



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2017

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

Pace, Andrea ; Dirven, Linda ; Koekkoek, Johan A F ; Golla, Heidrun ; Fleming, Jane ; Rudà, Roberta ; Marosi, Christine ; Le Rhun, Emilie ; Grant, Robin ; Oliver, Kathy ; Oberg, Ingela ; Bulbeck, Helen J ; Rooney, Alasdair G ; Henriksson, Roger ; Pasmán, H Roeline W ; Oberndorfer, Stefan ; Weller, Michael ; Taphoorn, Martin J B ; European Association of Neuro-Oncology

Abstract: 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.

DOI: [https://doi.org/10.1016/S1470-2045\(17\)30345-5](https://doi.org/10.1016/S1470-2045(17)30345-5)

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-141055>

Journal Article

Accepted Version

Originally published at:

Pace, Andrea; Dirven, Linda; Koekkoek, Johan A F; Golla, Heidrun; Fleming, Jane; Rudà, Roberta; Marosi, Christine; Le Rhun, Emilie; Grant, Robin; Oliver, Kathy; Oberg, Ingela; Bulbeck, Helen J; Rooney, Alasdair G; Henriksson, Roger; Pasmán, H Roeline W; Oberndorfer, Stefan; Weller, Michael; Taphoorn, Martin J B; European Association of Neuro-Oncology (2017). European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. *Lancet Oncology*, 18(6):e330-e340. DOI: [https://doi.org/10.1016/S1470-2045\(17\)30345-5](https://doi.org/10.1016/S1470-2045(17)30345-5)

EANO guidelines for palliative care in adult glioma patients

Andrea Pace¹, Linda Dirven^{2,3}, Johan AF Koekkoek^{2,3}, Heidrun Golla⁴, Jane Fleming⁵, Roberta Rudà⁶, Christine Marosi⁷, Emilie Le Rhun^{8,9}, Robin Grant¹⁰, Kathy Oliver¹¹, Ingela Oberg¹², Helen J Bulbeck¹³, Alisdair G Rooney¹⁴, Roger Henriksson^{15,16}, H Roeline W Pasman¹⁷, Stefan Oberndorfer¹⁸, Michael Weller¹⁹, Martin JB Taphoorn^{2,3}, on behalf of the European Association of Neuro-Oncology Task Force on Palliative Care

¹ Neuro-Oncology Unit, Regina Elena Cancer Institute, Rome, Italy

² Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands

³ Department of Neurology, Haaglanden Medical Center, The Hague, the Netherlands

⁴ Department of Palliative Medicine, University Hospital of Cologne, Cologne, Germany

⁵ Department of Palliative Medicine, University Hospital Waterford, Ireland

⁶ Department of Neuro-Oncology, University and City of Health and Science Hospital, Turin, Italy

⁷ Department of Internal Medicine I, Clinical Division of Medical Oncology, Medical University of Vienna, Vienna, Austria

⁸ Neuro-oncology, Department of Neurosurgery, University Hospital, Lille, France

⁹ Breast Unit, Department of Medical Oncology, Oscar Lambret Center, Lille, France

¹⁰ Edinburgh Centre for Neuro-Oncology, Western General Hospital, Edinburgh, Scotland, United Kingdom

¹¹ International Brain Tumour Alliance, United Kingdom

¹² Department of neuroscience, Cambridge University Hospitals, Cambridge, United Kingdom

¹³ Brainstrust (the brain cancer people), Cowes, Isle of Wight, United Kingdom

¹⁴ Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, Scotland, United Kingdom

¹⁵ Regional Cancer Center Stockholm Gotland, Stockholm, Sweden

¹⁶ Department of Radiation Sciences and Oncology, Umeå University, Umeå, Sweden

¹⁷ Department of Public and Occupational Health, The EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, The Netherlands

¹⁸ Department Neurology, University Clinic St. Pölten, KLPU and KLI-Neurology and Neuropsychology, St. Pölten, Austria

¹⁹ Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland

Abstract

Patients affected by gliomas present with complex palliative care needs throughout their disease trajectory. The significantly life-limiting nature of gliomas and the presence of specific symptoms related to neurological deterioration necessitates an appropriate and early palliative approach. The multidisciplinary palliative care task force of the European Association of Neuro-Oncology (EANO) performed a systematic review of the scientific literature available to formulate the best possible evidence-based recommendations on palliative care for adult glioma patients, with the goal to reduce symptom burden and improve the quality of life of patients and their caregiver, particularly in the end of life (EOL) phase. Where recommendations could not be made because of lack of evidence, the task force formulated expert opinion.

Introduction

Palliative care (PC) does not primarily aim at prolongation of life or cure, but at relief of symptoms and sustained or improved functioning and quality of life. PC encompasses patient symptoms and needs (physical, mental, social and existential/spiritual) throughout the disease journey of a life-threatening illness. Recent evidence for the effectiveness of PC for patients with cancer, showing that early PC increases the quality of life, length of survival and reduces hospital care for patients with lung cancer¹, has contributed to a change in the concept of PC and a broader interest in its integration into to current standards of care across oncology. Accordingly, the World Health Organisation (WHO) definition states that PC is already applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life.² Moreover, specialized and experienced PC team involvement in cancer patients may improve symptom management and caregiver satisfaction as well as reduce health costs³, underscoring the importance of (early) PC.

There is an increasing awareness of the importance of PC not only in the field of oncology but also in neurology and other branches of medicine. Patients with gliomas, i.e., primary brain tumours thought to originate from neuroglial precursor cells, suffer from both a progressive neurological disease and cancer. Since the far majority of glioma patients cannot be cured, PC is particularly important in this patient group, throughout the disease trajectory including the end of life (EOL) phase. Currently, no definition of the EOL phase exist, therefore, in this guideline we refer to the EOL phase as the last three months of life.⁴

Given the growing awareness for PC in glioma patients and despite the limited evidence from clinical studies on PC, and more specifically on PC in the EOL phase in glioma, a systematic literature review was performed by the European Association of Neuro-Oncology (EANO) palliative care task force to identify all relevant literature on PC in primary brain tumours.

This guideline aims to summarize research findings in order to provide evidence-based PC guidelines for adult glioma patients, supplemented with expert opinion in case of lack of evidence, with the goal to improve the quality of PC, particularly in the last stage of disease. The quality of evidence has been classified according to the European Federation of Neurological Societies guidelines.⁵ In addition, missing, but relevant studies for this guideline have been added by task force members.

Literature search

A systematic literature search was conducted in the e-resources PubMed, Embase, Cinahl, PsychInfo, Cochrane Library, Web of Science, Academic Search Premier and ScienceDirect up to February 2016. The search strategy consisted of a combination of two search strings; one related to symptom management / palliative care (including care in the EOL phase) and one related to glioma. The full search strategy for PubMed is provided in Supplementary File 1. After screening all retrieved titles and abstracts, full texts of potential relevant articles were checked for eligibility. Any uncertainty about the relevance of a specific study was resolved by consensus.

The following inclusion criteria were applied: original studies involving glioma or brain tumour patients (n≥10 or ≥25% of the total study population); description of symptom management, patient and caregiver palliative care needs, or care in the EOL phase; available full text in English, German, French or Dutch.

The literature search yielded 6160 unique articles, of which 223 were classified as eligible (see Figure 1 for the results of the selection procedure). Three main areas of PC were designated: symptom management (1); patient and caregiver needs (2); care in the EOL phase (3).

Symptom management

Pain/Headache

Headache is the main type of pain in brain tumour patients, occurring in 23-90%, with an increase in frequency and severity over time. The pain mostly results from brain tumour growth and/or surrounding oedema and indicates raised intracranial pressure. In contrast, bodily pain tends to play a more predominant role in systemic cancers (32-90%) and is less frequently reported in patients with brain tumours (10-30%), although the prevalence increases in the last weeks of life.

The most frequent treatment for headache in glioma patients is the use of corticosteroids (56-87%)^{6,7}, usually dexamethasone in conjunction with gastric protection (81-86%).^{7,8} Dexamethasone once a day is the preferred corticosteroid based on side-effect profile, but still has a wide range of side-effects (e.g., Cushing effect, muscle weakness and diabetes mellitus), increasing with higher dose and longer duration of treatment.^{9,10} A randomized controlled trial (RCT) on the use of dexamethasone in brain tumours indicated that an effective starting dose is 4 mg/day, with a maximum effective dose of 16 mg/day for symptom control.¹¹ However, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and co-analgesics should also be considered in the treatment of headache in patients with primary brain tumours.⁷ The use of opioids for moderate and severe pain may involve oral, parenteral, or transdermal routes based on patient need and the care setting. Near death the use of opioids (especially subcutaneous, transdermal) increased and predominated, partly pragmatically.¹²

Epilepsy

Seizures occur in up to 90% of glioma patients in the course of the disease, depending on the glioma subtype, tumour location, proximity to the brain cortex and genetic factors. Seizures often persist during the EOL phase and even de novo seizures may develop during the last weeks before death. Uncontrolled seizures may lead to rehospitalisation, which is often not preferred by patients in the EOL phase, and may subsequently decrease their quality of life. The caregiver, who may already suffer from a heavy burden of care, may experience additional distress in case of ongoing seizures. Therefore, adequate seizure management until death is essential in patients with glioma. Eleven studies evaluated seizure prevalence in glioma patients at some point during the EOL phase, showing prevalence ranging between 6% and 56%. During the last month before death seizure prevalence ranged

from 30-37%, with one study showing an increase in prevalence towards death. Patients with a history of epilepsy have the highest risk to develop seizures during the EOL, particularly those with a history of status epilepticus.

Seizure management during the EOL phase is often hampered by swallowing difficulties or an impaired consciousness, eventually occurring in most patients during the last days before death. As these patients are not able to swallow oral antiepileptic drugs (AEDs), they need alternative administration routes to prevent sub-therapeutic AED serum levels. To date, there are no data regarding the preferred drug. In patients with non-brain tumour-related epilepsy, intranasal midazolam and rectal diazepam have shown similar efficacy in the acute treatment of seizures.¹³ In a prospective study among 25 glioma patients, intranasal midazolam appeared to be a feasible way to treat acute seizures, providing an important level of comfort among patient's caregivers as well.¹⁴ In the same study, the use of buccal clonazepam was considered appropriate in case of swallowing difficulties. Subcutaneous midazolam, subcutaneous levetiracetam, and subcutaneous phenobarbital are suitable alternatives to oral treatment. Intramuscular phenobarbital in patients assisted at home or intravenous levetiracetam in hospitalized patients can be an option. In patients with refractory epilepsy and a short life expectancy up to two weeks, palliative sedation with subcutaneous midazolam may be considered.

Venous thromboembolism

Patients with cancer have an increased risk of venous thromboembolism (VTE). These complications aggravate their prognosis and lead to increased morbidity and mortality. The observed incidence of VTE in patients with gliomas, belonging to the subgroup with the highest tumour associated VTE risk, ranged from 7.5-20% in retrospective studies, and from 14-20% at one year and 32% at two years in prospective studies. Although the risk of VTE peaks within the first six months after surgery, deep vein thrombosis, preferentially in limbs with impaired motility with and without pulmonary embolism, can occur at any time.

As the perioperative risk of intracranial haemorrhage (ICH) increases when prophylaxis is started before induction of anesthesia, VTE prophylaxis with low molecular heparin (LMWH) should be started postoperatively within 24 hours.^{15,16} VTE prophylaxis in the postsurgical period is routinely done with LMWH for 7 to 10 days. To date, no study has proven an advantage by prolonging prophylaxis beyond the perioperative period. In a phase II study using tinzaparin for 12 months, 2/40 patients developed ICH and 4/40 patients VTE.¹⁷ In another phase II study including 45 patients, no ICH, no VTE and no survival gain were observed with dalteparin use for a median of 6 months.¹⁸ The only placebo controlled trial, recruiting 186 patients, found 11% VTE in the dalteparin arm and 17% in the placebo arm. Moreover, five ICHs occurred in the dalteparin arm versus one in the placebo arm.¹⁹

Anticoagulation with LMWH is safe in most glioma patients, but should be avoided in case of recent tumoural bleeding, thrombocytopenia under 50.000 platelets/mm³ and usual contra-indications.¹⁶ There are yet no data on new oral anticoagulants in brain tumour patients and on their potential interactions with chemotherapy or seizure medication. The duration of anticoagulant treatment as secondary prophylaxis in glioma patients after VTE should be planned individually, weighing the risk of ICH against the recurrence risk of VTE in a

patient whose tumour cannot be considered stable²⁰, but likely results in lifelong prophylaxis in most brain tumour patients after VTE⁸.

Fatigue

Cancer-related fatigue is also a common symptom in patients with brain tumours. The biological mechanisms leading to cancer-related fatigue are complex and not yet fully elucidated. Most studies have been conducted in rodents. Human data come from patients with solid tumours such as breast cancer or lung cancer. The potential mechanisms studied involve increased blood levels of inflammatory cytokines influencing neuroendocrine function and decreased levels of glutamine and tryptophan in the brain with or without disturbance of circadian rhythms.

Management of fatigue can be non-pharmacological (physical exercise/ cognitive behavioural therapies) or pharmacological. A recent Cochrane review did not find strong evidence to support any pharmacological or non-pharmacological treatment for fatigue in patients with brain tumours.²¹ A 6-week crossover study of modafinil versus placebo in stable brain tumour patients with moderate fatigue showed reduction in fatigue severity in both arms, but no significant benefit from modafinil over placebo.²² Several RCTs examined the effect of methylphenidate or armodafinil on fatigue in patients undergoing radiotherapy for brain metastases.^{23,24} These studies failed to find a significant reduction in fatigue, although post-hoc analyses noted improvement at 4-week follow-up in those with high baseline fatigue and a trend towards improvement at 6-week follow-up using armodafinil.²³ Thus, there is no evidence suggesting a significant benefit from modafinil, armodafinil, methylphenidate or donepezil for the treatment of fatigue in stable brain tumour patients after treatment. However, one study reported improvement in fatigue, but not of activity or motivation, and post-hoc analyses suggested an improvement in fatigue if modafinil or methylphenidate study groups were combined versus placebo²⁵, while another study reported improvement in fatigue scores only at certain time points: 8 or 12 weeks with methylphenidate²⁶ or after 24 weeks with donepezil²⁷.

Mood and behavioural disorders

Mood and behavioural disorders are a major comorbidity for patients and their families living with a brain tumour, with six-month prevalence rates of up to 20% for clinical depression and up to 60% for personality change. Although the management of these disorders in cancer has been reviewed²⁸, brain tumour-specific guidance is required.

No RCT has specifically examined drug treatment of clinically depressed patients with a primary brain tumour.²⁹ A number of uncontrolled cohort studies, that measured depressive symptoms as secondary outcomes on rating scales, provide limited evidence in favour of methylphenidate^{25,30}, oxcarbazepine³¹, bupropion SR³², ginkgo biloba³³ and donepezil²⁷. It remains unknown whether any of these treatments are effective for clinically significant depressive disorder, or indeed any better than placebo.

Evidence for non-pharmacological interventions includes an RCT of a multimodal psychosocial intervention, which showed clinically significant benefit on depressive symptoms.³⁴ Other studies report no evidence of benefit on depressive symptoms.^{22,23,35-37} These negative results are difficult to interpret because these studies were neither focused on, nor powered to exclude an effect on depression.

Similarly, there is limited and preliminary evidence to suggest a possible beneficial role for massage therapy³⁸, acceptance and commitment therapy³⁹, or telephone based support for anxiety³⁶.

Neuro-rehabilitation

Neuro-rehabilitation aims at enabling patients to reach/maintain their optimal physical, sensory, intellectual, psychological and social functional levels. Brain tumour patients commonly have multiple deficits including all the above areas.

No RCT has examined the value of specialist post-operative rehabilitation in patients with primary brain tumours. Most studies in glioma are retrospective cohort studies studying patients with neurological deficits that warrant specialised inpatient neuro-rehabilitation⁴⁰, and only a few studies examine outpatient rehabilitation.⁴¹ Some studies match controls with other conditions, e.g. stroke or traumatic brain injury.^{40,42} A review of 11 retrospective studies suggests a mean 36% improvement in functional independence, with a median length of inpatient stay of 1.5 months.⁴³ Matched case control studies suggest similar functional improvements to those seen post stroke and head injury.^{40,42}

There is limited evidence to suggest that early physical training, massage therapy, and ambulatory rehabilitation may improve functional outcome, reduce stress, and improve quality of life in patients with glioma.⁴⁴ Importantly, getting rehabilitation during radiotherapy does not appear to limit engagement with rehabilitation. Post-radiotherapy rehabilitation can lead to functional gains, some of which will persist at 6 months.³⁷ There is no evidence that rehabilitation improves survival, although strenuous exercise behaviour was an independent prognostic factor for survival in malignant glioma patients.⁴⁵

Cognition

Intact cognitive abilities, such as executive functions, verbal fluency, memory and attention, and visuoconstructive skills, are a prerequisite for adequate communication, independent functioning, and active participation in daily life. In brain tumour patients, cognitive abilities may 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 (e.g., 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 brain tumour patients have cognitive disturbances before treatment, only moderately correlated with cognitive complaints.

Medical treatment to prevent cognitive decline in irradiated brain tumour patients has not been proven successful. Donepezil, an acetylcholinesterase inhibitor, had some statistically significant positive effects on attention and memory in a non-randomized study in 24 patients, that was not confirmed in a randomized placebo-controlled trial of 198 brain tumour survivors (66% primary brain tumour) >6 months following completion of cranial radiotherapy.^{27,46} Psychostimulants, like methylphenidate and modafinil, have not been proven successful in terms of improved cognitive functions either. Methylphenidate, looking promising in a non-randomized study in 30 glioma patients with respect to both cognition and motor functioning³⁰, did not improve cognitive function in a randomized placebo-controlled trial of 68 brain tumour patients during cranial radiotherapy³⁵. Comparing methylphenidate and modafinil in a randomized open-label pilot study in 24 brain tumour patients, no clear benefit of one drug compared to the other was found.²⁵ Modafinil, in a more recent double-blind placebo-controlled crossover trial in 37 primary brain tumour patients, did not exceed the (positive) effects of placebo in terms of cognitive functioning.²² In three randomized studies the effect of cognitive rehabilitation to improve cognitive functioning was examined.⁴⁷⁻⁴⁹ In one of these studies, virtual reality training was added to standard computer-based cognitive rehabilitation in 19 of 38 brain tumour patients and significantly improved several cognitive outcomes.⁴⁸ The largest randomized controlled study included 140 mainly low-grade glioma patients with both cognitive complaints and cognitive deficits.⁴⁷ Immediately post-treatment evaluation showed significant subjective improvement in the intervention group, while at 6 months evaluation, the intervention group had significantly improved attention and verbal memory, as well as less mental fatigue. Young patients had the most benefit from cognitive rehabilitation. Another randomized study in 58 primary brain tumour patients demonstrated significant improvement in the domains visual attention and verbal memory in the treatment group, immediately following the 4-week training.⁴⁹

Patients' and caregivers' needs

PC and care in the EOL phase are often intertwined but meanings vary greatly regarding the care needs of glioma patients and their caregivers. In addition to the physical burdens and deficits, the deleterious psychosocial effect of glioma and its treatment, affecting both patient and caregiver, is profound. A recent systematic review reported that dealing with such changes can be overwhelming for both patients and caregivers resulting in psychosocial problems such as depression, anxiety and isolation. Research continues to focus on describing patient and caregiver experience rather than establishing the best methods of providing care or information or developing and trialling new supportive care interventions.

Patients

Continuous re-evaluation of the patient's support needs and information is required as these change over time with disease progression.⁵⁰ There is a strong case for multidisciplinary support programmes to address patients'

problems, thus helping them to reduce their burden.^{51,52} Standards of care (including existential support) may be enhanced by moving towards a proactive approach, extending care goals beyond medical needs.⁵¹ This ongoing support may best be served by having one dedicated and central point of contact for continuity of communication with a health professional – most likely to be the specialist nurse.⁵³

Approximately half of distressed cancer patients do not access psychosocial services, with some blankly refusing as they see it as a sign of personal weakness.⁵⁴ Patients with gliomas are often referred to these services late in the illness trajectory, with few participating in EOL decisions whilst they are cognitively and communicatively intact.^{50,55} Early referral to PC and psychosocial support services is therefore essential.⁵³ Low referral to and use of psychosocial services may limit patients' abilities to cope with their condition and the changes they experience through their disease trajectory.^{55,56} Understanding glioma patients' use of these services, along with their physical and psychosocial experiences, is crucial to developing service delivery models to help meet their substantial needs.^{50,56}

Caregivers

Due to the highly disabling disease, there is a huge degree of reliance placed on the caregiver to support the glioma patient resulting in caregiver stress, anxiety, exhaustion, reduced quality of life and a range of other substantial negative effects. This distress has been reported as relating to the changing sense of identity, loss of (previous) relationship with the patient (owing to the patient's personality changes), a sense of isolation and guilt, and fears regarding the impending death/loss 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.⁵⁷

Anxiety relating to the future death of the patient is widely reported in the literature with some studies suggesting that this fear is intense and inescapable in the context of glioma. This anxiety can be reduced through physicians/health professionals having more open communication with caregivers especially at the point where cognitive and personality changes limit the ability of the patient to advocate for themselves.⁵⁷

Caregivers have indicated they want information on how to reduce stress and are interested to participate in stress-reduction programs.⁵⁸ An effective and useful way to provide information to caregivers is with the appointment of a specialist nurse.⁵⁹ A recent RCT showed that the quality of life of caregivers can be maintained and feelings of mastery enhanced with psychoeducation and cognitive behavioural therapy.⁶⁰

End of Life care

Delirium

Most glioma patients have a progressive decline in the level of consciousness in the last stage of disease (71% experience reduced consciousness in the last three months and 81-95% in the last week before dying). Apart from reduced consciousness due to progressive tumour growth leading to increased intracranial pressure, alterations in

consciousness and reduced awareness and inattention, respectively, may be part of the complex neuropsychiatric syndrome of delirium. Delirium could be hyperactive (10-54%), hypoactive (46-49%), or mixed psychomotoric subtypes (41%). Its underlying causes and risk factors are multifactorial. For example, often prescribed agents in the PC setting like benzodiazepines, corticosteroids or opioids are associated with increased risk of delirium. In PC patients, delirium represents the third most frequent symptom near death and appears in up to 90% in the dying phase. In glioma patients, delirium was described in up to 62% patients, with increasing incidence in the last week before dying. There are few RCTs or open-label trials investigating the use of antipsychotics for treating delirium in hospitalised cancer and terminally ill patients, among them only a few brain tumour patients.⁶¹ Olanzapine, risperidone, aripiprazole and haloperidol were found to be equally effective; extrapyramidal symptoms were most frequently reported in patients treated with haloperidol whereas sedative effects predominately occurred during treatment with olanzapine.⁶² A recently published RCT among patients in PC compared risperidone and haloperidol (maximum dose up to 4mg/d) to placebo and did not find a benefit of pharmacological treatment, but instead resulted in more adverse effects.⁶³ So far, no non-pharmacological trials on delirium treatment in cancer and/or terminally ill patients exist.

An undifferentiated treatment for delirium in brain tumour patients with various psychopharmacological agents (e.g., antipsychotics, antidepressants, benzodiazepines) was prescribed in about 50%.⁶² Palliative sedation in brain tumour patients due to delirium was reported in up to 30%.⁶¹ This treatment option is frequently required in refractory delirium in the EOL phase.⁶⁴

Nutrition, Hydration, Respiration

In the last weeks or days of life brain tumour patients often have difficulty swallowing, both due to the inability to swallow (dysphagia) and in combination with decreased consciousness. Dysphagia is reported as one of the more frequent symptoms in the EOL phase of brain tumour patients, however with a frequency ranging widely from 10-85%, increasing towards dying. Loss of the ability to swallow may induce pulmonary aspiration and may hamper nutrition, hydration, as well as oral administration of medication.

Difficulty to swallow salivary secretion in the oropharynx, particularly in unconscious terminal patients, may produce noisy and uncomfortable respiration both during inspiration and expiration, which is called death rattle. These respiratory symptoms have been reported in 12-23% of brain tumour patients in the last weeks of life and may severely affect a peaceful process of dying, particularly disturbing caregiver and family.^{6,65} Treatment may involve change of posture to drain saliva, or medication with injectable scopolamine, an anticholinergic agent. A Cochrane review, however, concluded that there was no evidence for the benefit of any pharmacological intervention for the treatment of death rattle.⁶⁶

Treatment decisions about nutrition and hydration in the EOL phase are among the most critical and ethically relevant issues in brain tumour patients. No intervention study has been conducted to evaluate the effects of parenteral nutrition and hydration in terminal brain tumour patients. Ethical and legal approaches to

withdrawal and withholding nutrition and hydration in terminal patients vary widely among different countries and cultures. However, there is consensus about the futility of artificial nutrition and hydration at the EOL in comatose glioma patients.

Advance care planning

Advance care planning (ACP) is a process by which patients and their physicians establish future goals of their care in the EOL phase, which offers patients the opportunity to define their goals and expectations. ACP is most effective when it is started in a timely fashion, allowing patients, their caregivers and physicians to proactively address the challenges together during the course of disease. ACP can lead to an advance directive (AD), i.e., a written statement about a person's preferences regarding future medical decisions.

ACP is particularly important for glioma patients because of their decreased decision-making capacities due to the presence of cognitive impairment, delirium, communication difficulties, loss of consciousness, and a rapid evolution of neurological symptoms. It is found that about half of glioma patients have problems with understanding treatment situations, choices and risks/benefits soon after diagnosis and about half are incompetent to participate in EOL decisions in the last weeks of life.^{67,68} Even when theoretically competent, patients are rarely involved in EOL decisions. Brain tumour patients may be not aware of their prognosis in up to 40% of cases, yet, only a minority of patients are unwilling to discuss EOL. Also only half of physicians and nurses/health care workers feel comfortable to talk about EOL and symptoms with patients.

There is some data available on ACP and ADs specific to glioma patients, but most studies have small numbers. Occurrence of ACP ranges from 44% to 85% in different studies. ACP concerns, for instance, preferences for non-treatment decisions or preferred place of death. Presence of ADs ranges from zero to 70% in different studies. One study found a positive association between recorded discussions about prognosis and recorded discussions about life-sustaining treatments and presence of a do-not-resuscitate order.

Effects of ACP or ADs in glioma patients are described in three different studies. One study found that in 68% of patients the preferred place of death was fulfilled.⁶⁹ Another study described that in only a minority (10%) preferences were not fulfilled.⁷⁰ A third study showed that EOL decisions were more often explicitly discussed in patients who died with dignity compared to patients who did not die with dignity. Furthermore, patients who died with dignity more often died at the preferred place of death.⁷¹ Outside the context of glioma patients in particular and cancer patients in general, there is some stronger evidence for effects of ACP: a randomized controlled trial showed that facilitated ACP in older patients who were admitted to a hospital improved the quality of EOL care, improved patient and family satisfaction, and reduced stress, anxiety, and depression in surviving relatives.⁷² Another randomized controlled trial in patients with congestive heart failure or end-stage renal disease showed that with facilitated ACP most patients received the care they desired.⁷³

Timely ACP seems important for most glioma patients to improve disease management. There are positive effects found of early palliative care 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 EOL.^{1,3}

Organisation of care in the EOL phase

Availability of PC services varies greatly within and between countries, and consequently place of death of brain tumour patients also varies. A recent cohort study⁷⁰ showed that most patients prefer to die at home (78% in The Netherlands, 69% in Scotland and 46% in Austria), although the actual place of death differed in 33% of the Dutch patients, 44% of the Austrian patients and 61% of the British patients. In The Netherlands, 60% of the patients died at home versus 37% and 29% in Austria and Scotland, respectively. In Austria, most patients died in a hospital (41%) while most patients (41%) in Scotland died in a hospice. Moreover, place of death was found to be independently associated with good quality of care.

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

Physical and cognitive dysfunctions occurring in brain tumour patients, with changes in behaviour and impairment in communication, may affect dignity and expose patients and relatives to stress^{71,74}, and can influence the organization of care such as place of care, place of death and decisions about EOL. A significant correlation has been shown between dying with dignity and the absence of communication deficits, good communication with the physicians, fewer transitions between health care settings, and dying at the preferred place of death.⁷¹ Reasons for admission to hospital include more frequently social issues and neurological and cognitive deficits for brain tumour patients than for other PC patients.⁷⁵ Patients are mainly referred to PC services in the last stage of disease only. However, an earlier and integrative approach is found to have positive impact on the quality of EOL and is recommended by several authors.

Conclusions and future directions

For glioma patients, which also holds true for cancer patients in general, PC is not confined to the EOL phase, but covers the whole disease trajectory from diagnosis and initial tumour treatment until death. With this concept in mind the systematic literature review for the PC guideline in adult glioma patients was performed. The best available, but clearly limited evidence, for PC in glioma patients, in the areas of symptom management, patient and caregiver needs, and care in the EOL phase, is supplemented with expert opinion to guide clinicians dealing with adult glioma patients.

Although studies in other diseases, such as systemic cancer, or progressive neurological diseases, may give further guidance for PC in adult glioma patients, the specific symptoms and needs of glioma patients and their families require more clinical studies in PC. Areas of PC that deserve special attention for research are fatigue; disorders of behaviour and mood; interventions for the needs of caregivers; and timing of ACP. An active PC culture within the neurooncological community, as well as collaborative research networks, facilitated by

organisations such as EANO, the Society for Neuro-Oncology (SNO), the Asian Society for Neuro-Oncology (ASNO) and the World Federation of Neuro-Oncology Societies (WFNOS) should further enhance the quality of PC for glioma patients and their families.

Table 1. Recommendations concerning treatment of relevant symptoms.

Recommendation	Quality of evidence
Pain/headache	
Corticosteroids (dexamethasone) are the mainstay of treatment for headache in patients with gliomas.	θθ
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).	θθ
<i>Expert opinion:</i> During care in the EOL phase, consideration needs to be given to the management of headache with corticosteroids. Benefits of corticosteroids (alleviating symptoms) should be weighed against side effects (such as delirium).	
Epilepsy	
When oral route is not an option, intranasal midazolam and buccal clonazepam are a feasible way to treat seizures in the EOL phase.	θθ
<i>Expert opinion:</i> Alternative AED administration routes need to be considered in case glioma patients with a history of epilepsy develop swallowing difficulties. The preferred route of administration depends on the local availability of AEDs as well as the place of care.	
Venous thromboembolism	
As the perioperative risk of ICH increases when prophylaxis is started before induction of anaesthesia, VTE prophylaxis with LMWH in brain tumour patients should be started postoperatively within 24 hours.	θθθθ
There is no proof to extend primary VTE prophylaxis beyond the postoperative period in glioma patients.	θθθθ
The duration of secondary prophylaxis in brain tumour patients after a VTE event should be planned individually, but is in most patients lifelong.	θθθ
Fatigue	
There is to date no proof of efficacy for any pharmacological intervention against fatigue in glioma patients.	θθθθ
There is to date no proof of efficacy for non-pharmacological interventions for fatigue in glioma patients.	θθθθ
Mood and behavioural disorders	
There is limited evidence of several pharmacological interventions (e.g., methylphenidate, donepezil) for mood disorders in glioma patients.	θθ
Multimodal psychosocial intervention may improve depressive symptoms in brain tumour patients.	θθθ
Neurorehabilitation	
Brain tumour patients may benefit from post-operative early rehabilitation, as well as rehabilitation after tumour-specific treatment.	θθ
Cognition	
Medical treatment to prevent or treat cognitive decline in brain tumour patients is not recommended.	θθθ
Cognitive rehabilitation has modest positive effects and should be considered especially in young glioma patients with relatively favourable prognosis.	θθθ
<i>Expert opinion:</i> Stable glioma patients with cognitive complaints and/or deficits may benefit from cognitive rehabilitation.	
<i>Expert opinion:</i> Consider reducing supportive medication in glioma patients as a potential cause of cognitive complaints and/or deficits.	

θθθθ=high quality; θθθ=Moderate quality; θθ=Low quality; θ=very low quality

Table 2. Recommendations concerning patients' and caregivers' needs

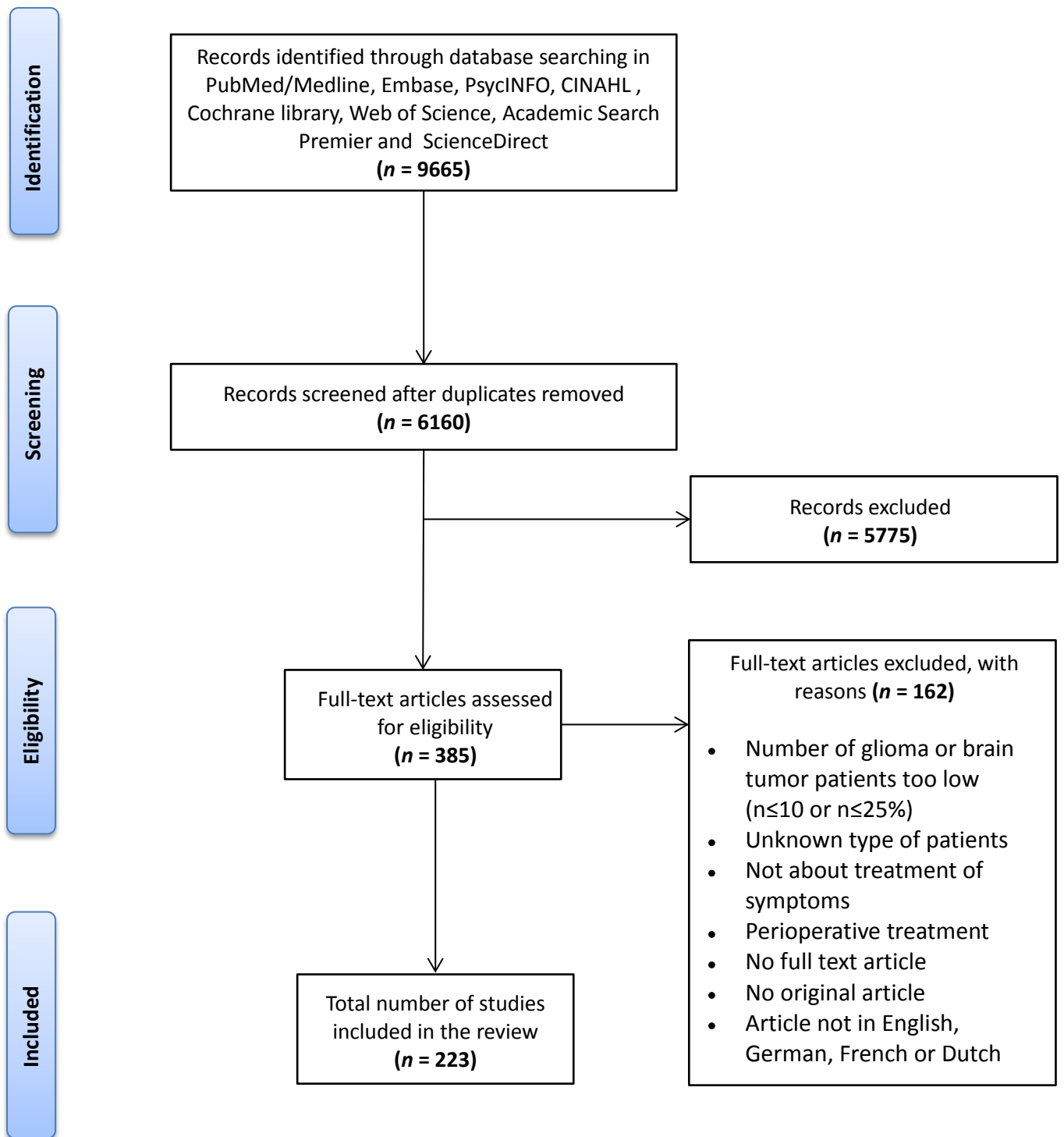
Recommendation	Quality of evidence
Patients' needs	
The need for on-going support may best be served by having one dedicated central point of contact for continuity of contact with a health professional – most likely a specialist nurse.	θ
Early referral to palliative care and psychosocial support should be implemented.	θ
Caregivers' needs	
Psychoeducation and cognitive behavioural therapy can increase feelings of mastery of caregivers and results in maintenance of their quality of life.	θθ
Medical professionals can mitigate caregiver stress by including the caregiver in medical consultations, requesting their feedback and acknowledging their role	θ
Caregiver anxiety relating to the future death of the patient can be alleviated by more open communication.	θ

θθθθ=high quality; θθθ=Moderate quality; θθ=Low quality; θ=very low quality

Table 3. Recommendations concerning care in the End of Life (EOL) phase

Recommendation	Quality of evidence
Delirium	
Olanzapine, risperidone, aripiprazole and haloperidol are equally effective in the treatment of delirium in cancer patients.	000
Risperidone and haloperidol (maximum dose up to 4 mg/d) are not more effective than placebo in the treatment of delirium in PC patients, and result in more adverse effects.	0000
In case of delirium first, underlying causes have to be identified and to be reacted on e.g. by adequate symptom control or changes in doses or kind of medication.	000
<i>Expert opinion:</i> If underlying causes of delirium are adequately identified and addressed, and despite this delirium could not be relieved, low-dose haloperidol is the first choice of treatment of delirium in glioma patients.	
<i>Expert opinion:</i> In case of refractory delirium palliative sedation with benzodiazepines (e.g. midazolam) may be indicated in glioma patients.	
Nutrition, hydration, respiration	
There is no effective pharmacological treatment for noisy respiration ('death rattle') in the EOL phase of glioma patients.	0000
<i>Expert opinion:</i> Parenteral nutrition and hydration are unlikely to benefit glioma patients in the EOL phase.	
Advance care planning	
Medical decision making may already be problematic for glioma patients soon after the time of diagnosis, due to cognitive deficits.	00
To improve dying with dignity in glioma patients, satisfaction with the physician in the last week of life should be enhanced, and transitions between health care settings avoided .	0
<i>Expert opinion:</i> ACP and the use of advanced directives should therefore be considered early in the disease trajectory.	
Organisation of care in the end-of-life phase	
The quality of perceived care in the EOL phase is enhanced by effective symptom control, satisfaction with information received, and adherence to preferred place of death. The quality is less dependent on the specific type of care in the EOL phase (e.g., hospice, home care).	0
<i>0000=high quality; 000=Moderate quality; 00=Low quality; 0=very low quality</i>	

Figure 1. Systematic literature procedure



Supplementary File 1. PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) search string used in the literature search

("Palliative Care"[Mesh] OR "palliative care"[all fields] OR "palliation"[tw] OR "palliative"[tw] OR "Palliative Therapy"[all fields] OR "Palliative Treatment"[all fields] OR "Palliative Surgery"[all fields] OR "Palliative Medicine"[Mesh] OR "Palliative Medicine"[all fields] OR "Hospice and Palliative Care Nursing"[Mesh] OR "Palliative Nursing"[all fields] OR "Hospice Nursing"[all fields] OR "Hospice"[all fields] OR "Hospices"[all fields] OR "Terminal Care"[Mesh] OR "Terminal Care"[all fields] OR "euthanasia"[all fields] OR "Hospice Care"[Mesh] OR "Hospice Care"[all fields] OR "end of life"[tw] OR "end-of-life"[tw] OR "end of life care"[tw] OR "end of life phase"[tw] OR "Advance Care Planning"[mesh] OR "Advance Directive"[all fields] OR "Living Will"[all fields] OR "Advance Care Planning"[all fields] OR "Advance Care"[all fields] OR "advance Directives"[all fields] OR "Living Wills"[all fields] OR "rehabilitation"[all fields] OR "neurorehabilitation"[all fields] OR "Rehabilitation"[Mesh] OR "rehabilitation"[Subheading] OR "death rattle"[all fields] OR death rattl*[all fields] OR "Deglutition Disorders"[Mesh] OR "dysphagia"[all fields] OR "comprehensive care"[all fields] OR "coordinated care"[tw] OR "decision making"[tw] OR "supportive care"[all fields] OR "Fatigue"[mesh] OR "fatigue"[tw] OR fatigue*[tw] OR "Depression"[Mesh] OR "depression"[tw] OR "personality changes"[tw] OR "personality change"[tw] OR "changes of personality"[tw] OR "change in personality"[tw] OR "thrombosis prophylaxis"[tw] OR "Thrombosis/prevention and control"[Mesh] OR "Caregivers"[mesh] OR "caregiver"[tw] OR "caregivers"[tw] OR "care-giver"[tw] OR "care-givers"[tw] OR "Carers"[tw] OR "Carer"[tw] OR "Pain/therapy"[Mesh] OR "Pain therapy"[tw] OR "Pain Management"[Mesh] OR "Pain Management"[tw] OR "Headache therapy"[tw] OR "Headache management"[tw] OR "Headache treatment"[tw]) AND ("Brain Neoplasms"[Mesh] OR "Glioma"[Mesh] OR astrocytoma*[tw] OR astroglioma*[tw] OR brain cancer*[tw] OR brain carcinoma*[tw] OR brain malign*[tw] OR brain neoplasm*[tw] OR "Brain Stem neoplasm"[tw] OR "Brain Stem neoplasms"[tw] OR Brain Stem tum*[tw] OR brain tumo*[tw] OR "brainstem neoplasms"[tw] OR "brain-stem neoplasms"[tw] OR "brainstem neoplasm"[tw] OR "brain-stem neoplasm"[tw] OR brainstem tum*[tw] OR brain-stem tum*[tw] OR "cancer of brain"[tw] OR "cancer of the brain"[tw] OR "cancer of the central nervous system"[tw] OR "cancer of the cns"[tw] OR central nervous system cancer*[tw] OR central nervous system malignan*[tw] OR central nervous system neoplasm*[tw] OR central nervous system tum*[tw] OR Cerebellar cancer[tw] OR Cerebellar neoplasm*[tw] OR Cerebellar tum*[tw] OR cerebral cancer*[tw] OR cerebral carcinoma*[tw] OR cerebral malignan*[tw] OR cerebral neoplasm*[tw] OR cerebral tum*[tw] OR Choroid Plexus Papilloma*[tw] OR Choroid Plexus tum*[tw] OR cns cancer*[tw] OR cns malignan*[tw] OR cns neoplasm*[tw] OR cns tum*[tw] OR ependimom*[tw] OR ependymom*[tw] OR Ganglioglioma*[tw] OR "glial cancer"[tw] OR glial malign*[tw] OR "glial neoplasm"[tw] OR glial tum*[tw] OR glioblastom*[tw] OR glioma*[tw] OR gliosarcoma*[tw] OR glyoma*[tw] OR Hypothalamic neoplasm*[tw] OR Hypothalamic tum*[tw] OR Infratentorial cancer*[tw] OR Infratentorial Neoplasm*[tw] OR Infratentorial tum*[tw] OR intracerebral cancer*[tw] OR intracerebral malignan*[tw] OR intracerebral neoplasm*[tw] OR intracerebral tum*[tw] OR intracranial cancer*[tw] OR intra-cranial cancer*[tw] OR intracranial carcinoma*[tw] OR intracranial malignan*[tw] OR intracranial neoplasm*[tw] OR intracranial tum*[tw] OR malignant brain*[tw] OR malignant glia*[tw] OR malignant primary brain*[tw] OR Medulloblastoma*[tw] OR Neurocytoma*[tw] OR neuroglioma*[tw] OR oligoastrocytoma*[tw] OR oligodendroblastoma*[tw] OR oligodendrogloma*[tw] OR oligoden-drogloma*[tw] OR oligo-dendrogloma*[tw] OR Pinealoma*[tw] OR Pinealomas[tw] OR Pituitary cancer*[tw] OR Pituitary neoplasm*[tw] OR Pituitary tum*[tw] OR subependimom*[tw] OR subependymom*[tw] OR Supratentorial cancer*[tw] OR Supratentorial Neoplasm*[tw] OR Supratentorial tum*[tw] OR "tumor of brain"[tw] OR "tumor of central nervous system"[tw] OR "tumor of cns"[tw] OR "tumor of the brain"[tw] OR "tumor of the central nervous system"[tw] OR "tumor of the cns"[tw] OR "tumour of brain"[tw] OR "tumour of the brain"[tw] OR "tumour of the central nervous system"[tw] OR "tumour of the cns"[tw] OR xanthoastrocytoma*[tw] OR xantoastrocytoma*[tw] OR ((neoplasm*[ti] OR neo-plasm*[ti] OR tumor*[ti] OR

tumour*[ti] OR cancer*[ti] OR malignan*[ti]) AND (glia*[ti] OR neuroglia*[ti])))) NOT (("Child"[mesh] NOT "Adult"[mesh]) OR ((child[ti] OR children[ti] OR childhood[ti] OR pediatr*[ti] OR paediatr*[ti]) NOT adult*[ti])) NOT ("Animals"[mesh] NOT "Humans"[mesh]) NOT ("Letter"[Publication Type] NOT "Clinical Study"[Publication Type]) AND ("Case Reports"[Publication Type] NOT "Clinical Study"[Publication Type])

References

1. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *The New England journal of medicine* 2010; **363**(8): 733-42.
2. WHO definition of Palliative Care. www.who.int/cancer/palliative/definition/en/ (accessed 04-01-2017).
3. Zimmermann C, Riechelmann R, Krzyzanowska M, Rodin G, Tannock I. Effectiveness of specialized palliative care: a systematic review. *Jama* 2008; **299**(14): 1698-709.
4. Sizoo EM, Pasmán HR, Dirven L, et al. The end-of-life phase of high-grade glioma patients: a systematic review. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2014; **22**(3): 847-57.
5. Leone MA, Brainin M, Boon P, Pugliatti M, Keindl M, Bassetti CL. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces - revised recommendations 2012. *European journal of neurology* 2013; **20**(3): 410-9.
6. Koekkoek JA, Dirven L, Sizoo EM, et al. Symptoms and medication management in the end of life phase of high-grade glioma patients. *Journal of neuro-oncology* 2014; **120**(3): 589-95.
7. 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. *The American journal of hospice & palliative care* 2016; **33**(10): 985-8.
8. 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-Pacific journal of clinical oncology* 2014; **10**(2): 162-7.
9. Hempen C, Weiss E, Hess CF. Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side-effects? *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2002; **10**(4): 322-8.
10. Lee EQ, Wen PY. Corticosteroids for peritumoral edema: time to overcome our addiction? *Neuro-oncology* 2016; **18**(9): 1191-2.
11. 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**(4): 675-80.
12. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *The Lancet Oncology* 2012; **13**(2): e58-68.

13. 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. *Archives of pediatrics & adolescent medicine* 2010; **164**(8): 747-53.
14. 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. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2016; **24**(4): 1633-8.
15. 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**(5): 1074-81.
16. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(17): 2189-204.
17. Perry SL, Bohlin C, Reardon DA, et al. Tinzaparin prophylaxis against venous thromboembolic complications in brain tumor patients. *Journal of neuro-oncology* 2009; **95**(1): 129-34.
18. 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 chemotherapy and pharmacology* 2008; **62**(2): 227-33.
19. 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. *Journal of thrombosis and haemostasis : JTH* 2010; **8**(9): 1959-65.
20. 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**(25): 3972-8.
21. Day J, Yust-Katz S, Cachia D, et al. Interventions for the management of fatigue in adults with a primary brain tumour. *The Cochrane database of systematic reviews* 2016; **4**: Cd011376.
22. 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-oncology* 2013; **15**(10): 1420-8.
23. 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-oncology* 2016; **18**(6): 849-54.
24. Page BR, Shaw EG, Lu L, et al. Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. *Neuro-oncology* 2015; **17**(10): 1393-401.

25. 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. *Journal of neuro-oncology* 2012; **107**(1): 165-74.
26. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**(18_suppl): 1503.
27. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006; **24**(9): 1415-20.
28. Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. *The Cochrane database of systematic reviews* 2015; (6): Cd011006.
29. Rooney A, Grant R. Pharmacological treatment of depression in patients with a primary brain tumour. *The Cochrane database of systematic reviews* 2013; (5): Cd006932.
30. Meyers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1998; **16**(7): 2522-7.
31. 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. *Journal of neuro-oncology* 2012; **106**(3): 651-6.
32. 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. *Psycho-oncology* 2006; **15**(3): 259-67.
33. 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. *Journal of neuro-oncology* 2012; **109**(2): 357-63.
34. 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. *Psycho-oncology* 2015; **24**(5): 540-7.
35. 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. *International journal of radiation oncology, biology, physics* 2007; **69**(5): 1496-501.
36. Jones S, Ownsworth T, Shum DH. Feasibility and utility of telephone-based psychological support for people with brain tumor: a single-case experimental study. *Frontiers in oncology* 2015; **5**: 71.

37. 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. *Journal of rehabilitation medicine* 2014; **46**(8): 754-60.
38. Keir ST. Effect of massage therapy on stress levels and quality of life in brain tumor patients--observations from a pilot study. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2011; **19**(5): 711-5.
39. 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. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2015; **23**(10): 2855-9.
40. Bilgin S, Kose N, Karakaya J, Mut M. Traumatic brain injury shows better functional recovery than brain tumor: a rehabilitative perspective. *European journal of physical and rehabilitation medicine* 2014; **50**(1): 17-23.
41. Pace A, Parisi C, Di Lelio M, et al. Home rehabilitation for brain tumor patients. *Journal of experimental & clinical cancer research : CR* 2007; **26**(3): 297-300.
42. Bartolo M, Zucchella C, Pace A, et al. Early rehabilitation after surgery improves functional outcome in inpatients with brain tumours. *Journal of neuro-oncology* 2012; **107**(3): 537-44.
43. Formica V, Del Monte G, Giacchetti I, et al. Rehabilitation in neuro-oncology: a meta-analysis of published data and a mono-institutional experience. *Integrative cancer therapies* 2011; **10**(2): 119-26.
44. 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 supportive & palliative care* 2016; **6**(1): 27-34.
45. Ruden E, Reardon DA, Coan AD, et al. Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011; **29**(21): 2918-23.
46. Rapp SR, Case LD, Peiffer A, et al. Dexamethasone for Irradiated Brain Tumor Survivors: A Phase III Randomized Placebo-Controlled Clinical Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(15): 1653-9.
47. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; **27**(22): 3712-22.
48. Yang S, Chun MH, Son YR. Effect of virtual reality on cognitive dysfunction in patients with brain tumor. *Annals of rehabilitation medicine* 2014; **38**(6): 726-33.

49. Zucchella C, Capone A, Codella V, et al. Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumor: a randomized, controlled trial. *Journal of neuro-oncology* 2013; **114**(1): 93-100.
50. Sterckx W, Coolbrandt A, Clement P, et al. Living with a high-grade glioma: A qualitative study of patients' experiences and care needs. *European journal of oncology nursing : the official journal of European Oncology Nursing Society* 2015; **19**(4): 383-90.
51. Janda M, Eakin EG, Bailey L, Walker D, Troy K. Supportive care needs of people with brain tumours and their carers. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2006; **14**(11): 1094-103.
52. 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. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2014; **22**(2): 389-97.
53. 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. *Palliative & supportive care* 2015; **13**(6): 1519-27.
54. 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. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2014; **22**(12): 3341-52.
55. Gofton TE, Graber J, Carver A. Identifying the palliative care needs of patients living with cerebral tumors and metastases: a retrospective analysis. *Journal of neuro-oncology* 2012; **108**(3): 527-34.
56. Langbecker D, Yates P. Primary brain tumor patients' supportive care needs and multidisciplinary rehabilitation, community and psychosocial support services: awareness, referral and utilization. *Journal of neuro-oncology* 2016; **127**(1): 91-102.
57. 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. *Neuro Oncology Practice* 2016; **3**(4): 232-44.
58. Swartz JJ, Keir ST. Program preferences to reduce stress in caregivers of patients with brain tumors. *Clinical journal of oncology nursing* 2007; **11**(5): 723-7.
59. Spetz A, Henriksson R, Bergenheim AT, Salander P. A specialist nurse-function in neurooncology: a qualitative study of possibilities, limitations, and pitfalls. *Palliative & supportive care* 2005; **3**(2): 121-30.
60. 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. *Journal of neuro-oncology* 2013; **111**(3): 303-11.
61. Breitbart W, Alici Y. Evidence-based treatment of delirium in patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2012; **30**(11): 1206-14.

62. Boettger S, Jenewein J, Breitbart W. Haloperidol, risperidone, olanzapine and aripiprazole in the management of delirium: A comparison of efficacy, safety, and side effects. *Palliative & supportive care* 2015; **13**(4): 1079-85.
63. 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 internal medicine* 2017; **177**(1): 34-42.
64. 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. *Journal of pain and symptom management* 2014; **48**(2): 215-30.
65. Pace A, Di Lorenzo C, Guariglia L, Jandolo B, Carapella CM, Pompili A. End of life issues in brain tumor patients. *Journal of neuro-oncology* 2009; **91**(1): 39-43.
66. Wee B, Hillier R. Interventions for noisy breathing in patients near to death. *The Cochrane database of systematic reviews* 2008; (1): Cd005177.
67. Sizoo EM, Pasman HR, Buttolo J, et al. Decision-making in the end-of-life phase of high-grade glioma patients. *European journal of cancer (Oxford, England : 1990)* 2012; **48**(2): 226-32.
68. Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. *Neurology* 2009; **73**(24): 2086-92.
69. Flechl B, Ackerl M, Sax C, et al. The caregivers' perspective on the end-of-life phase of glioblastoma patients. *Journal of neuro-oncology* 2013; **112**(3): 403-11.
70. Koekkoek JA, Dirven L, Reijneveld JC, et al. End of life care in high-grade glioma patients in three European countries: a comparative study. *Journal of neuro-oncology* 2014; **120**(2): 303-10.
71. Sizoo EM, Taphoorn MJ, Uitdehaag B, et al. The end-of-life phase of high-grade glioma patients: dying with dignity? *The oncologist* 2013; **18**(2): 198-203.
72. 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 (Clinical research ed)* 2010; **340**: c1345.
73. Kirchoff KT, Hammes BJ, Kehl KA, Briggs LA, Brown RL. Effect of a disease-specific advance care planning intervention on end-of-life care. *Journal of the American Geriatrics Society* 2012; **60**(5): 946-50.
74. Pace A, Villani V, Di Pasquale A, et al. Home care for brain tumor patients. *Neuro-oncology practice* 2014; **1**(1): 8-12.
75. Ostgathe C, Voltz R. Quality indicators in end-of-life care. *Current opinion in supportive and palliative care* 2010; **4**(3): 170-3.