Palliative Care and Palliative Rehabilitation: Approaches to the End-of-Life

16

Andrea Pace and Veronica Villani

16.1 Introduction

The concept of palliative care is an emerging field in neuro-oncology. The WHO definition of palliative care (PC) affirms that “palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (www.who.int/cancer/palliative/definition/en/).

However, brain tumour (BT) patients are different respect from other cancer patients because of trajectory of the disease, short life expectancy and complexity of palliative care needs due to specific symptoms related to neurological deterioration and therefore they require a specific and appropriate palliative care approach especially in the last stage of disease when incidence of neurological symptoms and psychosocial troubles becomes higher [1].

Despite the advance in treatment options has lengthened the life expectancy, BT patients suffer significant functional and psychosocial impairments that limit daily activity and quality of life.

During the course of the disease, BT patients present with multiple neurological deficits that can be due either to primary tumour effects and/or the adverse effects of oncologic treatment [2–5]. The localization of the tumour leads to several neurological symptoms including focal symptoms (hemiparesis, seizures and speech difficulties) and neurocognitive deficits (aphasia, impaired attention, concentration difficulty, reduced short-term memory and behaviour changes). One study found that 75.4% of BT patients presented more than three concurrent deficits, and 39.2% had more than five [6].

A. Pace (✉) · V. Villani
Neurooncology Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy
e-mail: andrea.pace@ifo.gov.it

M. Bartolo et al. (eds.), *Neurorehabilitation in Neuro-Oncology*,
https://doi.org/10.1007/978-3-319-95684-8_16

There is a large consensus on the need to improve the quality of palliative and supportive care for neuro-oncological patients. However, several papers have reported a lack of knowledge and of evidence-based guidelines about supportive care in BTs and confirm that there is a great need for education in palliative care and end-of-life decision-making in neuro-oncology setting [7, 8].

In this chapter, we will address palliative care issues in BT patients at the end-of-life (EoL) and the role of palliative rehabilitation interventions in advanced stage of disease.

16.2 Palliative Care Issues in Brain Tumour Patients

To date, palliative care in neuro-oncologic patients and the ongoing needs for care from discharge to the terminal phase of disease are not well documented. Literature data reported this to be a heterogeneous group of patients with complex needs [9].

Care needs increase in the last stage of disease with a high incidence of neurological symptoms and psychosocial problems often inducing caregivers and/or family members to hospitalize the patient [1]. The main goal of palliative care in neuro-oncology is the control of symptoms during the course of disease and particularly in advanced stage and at the end of life. Malignant BT patients at the end of life require specific palliative interventions, with a multidisciplinary approach performed by a well-trained neuro-oncological team, for the control of pain, confusion, agitation, delirium or seizures management with the aim to allow the patient to experience a peaceful death [10].

Table 16.1 reports the symptoms observed in the last weeks/months of life of BT patients in recent studies (Table 16.1) [10–14]. A recent study showed that in the last

Table 16.1 Symptoms in brain tumour patients at the end of life reported in the literature

Symptoms	Sizoo et al. [11]	Pace et al. [10]	Faithfull et al. [12]	Koekkoek et al. [13]	Oberndorfer et al. [14]
Drowsiness, loss of consciousness	87	85		75	90
Seizures/epilepsy	45	30	56	25.9	48
Cognitive/psychological cognitive deficits/ memory loss confusion	33		39	44.7	
Anxiety/depression	29				
Agitation/delirium/ confusion		15	31	45	
Dysphagia nausea/ vomiting	71	85	10	24.5	79
Headache	33	36	62	34.6	38
Dyspnoea/death rattle / pneumonia	16	12			
Fatigue	25		44		

stage of disease of BT patients disease-specific symptoms such as somnolence, focal neurological deficits, cognitive disturbances and dysphagia are more prevalent respect from non-disease-specific symptoms [13].

Considering that randomized controlled trials are difficult to conduct in the palliative care setting and are sometimes unethical, alternative research methodologies need to be utilized, including qualitative studies, observational studies and expert opinion recommendations.

Recently, the European Association of Neuro-Oncology (EANO) guidelines on palliative care in neuro-oncology have underscored the need to establish the best methods to provide palliative care and to develop and assess adequate supportive care interventions [15]. EANO guidelines provided a systematic review of the available scientific literature integrated with expert opinions and formulated the best possible evidence-based recommendations for the palliative care of adult patients with glioma, particularly in the end-of-life phase.

One of the most important issues in palliative care is the timing of delivery. Recent randomized controlled trials have documented the significant benefits of early provision of palliative care to cancer patients [16]. Early integration of palliative care, compared with normal care, is related to significant improvement of quality of life, better symptom control, reduction of health expenditures and in some cases also an improvement of survival. However, at present the majority of BT patients receive palliative care interventions only in the last weeks or days before death [17].

Palliative care should not be considered to be synonymous with end-of-life care. The modern concept of palliative care highlights the importance of early integration of palliative care with oncological treatments. Several authors have proposed that for patients with cancer, palliative care should start early in the course of disease and should be delivered along the entire disease trajectory from diagnosis and initial tumour treatment until death [18].

The identification of the beginning of the dying phase is crucial to avoid suboptimal care. Palliative care goal at the EOL phase should be primarily aimed at reducing symptom burden while maintaining quality of life as long as possible without inappropriate prolongation of life. However, there is currently no validated instrument for determining the beginning of the dying phase and no common definition of end of life does exist.

Recently, pathways that can support clinicians in the process of identifying the beginning of the dying phase have been developed in cancer patients and in patients affected by neurological degenerative diseases [19, 20]. The knowledge of early predictors of end-of-life stage and the assessment for changes in signs and symptoms that may suggest a person is dying may help clinicians to plan and deliver appropriate care that integrates active and palliative management.

In general cancer populations several symptoms have been identified as potential predictors of entering in the last stage of disease: changes in breathing, general deterioration, lowering of consciousness, caregivers' clinical judgement and lowered oral intake [21].

In patients with progressive neurological disease several trigger symptoms have been suggested for the recognition of end of life such as swallowing problems, recurring infections, marked decline in functional status, first episode of aspiration pneumonia, cognitive difficulties, weight loss and significant complex symptoms [20]. There is evidence that these triggers may help in the recognition of the end of life and that early recognition of the final stages can be useful in allowing the focus of care to be clarified and a palliative care approach initiated.

Nevertheless, several studies showed that end-of-life phase of brain tumour patients is quite different respect from the expected trajectory observed in general cancer population [22]. Additionally, disease history and needs of care in the last stage of BT patients have few similarities with other progressive neurologic diseases.

Most of symptoms observed in BT patients approaching death occur in the last month of life and do not allow to plan in advance the appropriate end-of-life care. The cluster of symptoms observed at the EoL in BT show that the decline in physical and cognitive functions is rapid in the last 4–6 weeks before death and it is difficult to identify trigger symptoms as early predictor of EoL stage [23].

Moreover, disease trajectory of BT appears to be very different respect from the pathway of general cancer population and from neuro-degenerative diseases, and is characterized by fluctuating episodes of neurological deterioration often followed by period of improvement or stability.

Despite the emerging evidence of the positive effects of PC and hospice, the neuro-oncology community still have difficulty to apply models of care based on triggered, targeted interventions that result in high-quality, cost-effective, patient-centred and coordinated care.

Recent data reported that BT hospice enrollment was generally late: 22.5% of patients entered hospice within 7 days of death, 35% within 14 days and 59.4% entered within 30 days of death [24, 25].

The finding that hospice referral in BT patients is predominantly late suggests that a substantial proportion of BT patients in the later stages of disease does not receive appropriate palliative care.

Therefore, it is important to promote models of care that should incorporate earlier palliative care referral, to facilitate the timing provision of adequate supportive and palliative care in BT patients and their families.

16.3 End-of-Life Issues/Treatment Decisions

BT patients who are approaching the EoL need high-quality of care that support them to live as well as possible until death, and to die with dignity.

Neuro-oncologists dedicate most of their effort to offer active treatment against the tumour but, according to several authors, they are not well trained to give adequate care to patients who have progressive disease and no other oncologic treatment options available [7]. Little is known about symptoms and needs of BT patients at the end of their life, and too many patients do not receive adequate palliative care so that the burden of care often falls to patients' families [26, 27]. Recent studies reported that BT patients at the end of life present a high incidence of distressing symptoms that may influence the quality of life during the process of dying [4, 11]. In order to allow the patient to experience a peaceful death, specific palliative interventions are requested for the control of pain, confusion, agitation, delirium or seizures [11]. The main goals of palliative care and end-of-life care in BTs patients are to offer adequate symptom control, relief of suffering, to avoid inappropriate prolongation of dying and to support the psychological and spiritual needs of patients and families. The lack of control of symptoms, in patients not included in palliative care programs, often lead to re-hospitalization with an increase in health system economic costs and a worsening of patient's quality of life [27].

However, there is an increasing attention to palliative care and end-of-life issues in neuro-oncology. In the last stage of disease BT patients present both complex needs similar to the general cancer population, and severe symptoms due to the growing tumour, to treatment side effects, and specific problems that require adequate management from a multidisciplinary neuro-oncology team.

Recently, several studies have explored the supportive care needs of BT patient in the last stage of disease. One study reported in a population of 231 BT patients assisted at home until death with a neuro-oncological palliative home-care program, a high incidence of distressing symptoms influencing the quality of life during the last stage of disease and during the process of dying [2]. Most frequent symptoms observed in the last 4 weeks of life were epilepsy (30%), headache (36%), drowsiness (85%), dysphagia (85%), death rattle (12%), agitation and delirium (15%). Two other papers reported similar data about end-of-life symptoms in BT [4, 11]. In a little series of BT patients dying in hospital an Austrian group described the symptoms in the last weeks of life reporting that most frequent clinical symptoms were decreased vigilance, fever, dysphagia, seizures and pain [4]. In the study of Sizoo et al. the clinical records of 55 patients death for high-grade glioma were retrospectively examined: the majority of the patients experienced loss of consciousness and difficulty with swallowing, often arising in the week before death. Seizures occurred in nearly half of the patients in the end-of-life phase and in one-third of the patients in the week before dying [11].

A recent review on BT EoL symptoms confirmed that drowsiness and loss of consciousness was the most common symptom (90%) and focal neurological deficits (3–62%), seizures (3–56%), dysphagia (7–85%) and headaches (4–62%) were also frequent [28].

Other common symptoms reported in the end-of-life phase were progressive neurological deficits, incontinence, progressive cognitive deficits and headache. However, although an increasing number of researches on the palliative care needs of patients with BT have been recently conducted, symptoms before death have been described in small, retrospective and single-site studies and in different setting of care [11].

Given the paucity of Class I literature data on supportive care issues in BT, it is difficult to draw guidelines and treatment recommendations for the treatment of the more frequent symptoms; however, recent studies may help to optimize the quality of care in the management of BT patients at the EoL [15].

16.3.1 End-of-Life Treatment Decision-Making Process

EoL treatment decisions in neuro-oncology present unique features and require specific approaches concerning the decisions relating to medical treatment, including withdrawing–withholding of nutrition and hydration of patients in prolonged vegetative state, withholding of steroid treatment and palliative sedation [2, 4, 5].

The most challenging treatment decisions at the EoL in BT patients are generally about withdrawing or withholding a treatment when it has the potential to prolong the patient's life. This may concern treatments such as artificial nutrition and hydration and steroid treatment.

Withholding is a planned decision not to undertake symptomatic therapies that were otherwise warranted; withdrawal is the discontinuation of symptomatic treatments that have been started. Terminal sedation is defined as the pharmacologically induced reduction of vigilance up to the point of the complete loss of consciousness with the aim of reducing or abolishing the perception of symptoms that would otherwise be intolerable ("refractory symptoms"). Few data are available on end-of-life decision-making process in BTs patients. The process of treatment decision-making in the terminal stage of brain tumour patients is often complicated by the presence of cognitive problems that may affect patients' competence to express treatment preferences [5]. Recent studies highlight that participation in EoL decision-making is only possible with advanced care planning [15].

A recent European study evaluating the EoL decision-making process in three European countries revealed that only 40% of competent patients are involved in EoL treatment decisions; fewer than 7% express their wishes in advance and more than 50% of decisions are made without involving the patients or their families [29]. However, considering that the large majority of BT patients become incompetent in participating to share treatment decisions, it is of outstanding importance to plan EoL treatment decisions in advance, discussing, when possible, also with families. The aim is to obtain a consensus about the withholding–withdrawing decisions between all participants, respecting both patients and families values.

There are wide disparities in the provision of palliative care in different countries. To receive good palliative care during the course of disease and particularly at the end of life is a human right and the access to the right care should be facilitated for every patient.

The relationship between palliative care and health-related QOL in advanced stage of disease of BT patients has been poorly evaluated; however, there is growing concern about the quality of care given at the end of life in these patients. Palliative care is now understood as an approach to care concerned with caring for the whole person faced with a range of physical, psychological and social needs. Studies reported that administrative data, and particularly hospital re-admission rate in the last stage of disease, may be considered a potential indicator of quality of EoL care [30]. However, prospective studies specifically addressing palliative care and EoL issues in BT patients are lacking. Nevertheless, there is a great need for education in palliative care and end-of-life care for brain tumour. A better knowledge of clinical and ethical issues could help to improve the educational training and quality of care of neuro-oncology services [7]. Palliative programs and home-care models of assistance may represent an alternative to in-hospital care for the management of patients with brain tumour and may improve the quality of care, especially in the last stage of disease. Neuro-oncological literature in recent years highlights the need to improve the approach to palliative care in brain tumour patients and to identify delivery models to better answer patients' and caregivers' needs. Recently, simultaneous care model based on early provision of supportive and palliative care interventions during the course of disease has been proposed, with proactive support for patients and their families at illness transition points such as diagnosis, conclusion of radiotherapy, tumour recurrence, deterioration to death and following death [18].

16.4 Ethical Concerns

In the recent years, patient autonomy has become an important issue and cancer patients express wish to be involved in treatment decisions. However, the high symptom burden of patients with brain tumours affects their quality of life as well as their ability to make treatment decisions. It is therefore warranted to involve patients with high-grade glioma in treatment decision-making early in the course of disease, with a focus on end-of-life care and advance care planning. Research in other cancers has shown that the early involvement of specialty palliative care improves quality of life and caregiver satisfaction [31].

Some studies have reported that capacity to make decisions relating to medical treatment is impaired in up to half of patients with malignant glioma [32, 33]. A study evaluating the medical decision-making capacity (MDC) in malignant glioma patients showed that more than 50% of patients have a compromised MDC compared to controls [32]. Also, this study investigated the relationship between cognitive functioning and consent capacity suggesting a correlation between medical capacity impairment and cognitive impairment.

The reduced medical capacity of brain tumour patients has relevant implications in different settings; it may influence the capacity to consent to medical treatment in the early stage of disease, the capacity to consent to clinical trial enrollment and most important from an ethical point of view, in the process of end-of-life treatment decisions. These patients have difficulty in understanding the treatment situation, choices, and risks and benefits associated with the choices, and providing a rational reason for their decision.

Changes in cognition often occur as a consequence of brain tumours and their treatment, including surgical resection, which has implications for decision-making capacity. From an ethical perspective, patients lacking capacity need to be protected, and an evidence-based approach to determine capacity is essential [34].

At present, there is a lack of consensus on the most effective process for assessing capacity in brain tumour patients. However, there does seem to be agreement that cognitive changes are associated with difficulties in making decisions [35]. Neuropsychological assessment is considered to be the "gold standard" for assessing cognitive functioning and decision-making in patients with a brain tumour, particularly as there is high heterogeneity in the cognitive profiles of these patients.

Considering that the large majority of brain tumour patients lose the competence to participate in a shared decision-making process, it is of outstanding importance to plan in advance treatment decisions about nutrition and hydration, discussing them with families and with patients, when it is possible. To discuss end-of-life issues with BT patients becomes progressively more difficult during the course of their disease because of cognitive disturbances, confusion and decreasing consciousness. According to a recent review of supportive care in neuro-oncology only a little proportion of BT patients had established advance directives about end-of-life treatment, and progressive neurological deficits and loss of consciousness often meant that decisions had to be made on their behalf [5]. A study exploring the decision-making process in the end-of-life phase of high-grade glioma patients reported that the physician did not discuss EoL treatment decisions preferences in 40% of patients. Since most cancer patients wish to be involved in decision-making at the end-of-life, the results of this study underscore that EoL decision-making process for BT patients warrants improvement and timely organization of advance care planning could contribute to improve end-of-life decision-making [5].

As the “shared decision” taken together by physicians, nurses and the patient's family may be the best approach to end-of-life decisions, common guidelines are needed.

Making decisions regarding medical treatment is often difficult, and such is especially true when the patient’s capacity to participate is questionable or even impossible. In such cases, it is important to carefully seek to assess the patient’s competence and decision-making capacity and, if necessary, empower a suitable surrogate to act on his or her behalf.

16.5 Caregivers’ Perspective at the End of Life

Very little is known about quality of life and well-being in caregivers of patients with brain tumours. Usually, carers’ own needs are neglected because the focus is on the patients. Recent publication reports that in the context of this severe and often devastating disease, the caregivers burden of suffering and despair is often neglected, suggesting a more global and comprehensive approach, possibly with pharmacological and psychological support, to the care of the affected family [36]. The severity of symptoms is not only detrimental to patients’ quality of life but also affects carers, who present high levels of distress, depression and significant reduction in their quality of life [8]. Two studies recently surveyed relatives of deceased BT patients with the aim to explore the caregivers’ perspective. In the Dutch study relatives were asked to fill a questionnaire detecting several aspects, including quality of care and quality of death [37]. The results of this study indicate that, in the perception of their relatives, one quarter of patients did not die with dignity and most important aspect related to good quality of care were the place of death and the satisfaction with health care providers of EoL care. In a similar study performed on

52 caregivers of deceased GBM, more frequent complains reported by relatives were low quality of life, burnout, financial difficulties and perception of insufficient information [38].

Several programs of caregivers support with family consultation, internet-based or telephone support groups have been recently suggested as methods for supporting caregivers' emotional needs [8]. More recently Philip et al. have proposed a collaborative framework of supportive and palliative care for patients with high-grade glioma and their caregivers based on the early integration of palliative care approach into neuro-oncology disease trajectory [18].

16.6 Palliative Rehabilitation in BT Patients

The role of rehabilitation in BT patients has been investigated in few studies [39, 40]. Many authors have reported that BT patients may benefit from inpatient rehabilitation and outpatient rehabilitation interventions. Nevertheless, a significant effect of rehabilitation therapies has been demonstrated mainly in acute inpatient rehabilitation with comparable functional gain in respect to other models of neurologic disability such as stroke or traumatic brain injury [39]. However, given the positive impact of rehabilitation interventions on functional outcome and patients' quality of life, there is an increasing consensus about the need to improve strategies for physical and cognitive disability management in BT patients. In general, rehabilitation in the early stages of disease aims at restoring function during or after cancer therapy, while in the advanced stages it is important for maintaining patients' independence and quality of life [41].

Although previous studies have demonstrated the efficacy of rehabilitation programs for brain tumour patients and the positive impact on quality of life in the early stage of disease, the role of rehabilitation in the last stage of disease of BT patients has not been adequately demonstrated. Qualitative data reflect the importance of physiotherapy from a patients' perspective within a palliative care setting [42]. According to the literature data rehabilitation for cancer patients is expected to be an important means of supporting the hopes of patients and their families, and attempting to maintain and improve patients' quality of life. Several studies supported the utilization of rehabilitation throughout the entire phase from the time of diagnosis to the terminal stage, with the aim to involve psychosocial aspects as well as physical aspects [43].

Rehabilitation should be included in the management of BT patients as important part of palliative care given that its positive effect is not limited to functional outcome but strongly influences patients' quality of life facilitating symptoms' palliation, prevention of complications and improvement in mobility and daily living activities.

Rehabilitation approach should not be related only to physiotherapy, and the goal of rehabilitation intervention is not only to achieve maximal functional recovery in patients who have progressive impairments of functions and decreased abilities.

Rehabilitation in palliative care context can be defined as multi-professional intervention to treat and manage the person holistically in the context of their impairments, function and adaptation to environmental disability, with the aim to improve experience of living with, functioning and societal participation [44].

Rehabilitation definition includes different models according to the clinical context and aims of interventions:

Restorative rehabilitation is aimed to obtain the maximal recovery of function in patients with remaining function and ability.

Supportive rehabilitation is aimed mainly to maintain patient autonomy and self-care ability and mobility for patients whose impairments of function and declining abilities are progressing using methods that are effective (e.g. guidance with regard to self-help devices, self-care and more skillful ways of doing things). Also includes preventing disuse, such as contractures, muscle atrophy, loss of muscle strength and decubitus.

Palliative rehabilitation enables patients in the terminal stage to lead a high QOL physically, psychologically and socially, while respecting their wishes. Rehabilitation intervention in this setting is designed to relieve symptoms, such as pain, dyspnoea and oedema and to prevent contractures and decubitus, correct positioning, breathing assistance, relaxation or the use of assistive devices [44].

Particularly important, in palliative care setting, is the role of education for patients and families about maintaining independence and quality of life, mobility training, correct patients' mobilization and supervising the patient in an appropriate program to prevent physical decline and complications. Also, rehabilitation interventions are aimed to prevent contractures, muscle atrophy, loss of muscle strength and decubitus. Qualitative data reflect the importance of physiotherapy from a patients' perspective within a palliative care setting [42]. In addition, it is now widely agreed that high-quality treatment and holistic palliative care approach towards the end of life should include rehabilitation interventions to optimize patients' autonomy and quality of life.

References

1. Catt S, Chalmers A, Fallowfield L. Psychosocial and supportive-care needs in high-grade glioma. Lancet Oncol. 2008;9(9):884–91.
2. Pace A, Di Lorenzo C, Guariglia L, Jandolo B, Carapella CM, Pompili A. End of life issues in brain tumor patients. J Neuro-Oncol. 2009;91(1):39–43.
3. Davies E, Higginson IJ. Communication, information and support for adults with malignant cerebral glioma: a systematic literature review. Support Care Cancer. 2003;11:21–9.
4. Oberndorfer S, Lindeck-Pozza E, Lahrmann H, Struhal W, Hitzenberger P, Grisold W. The end of life hospital setting in patients with glioblastoma. J Palliat Med. 2008;11:26–30.
5. Sizoo EM, Pasman HR, Buttolo J, Heimans JJ, Klein M, Deliens L, Reijneveld JC, Taphoorn MJ. Decision-making in the end-of-life phase of high-grade glioma patients. Eur J Cancer. 2012;48(2):226–32.
6. Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB. Incidence of neurological deficits and rehabilitation of patients with brain tumours. Am J Rehabil Med. 2001;80:346–50.

7. Carver AC, Vickrey BG, Bernat JL, Keran C, Ringel SP, Foley KM. End-of-life care. A survey of US neurologists' attitudes, behavior and knowledge. Neurology. 1999;53:284–93.
8. Ford E, Catt S, Chalmers A, Fallowfield L. Systematic review of supportive care needs in patients with primary malignant brain tumors. Neuro-Oncology. 2012;14(4):392–404.
9. Ostgathe C, Gaertner J, Kotterba M, et al. Hospice and Palliative Care Evaluation (HOPE) Working Group in Germany. Differential palliative care issues in patients with primary and secondary brain tumours. Support Care Cancer. 2010;18(9):1157–63. https://doi.org/10.1007/s00520-009-0735-y. Epub 2009 Sep 8.
10. Pace A, Di Lorenzo C, Guariglia L, et al. End of life issues in brain tumor patients. J Neuro-Oncol. 2009;91(1):39–43.
11. Sizoo EM, Braam L, Postma TJ, et al. Symptoms and problems in the end-of-life phase of high-grade glioma patients. Neuro-Oncology. 2010;12(11):1162–6.
12. Faithfull S, Cook K, Lucas C. Palliative care of patients with a primary malignant brain tumour: case review of service use and support pro- vided. Palliat Med. 2005;19(7):545–50.
13. Koekkoek JA, Dirven L, Sizoo EM, et al. Symptoms and medication management in the end of life phase of high-grade glioma patients. J Neuro-Oncol. 2014;120:589–95.
14. Oberndorfer S, Lindeck-Pozza E, Lahrmann H, et al. The end of life hospital setting in patients with glioblastoma. J Palliat Med. 2008;11:26–30.
15. Pace A, Dirven L, Koekkoek JAF, Golla H, Fleming J, Rudà R, Marosi C, Le Rhun E, Grant R, Oliver K, Oberg I, Bulbeck HJ, Rooney AG, Henriksson R, Pasman HRW, Oberndorfer S, Weller M, Taphoorn MJB. European Association of Neuro-Oncology palliative care task force. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. Lancet Oncol. 2017;18(6):e330–40.
16. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ. Early palliative care for patients with metastatic non–small-cell lung cancer. N Engl J Med. 2010;363(8):733–42. 19.
17. Walbert T, Pace A. End-of-life care in patients with primary malignant brain tumors: early is better. Neuro-Oncology. 2016;18(1):7–8.
18. Philip J, Collins A, Brand C, et al. A proposed framework of supportive and palliative care for people with high grade glioma. Neuro-Oncology. 2017;20(3):391–9. https://doi.org/10.1093/neuonc/nox140.
19. Oliver D. Palliative care for people with progressive neurological disease: what is the role? J Palliat Care. 2014;30(4):298–301.
20. Hussain J, Adams D, Allgar V, Campbell C. Triggers in advanced neurological conditions: prediction and management of the terminal phase. BMJ Support Palliat Care. 2014;4(1):30–7.
21. Eychmüller S, Domeisen Benedetti F, Latten R, et al. "Diagnosing dying" in cancer patients – a systematic literature review. Eur J Palliat Care. 2013;20:292–6.
22. Philip J, Collins A, Brand CA, Gold M, Moore G, Sundararajan V, Murphy MA, Lethborg C. Health care professionals' perspectives of living and dying with primary malignant glioma: implications for a unique cancer trajectory. Palliat Support Care. 2015;13(6):1519–27.
23. Pace A, Benincasa D, Villani V. Trigger symptoms at the end of life in brain tumor patients. WFNO Magazine. 2016;1(3):74–8.
24. Dover LL, Dulaney CR, Williams CP, Fiveash JB, Jackson BE, Warren PP, Kvale EA, Boggs DH, Rocque GB. Hospice care, cancer-directed therapy, and Medicare expenditures among older patients dying with malignant brain tumors. Neuro-Oncology. 2017;20(7):986–93. https://doi.org/10.1093/neuonc/nox220.
25. Diamond EL, Russell D, Kryza-Lacombe M, Bowles KH, Applebaum AJ, Dennis J, DeAngelis LM, Prigerson HG. Rates and risks for late referral to hospice in patients with primary malignant brain tumors. Neuro-Oncology. 2016;18(1):78–86.
26. Batchelor TT, Byrne TN. Supportive care of brain tumor patients. Hematol Oncol Clin North Am. 2006;20(6):1337–61.
27. Pace A, Metro G, Fabi A. Supportive care in neurooncology. Curr Opin Oncol. 2010 Nov;22(6):621–6.

28. Walbert T, Khan M. End-of-life symptoms and care in patients with primary malignant brain tumors: a systematic literature review. J Neuro-Oncol. 2014;117(2):217–24.
29. 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 Neuro-Oncol. 2014;120:303–10.
30. Earle CC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. J Clin Oncol. 2003;21(6):1133–8. Review.
31. McDonald J, Swami N, Hannon B, et al. Impact of early palliative care on caregivers of patients with advanced cancer: cluster randomised trial. Ann Oncol. 2017;28(1):163–8.
32. Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. Neurology. 2009;73:2086–92.
33. Marson DC, Martin RC, Triebel KL, Nabors LB. Capacity to consent to research participation in adults with malignant glioma. J Clin Oncol. 2010;28:3844–50.
34. Kim SY, Marson DC. Assessing decisional capacity in patients with brain tumors. Neurology. 2014;83(6):482–3.
35. Dwan TM, Ownsworth T, Chambers S, Walker DG, Shum DH. Neuropsychological assessment of individuals with brain tumor: comparison of approaches used in the classification of impairment. Front Oncol. 2015;5:56.
36. Finocchiaro CY, Petruzzi A, Lamperti E, Botturi A, Gaviani P, Silvani A, Sarno L, Salmaggi A. The burden of brain tumor: a single-institution study on psychological patterns in caregivers. J Neuro-Oncol. 2012;107(1):175–81.
37. Sizoo EM, Taphoorn MJ, Uitdehaag B, Heimans JJ, Deliens L, Reijneveld JC, Pasman HR. The end-of-life phase of high-grade glioma patients: dying with dignity? Oncologist. 2013;18(2):198–203.
38. Flechl B, Ackerl M, Sax C, Oberndorfer S, Calabek B, Sizoo E, Reijneveld J, Crevenna R, Keilani M, Gaiger A, Dieckmann K, Preusser M, Taphoorn MJ, Marosi C. The caregivers' perspective on the end-of-life phase of glioblastoma patients. J Neuro-Oncol. 2013;112(3):403–11.
39. Huang ME, Wartella JE, Kreutzer JS. Functional outcome and quality of life in patients with brain tumor: a preliminary report. Arch Phys Med Rehabil. 2001;82(11):1540–6.
40. Bartolo M, Zucchella C, Pace A, Lanzetta G, Vecchione C, Bartolo M, Grillea G, Serrao M, Pierelli F, Tassorelli C, Sandrini G. Early rehabilitation after surgery improves functional outcome in brain tumors inpatients. J Neuro-Oncol. 2012;107(3):537–44. IF 3.115.
41. Santiago-Palma J, Payne R. Palliative care and rehabilitation. Cancer. 2001;92:1049–52.
42. Dahlin Y, Heiwe S. Patients' experiences of physical therapy within palliative cancer care. J Palliat Care. 2009;25(1):12–20. PubMed PMID: 19445338.
43. Hansen A, Rosenbek Minet LK, Søgaard K, Jarden JO. The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among patients with primary glioma: an RCT study protocol. BMJ Open. 2014;4(10):e005490.
44. Barawid E, Covarrubias N, Tribuzio B, Liao S. The benefits of rehabilitation for palliative care patients. Am J Hosp Palliat Care. 2015;32(1):34–43. https://doi.org/10.1177/1049909113514474.