuscitate order.

The effects of advance care planning or advance directives in patients with glioma are described in three different studies. One study[95] found that, for 16 (67%) of 24 patients who preferred to die at home, the preferred place of death was fulfilled. Another study[44] reported that, in only a minority of patients (20 [10%] of 207 patients), the decisions made by the physician were not in accordance with the preferences of the patients. A third study[43] showed that decisions related to end of life were more often explicitly discussed with patients who died with dignity (eg, with fewer communication deficits and fewer transitions between health-care settings in the end-of-life phase) than with those who died without. Furthermore, patients who died with dignity more often died at the preferred place of death. Outside the context of patients with glioma in particular and patients with cancer in general, strong evidence exists for the effects of advance care planning. A randomised trial[97] showed that facilitated advance care planning in older patients who were admitted to a hospital improved the quality of end-of-life care and patient and family satisfaction, and reduced stress, anxiety, and depression in surviving relatives. Another randomised trial[98] of patients with congestive heart failure or end-stage renal disease showed that, with facilitated advance care planning, most patients received the care they desired.

Timely advance care planning seems important for most patients with glioma to improve disease management. Positive effects for early palliative care were found in patients with other cancer types, such as improved health-related quality of life, mood, symptom control, and satisfaction with care, as well as less aggressive care at the end of life.[2,3]

Organisation of care in the end-of-life phase

The availability of palliative care services varies greatly within and between countries and, consequently, the place of death of patients with brain tumours also varies. One cohort study[44] showed that many patients prefer to die at home (64 [78%] of 82 patients in the Netherlands, 36 [69%] of 52 patients in the UK, and 31 [46%] of 68 patients in Austria), although the actual place of death differed for 23 (33%) of 69 patients in the Netherlands, 21 (44%) of 48 patients in Austria, and 27 (61%) of 44 patients in the UK. In the Netherlands, 50 (60%) of 83 patients died at home compared to 26 (37%) of 71 patients in Austria and 15 (29%) of 51 patients in the UK. In Austria, a large proportion of patients died in a hospital (29 [41%] of 71 patients), whereas many patients (21 [41%] of 51 patients) in the UK died in a hospice. Moreover, place of death was found to be independently associated with good quality of care, as was effective symptom control, and satisfaction with the type of information received.[44]

Factors associated with a low probability of dying at home included repeated admission to the emergency room, prolonged duration as a hospital inpatient, low involvement of general practitioners and few home visits, and accessibility of acute care beds.

Physical and cognitive dysfunctions in patients with brain tumours, with changes in behaviour and impairment in communication, might affect dignity and expose patients and relatives to stress[43,99] and can influence the organisation of care, such as place of care, place of death, and decisions about end of life. Dying with dignity was significantly correlated with the absence of communication deficits, good communication with physicians, fewer transitions between health-care settings, and dying at the preferred place of death.[43] Reasons for admission to hospital more frequently include social issues and neurological and cognitive deficits for patients with brain tumours than for other patients in need of palliative care.[100] Generally, patients are only referred to palliative care services in the last stage of disease. However, an earlier and integrative approach was found to have a positive effect on the quality of end of life and was recommended by several studies.[43,99]

Conclusions

For patients with glioma, and for patients with cancer in general, palliative care is not confined to the end-of-life phase, but covers the entire disease trajectory from diagnosis and initial tumour treatment until death. With this concept in mind, we did a systematic literature

review for development of palliative care guidelines for adult patients with glioma. To guide clinicians managing adult patients with glioma, we supplemented the best available, but clearly limited, evidence for palliative care in patients with glioma—in the areas of symptom management, patient and caregiver needs, and care in the end-of-life phase—with either evidence from studies of patients with systemic cancer or expert opinion.

Although studies of other diseases, such as systemic cancer or progressive neurological diseases, might give further guidance for palliative care in adult patients with glioma, the specific symptoms and needs of patients with glioma and their families require more clinical studies of palliative care. Areas of palliative care that deserve attention for research are fatigue, disorders of behaviour and mood, interventions for the needs of caregivers, and timing of advance care planning. An active palliative care culture within the neuro-oncological community, as well as collaborative research networks, facilitated by organisations such as EANO, the Society for Neuro-Oncology, the Asian Society for Neuro-Oncology, and the World Federation of Neuro-Oncology Societies, should further enhance the quality of palliative care for patients with glioma and their families.

Contributors

All authors contributed substantially to the design and concept of this Review. LD and JAFK did the systematic literature search. Each author prepared a part of the article (based on their expertise) and AP, in collaboration with MJBT and LD, combined their input. All authors critically revised the article for important intellectual content and approved the version to be published.

Declaration of interests

ELR reports non-financial support from Mundipharma and Amgen, outside of the submitted work. MJBT reports personal fees from Hoffmann-La Roche, outside of the submitted work. MW reports grants and personal fees from Roche and Novocure and personal fees from MSD, outside of the submitted work. KO reports personal fees from GlaxoSmithKline, Eli Lilly, Bristol-Myers Squibb, and Sarcoma Patients Euronet, outside of the submitted work, and is chair and co-director of the International Brain Tumour Alliance (IBTA). The IBTA accepts educational and non-directed grants for its work from a number of pharmaceutical and medical device companies, and also accepts a small number of donations from the general public and, on occasion, private trusts or bequests. All other authors declare no competing interests.

References

1 WHO. WHO definition of palliative care. www.who.int/cancer/palliative/definition/en/ (accessed Jan 4, 2017).

2 Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363:** 733–42.

3 Zimmermann C, Riechelmann R, Krzyzanowska M, Rodin G, Tannock I. Effectiveness of specialized palliative care: a systematic review. *JAMA* 2008; **299:** 1698–709.

4 Sizoo EM, Pasman HR, Dirven L, et al. The end-of-life phase of high-grade glioma patients: a systematic review. *Support Care Cancer* 2014; **22:** 847–57.

5 Leone MA, Brainin M, Boon P, Pugliatti M, Keindl M, Bassetti CL, for the European Federation of Neurological Societies. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2012. *Eur J Neurol* 2013; **20:** 410–19.

6 Koekkoek JA, Dirven L, Sizoo EM, et al. Symptoms and medication management in the end of life phase of high-grade glioma patients. *J Neurooncol* 2014; **120:** 589–95.

7 Vecht CJ, Hovestadt A, Verbiest HB, van Vliet JJ, van Putten WL. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. *Neurology* 1994; **44:** 675–80.

8 Thier K, Calabek B, Tinchon A, Grisold W, Oberndorfer S. The last 10 days of patients with glioblastoma: assessment of clinical signs and symptoms as well as treatment. *Am J Hosp Palliat Care* 2016; **33:** 985–88.

9 Koekkoek JA, Postma TJ, Heimans JJ, Reijneveld JC, Taphoorn MJ. Antiepileptic drug treatment in the end-of-life phase of glioma patients: a feasibility study. *Support Care Cancer* 2016; **24:** 1633–38.

10 Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. *Neurosurgery* 1998; **43:** 1074–81.

11 Lyman GH, Khorana AA, Kuderer NM, et al, for the American Society of Clinical Oncology Clinical Practice. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013; **31:** 2189–204.

12 Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. *J Thromb Haemost* 2010; **8:** 1959–65.

13 Chen JY, Hovey E, Rosenthal M, Livingstone A, Simes J. Neuro-oncology practices in Australia: a Cooperative Group for Neuro-Oncology patterns of care study. *Asia Pac J Clin Oncol* 2014; **10:** 162–67.

14 Chee CE, Ashrani AA, Marks RS, et al. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. *Blood* 2014; **123:** 3972–78.

15 Day J, Yust-Katz S, Cachia D, et al. Interventions for the management of fatigue in adults with a primary brain tumour. *Cochrane Database Syst Rev* 2016; **4:** Cd011376.

16 Gehring K, Patwardhan SY, Collins R, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. *J Neurooncol* 2012; **107:** 165–74.

17 Shaw EG, Rosdhal R, D'Agostino RB Jr, et al. Phase II study of donepezil in irradiated brain tumor patients: effect on cognitive function, mood, and quality of life. *J Clin Oncol* 2006; **24:** 1415–20.

18 Meyers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. *J Clin Oncol* 1998; **16:** 2522–27.

19 Maschio M, Dinapoli L, Sperati F, et al. Oxcarbazepine monotherapy in patients with brain tumor-related epilepsy: open-label pilot study for assessing the efficacy, tolerability and impact on quality of life. *J Neurooncol* 2012; **106:** 651–56.

20 Moss EL, Simpson JS, Pelletier G, Forsyth P. An open-label study of the effects of bupropion SR on fatigue, depression and quality of life of mixed-site cancer patients and their partners. *Psychooncology* 2006; **15:** 259–67.

21 Attia A, Rapp SR, Case LD, et al. Phase II study of Ginkgo biloba in irradiated brain tumor patients: effect on cognitive function, quality of life, and mood. *J Neurooncol* 2012; **109:** 357–63.

22 Ownsworth T, Chambers S, Damborg E, Casey L, Walker DG, Shum DH. Evaluation of the making sense of brain tumor program: a randomized controlled trial of a home-based psychosocial intervention. *Psychooncology* 2015; **24:** 540–47.

23 Khan F, Amatya B, Drummond K, Galea M. Effectiveness of integrated multidisciplinary rehabilitation in primary brain cancer survivors in an Australian community cohort: a controlled clinical trial. *J Rehabil Med* 2014; **46:** 754–60.

24 Bartolo M, Zucchella C, Pace A, et al. Early rehabilitation after surgery improves functional outcome in inpatients with brain tumours. *J Neurooncol* 2012; **107:** 537–44.

25 Formica V, Del Monte G, Giacchetti I, et al. Rehabilitation in neuro-oncology: a meta-analysis of published data and a mono-institutional experience. *Integr Cancer Ther* 2011; **10:** 119–26.

26 Boele FW, Douw L, de Groot M, et al. The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial. *Neuro Oncol* 2013; **15:** 1420–28.

27 Butler JM Jr, Case LD, Atkins J, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. *Int J Radiat Oncol Biol Phys* 2007; **69:** 1496–501.

28 Rapp SR, Case LD, Peiffer A, et al. Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. *J Clin Oncol* 2015; **33:** 1653–59.

29 Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol* 2009; **27:** 3712–22.

30 Yang S, Chun MH, Son YR. Effect of virtual reality on cognitive dysfunction in patients with brain tumor. *Ann Rehabil Med* 2014; **38:** 726–33.

31 Zucchella C, Capone A, Codella V, et al. Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumor: a randomized, controlled trial. *J Neurooncol* 2013; **114:** 93–100.

32 Philip J, Collins A, Brand CA, et al. Health care professionals' perspectives of living and dying with primary malignant glioma: implications for a unique cancer trajectory. *Palliat Support Care* 2015; **13:** 1519–27.

33 Gofton TE, Graber J, Carver A. Identifying the palliative care needs of patients living with cerebral tumors and metastases: a retrospective analysis. *J Neurooncol* 2012; **108:** 527–34.

34 Langbecker D, Yates P. Primary brain tumor patients' supportive care needs and multidisciplinary rehabilitation, community and psychosocial support services: awareness, referral and utilization. *J Neurooncol* 2016; **127:** 91–102.

35 Boele FW, Hoeben W, Hilverda K, et al. Enhancing quality of life and mastery of informal caregivers of high-grade glioma patients: a randomized controlled trial. *J Neurooncol* 2013; **111:** 303–11.

36 Applebaum AJ, Kryza-Lacombe M, Buthorn J, DeRosa A, Corner G, Diamond EI. Existential distress among caregivers of patients with brain tumours: a review of the literature. *Neurooncol Pract* 2016; **3:** 232–44.

37 Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: a comparison of efficacy, safety, and side effects. *Palliat Support Care* 2015; **13:** 1079–85.

38 Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. *JAMA Intern Med* 2017; **177:** 34–42.

39 Breitbart W, Alici Y. Evidence-based treatment of delirium in patients with cancer. *J Clin Oncol* 2012; **30:** 1206–14.

40 Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *Cochrane Database Syst Rev* 2012; **1:** Cd005177.

41 Sizoo EM, Pasman HR, Buttolo J, et al. Decision-making in the end-of-life phase of high-grade glioma patients. *Eur J Cancer* 2012; **48:** 226–32.

42 Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. *Neurology* 2009; **73:** 2086–92.

43 Sizoo EM, Taphoorn MJ, Uitdehaag B, et al. The end-of-life phase of high-grade glioma patients: dying with dignity? *Oncologist* 2013; **18:** 198–203.

44 Koekkoek JA, Dirven L, Reijneveld JC, et al. End of life care in high-grade glioma patients in three European countries: a comparative study. *J Neurooncol* 2014; **120:** 303–10.

45 Sizoo EM, Braam L, Postma TJ, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. *Neuro Oncol* 2010; **12:** 1162–66.

46 Girvan AC, Carter GC, Li L, et al. Glioblastoma treatment patterns, survival, and healthcare resource use in real-world clinical practice in the USA. *Drugs Context* 2015; **4:** 212274.

47 Bausewein C, Hau P, Borasio GD, Voltz R. How do patients with primary brain tumours die? *Palliat Med* 2003; **17:** 558–59.

48 Pace A, Di Lorenzo C, Guariglia L, Jandolo B, Carapella CM, Pompili A. End of life issues in brain tumor patients. *J Neurooncol* 2009; **91:** 39–43.

49 Oberndorfer S, Lindeck-Pozza E, Lahrmann H, et al. The end-of-life hospital setting in patients with glioblastoma. *J Palliat Med* 2008; **11:** 26–31.

50 Hempen C, Weiss E, Hess CF. Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side-effects? *Support Care Cancer* 2002; **10:** 322–28.

51 Lee EQ, Wen PY. Corticosteroids for peritumoral edema: time to overcome our addiction? *Neuro Oncol* 2016; **18:** 1191–92.

52 Caraceni A, Hanks G, Kaasa S, et al, for the European Palliative Care Research Collaborative (EPCRC), on behalf of the European Association for Palliative Care (EAPC). Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012; **13:** e58–68.

53 Rudà R, Bello L, Duffau H, Soffietti R. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. *Neuro Oncol* 2012; **14** (suppl 4)**:** iv55–64.

54 Weller M, Stupp R, Wick W. Epilepsy meets cancer: when, why, and what to do about it? *Lancet Oncol* 2012; **13:** e375–82.

55 Koekkoek JAF, Dirven L, Reijneveld JC, et al. Epilepsy in the end of life phase of brain tumor patients: a systematic review. *Neuro Oncol Pract* 2014; **1:** 134–40.

56 Holsti M, Dudley N, Schunk J, et al. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. *Arch Pediatr Adolesc Med* 2010; **164:** 747–53.

57 Semrad TJ, O'Donnell R, Wun T, et al. Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. *J Neurosurg* 2007; **106:** 601–08.

58 Brandes AA, Scelzi E, Salmistraro G, et al. Incidence of risk of thromboembolism during treatment high-grade gliomas: a prospective study. *Eur J Cancer* 1997; **33:** 1592–96.

59 Simanek R, Vormittag R, Hassler M, et al. Venous thromboembolism and survival in patients with high-grade glioma. *Neuro Oncol* 2007; **9:** 89–95.

60 Perry SL, Bohlin C, Reardon DA, et al. Tinzaparin prophylaxis against venous thromboembolic complications in brain tumor patients. *J Neurooncol* 2009; **95:** 129–34.

61 Robins HI, O'Neill A, Gilbert M, et al. Effect of dalteparin and radiation on survival and thromboembolic events in glioblastoma multiforme: a phase II ECOG trial. *Cancer Chemother Pharmacol* 2008; **62:** 227–33.

62 Grant R, Brown PD. Fatigue randomized controlled trials—how tired is "too tired" in patients undergoing glioma treatment? *Neuro Oncol* 2016; **18:** 759–60.

63 Lee EQ, Muzikansky A, Drappatz J, et al. A randomized, placebo-controlled pilot trial of armodafinil for fatigue in patients with gliomas undergoing radiotherapy. *Neuro Oncol* 2016; **18:** 849–54.

64 Page BR, Shaw EG, Lu L, et al. Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. *Neuro Oncol* 2015; **17:** 1393–401.

65 Kaleita TA, Wellisch DK, Graham CA, et al. Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors. *Proc Am Soc Clin Oncol* 2006; **24** (suppl 18)**:** 1503.

66 Rooney AG, McNamara S, Mackinnon M, et al. Frequency, clinical associations, and longitudinal course of major depressive disorder in adults with cerebral glioma. *J Clin Oncol* 2011; **29:** 4307–12.

67 Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. *Cochrane Database Syst Rev* 2015; **6:** Cd011006.

68 Rooney A, Grant R. Pharmacological treatment of depression in patients with a primary brain tumour. *Cochrane Database Syst Rev* 2013; **3:** Cd006932.

69 Keir ST. Effect of massage therapy on stress levels and quality of life in brain tumor patients—observations from a pilot study. *Support Care Cancer* 2011; **19:** 711–15.

70 Kangas M, McDonald S, Williams JR, Smee RI. Acceptance and commitment therapy program for distressed adults with a primary brain tumor: a case series study. *Support Care Cancer* 2015; **23:** 2855–59.

71 Jones S, Ownsworth T, Shum DH. Feasibility and utility of telephone-based psychological support for people with brain tumor: a single-case experimental study. *Front Oncol* 2015; **5:** 71.

72 Bilgin S, Kose N, Karakaya J, Mut M. Traumatic brain injury shows better functional recovery than brain tumor: a rehabilitative perspective. *Eur J Phys Rehabil Med* 2014; **50:** 17–23.

73 Roberts PS, Nuno M, Sherman D, et al. The impact of inpatient rehabilitation on function and survival of newly diagnosed patients with glioblastoma. *PM R* 2014; **6:** 514–21.

74 O'Dell MW, Barr K, Spanier D, Warnick RE. Functional outcome of inpatient rehabilitation in persons with brain tumor. *Arch Phys Med Rehabil* 1998; **79:** 1530–34.

75 Pace A, Parisi C, Di Lelio M, et al. Home rehabilitation for brain tumor patients. *J Exp Clin Cancer Res* 2007; **26:** 297–300.

76 Pompili A, Telera S, Vilani V, Pace A. Home palliative care and end of life issues in glioblastoma multiforme: results and comments from a homogenous cohort of patients. *Neurosurg Focus* 2014; **37:** 1–4.

77 Piil K, Juhler M, Jakobsen J, Jarden M. Controlled rehabilitative and supportive care intervention trials in patients with high-grade gliomas and their caregivers: a systematic review. *BMJ Support Palliat Care* 2016; **6:** 27–34.

78 Khan F, Amatya B, Ng L, Drummond K, Galea M. Multidisciplinary rehabilitation after primary brain tumour treatment. *Cochrane Database Syst Rev* 2015; **8:** CD009509.

79 Ruden E, Reardon DA, Coan AD, et al. Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. *J Clin Oncol* 2011; **29:** 2918–23.

80 Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery* 2000; **47:** 324–33.

81 Gehring K, Taphoorn MJ, Sitskoorn MM, Aaronson NK. Predictors of subjective versus objective cognitive functioning in patients with stable grades II and III glioma. *Neuroocol Pract* 2015; **2:** 20–31.

82 Zwinkels H, Dirven L, Vissers T, et al. Prevalence of changes in personality and behavior in adult glioma patients: a systematic review. *Neurooncol Pract* 2016; 3: 222–31.

83 Sterckx W, Coolbrandt A, Clement P, et al. Living with a high-grade glioma: a qualitative study of patients' experiences and care needs. *Eur J Oncol Nurs* 2015; **19:** 383–90.

84 Janda M, Eakin EG, Bailey L, Walker D, Troy K. Supportive care needs of people with brain tumours and their carers. *Support Care Cancer* 2006; **14:** 1094–103.

85 Philip J, Collins A, Brand CA, et al. "I'm just waiting…": an exploration of the experience of living and dying with primary malignant glioma. *Support Care Cancer* 2014; **22:** 389–97.

86 Golla H, Ale Ahmad M, Galushko M, et al. Glioblastoma multiforme from diagnosis to death: a prospective, hospital-based, cohort, pilot feasibility study of patient reported symptoms and needs. *Support Care Cancer* 2014; **22:** 3341–52.

87 Adelbratt S, Strang P. Death anxiety in brain tumour patients and their spouses. *Palliat Med* 2000; **14:** 499–507.

88 Milberg A, Strang P, Jakobsson M. Next of kin's experience of powerlessness and helplessness in palliative home care. *Support Care Cancer* 2004; **12:** 120–28.

89 Swartz JJ, Keir ST. Program preferences to reduce stress in caregivers of patients with brain tumors. *Clin J Oncol Nurs* 2007; **11:** 723–27.

90 Spetz A, Henriksson R, Bergenheim AT, Salander P. A specialist nurse-function in neurooncology: a qualitative study of possibilities, limitations, and pitfalls. *Palliat Support Care* 2005; **3:** 121–30.

91 Agar M, Lawlor P. Delirium in cancer patients: a focus on treatment-induced psychopathology. *Curr Opin Oncol* 2008; **20:** 360–66.

92 Hall P, Schroder C, Weaver L. The last 48 hours of life in long-term care: a focused chart audit. *J Am Geriatr Soc* 2002; **50:** 501–06.

93 Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med* 2000; **160:** 786–94.

94 Bush SH, Leonard MM, Agar M, et al. End-of-life delirium: issues regarding recognition, optimal management, and the role of sedation in the dying phase. *J Pain Symptom Manage* 2014; **48:** 215–30.

95 Flechl B, Ackerl M, Sax C, et al. The caregivers' perspective on the end-of-life phase of glioblastoma patients. *J Neurooncol* 2013; **112:** 403–11.

96 Bradley EH, Hallemeier AG, Fried TR, et al. Documentation of discussions about prognosis with terminally ill patients. *Am J Med* 2001; **111:** 218–23.

97 Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ* 2010; **340:** c1345.

98 Kirchhoff KT, Hammes BJ, Kehl KA, Briggs LA, Brown RL. Effect of a disease-specific advance care planning intervention on end-of-life care. *J Am Geriatr Soc* 2012; **60:** 946–50.

99 Pace A, Villani V, Di Pasquale A, et al. Home care for brain tumor patients. *Neurooncol Pract* 2014; **1:** 8–12.

100 Ostgathe C, Voltz R. Quality indicators in end-of-life care. *Curr Opin Support Palliat Care* 2010; **4:** 170–73.