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The end-of-life phase of high-grade glioma patients

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2013

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
Sizoo, E. M. (2013). *The end-of-life phase of high-grade glioma patients: Towards a dignified death*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Chapter 1.2

The end-of-life phase of high-grade glioma patients: A systematic review

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Abstract

Background

High grade gliomas (HGG) are rare and incurable yet, and these neoplasms result in a disproportionate share of cancer morbidity and mortality. Treatment of HGG patients is not merely directed towards prolonging life, but also towards quality of life, which becomes the major goal in the end of life (EOL). The latter has received increasing attention over the last decade.

Methods

We reviewed the literature related to the EOL phase of HGG patients from 1966 up to April 2012. Articles were retrieved from PubMed, Embase, Cinahl, Psychinfo and Cochrane database.

Results

The search yielded 695 articles, of which 17 were classified eligible according to pre-defined inclusion criteria. Reviewed topics were: symptoms and signs; quality of life and quality of dying; caregiver burden; organization and location of palliative care; supportive treatment; EOL decision-making. Nearly all identified studies wereobservational, with only two non-randomized intervention studies. Symptom burden is high in the EOL affecting quality of life of both patient and carer. Palliative care services are more intensively used compared to other cancer patients. Cognitive deficits increase as the disease progresses, hampering communication and decision-making.

Conclusion

The currently available data make clear that the EOL phase of HGG is different from other patient groups, but also ask for more clinical studies in HGG on supportive medication, advance care planning and decision-making. The organization of care, development of guidelines and interventions to decrease caregiver burden in the EOL phase are relevant issues as well.

Introduction

High-grade gliomas (HGG) are the most common primary brain tumours in adults. Although the annual incidence of HGG is relatively low with 3-4 per 100.000[27] and brain tumours constitute only 2% of all malignancies, these neoplasms result in a disproportionate share of cancer morbidity and mortality. Patients with HGGs share attributes with other cancer patients going through similar therapies such as surgery, radiotherapy and chemotherapy. However, unlike other cancer types, progress in the development of highly effective therapies for HGG is limited. Patients with HGG cannot be cured from their disease and only temporarily benefit from treatment.[9, 28] Median survival ranges from < 1 to 5 years depending on histological subtype, tumour grade, age, and performance status at the time of diagnosis.[27, 29] Further, HGG patients have also progressive neurological deterioration, making the course of disease different from other malignancies. Indeed, they show physical deterioration like patients suffering from motor neuron disease, and progressive cognitive deficit like dementia patients.[30]

All HGG patients will sooner or later be confronted with the end-of-life (EOL) phase of their disease, which starts when the patient's condition declines and tumour-directed treatment is no longer possible. The EOL phase is usually confined to the last three months of life. EOL care should be aimed at survival prolongation, satisfactory quality of life and the prevention and relief of suffering.[31, 32] Of paramount importance are symptom control and attention to the psychological, social, and spiritual condition of both the patients and their families.[33] Caregivers may even suffer more severely from patients' personality and cognitive changes than patients themselves.[34] Furthermore, patients and their informal caregivers (partner, relative, friend or neighbour) will be faced with medical EOL decisions such as withholding or withdrawing life-sustaining treatment, and the administration of drugs for the prevention or relief of suffering with a potential life-shortening effect.[35]

In the last decade reviews have aimed to provide guidelines for supportive treatment in brain tumour patients.[36-41] A systematic review of supportive care needs in HGG patients underlined that physical as well as cognitive and emotional symptoms at the EOL require more recognition.[42] Nevertheless, none of these reviews specifically addressed actual EOL treatment measures. The specific neurological symptomatology of HGG patients[4] affects decision-making capacity relatively early in the disease[43], and becomes even more prominent in the EOL phase of the disease[37].Therefore, current guidelines for EOL care and treatment of systemic cancer patients are insufficient for physicians caring for HGG patients in the EOL phase.

The primary aim of this systematic review is to outline the current knowledge on the EOL phase of HGG patients. Secondly, we aim to identify interventions that improve quality of life and dying, and/or quality of care for HGG patients in the EOL phase. This overview could be a first step towards development of specific guidelines for physicians caring for HGG patients in the EOL phase.

Methods

Search strategy

We conducted a systematic search in the e-resources PubMed, Embase, Cinahl, PsychInfo, and the Cochrane Library covering >1966 to April 2012. The search strategy consisted of a combination of two search strings; one related to the EOL and one related to primary brain tumours. The full search strings are described in Figure 1. All retrieved titles and abstracts were screened by two authors (EMS and LD). The full texts of potential relevant articles were read by the same authors. Furthermore, the reference lists of relevant articles and reviews were screened for additional studies. Any uncertainty about a study's relevance was resolved in conference with two other co-authors (HRWP and MJBT).

Inclusion and exclusion criteria studies

We included only original studies involving: HGG patients (majority of the population or reported on separately as a subpopulation); specific description of the actual EOL phase; available full text in English, German or Dutch in peer-reviewed journal. We excluded case reports.

Results

Search results (Figure 1)

The search yielded 695 unique articles, of which 17 were classified eligible according to the pre-defined inclusion criteria (see Figure 1 for the results of the selection procedure). The main characteristics of these 17 relevant studies are described in Table 1. One study concerned an intervention in primary brain tumours using a control group, but in a retrospective manner, and one study described observations from a group intervention in caregivers.[34, 44] Furthermore, we identified five qualitative studies on (semi-structured) interviews and ten quantitative studies (seven chart reviews; three studies reporting on questionnaires). Based on the content of the eligible studies, we classified EOL data into following six topics: symptoms and signs (A); quality of life in the EOL and quality of dying (B); caregiver burden (C); organization and location of palliative care (D); supportive treatment (E); EOL decision-making (F). All eligible studies are discussed in the context of these six topics in the following sections.

A. Symptoms and signs

Cavers et al. interviewed glioma patients and their caregivers throughout the disease course, and in addition, caregivers as well following bereavement. Tumour progression was found to

be accompanied by an increase in number and severity of physical symptoms, and concomitant cognitive decline.[45]

Furthermore, six quantitative studies reported on the incidence of symptoms and signs in the EOL phase of HGG patients with follow-up until death. All studies showed that disease-specific symptoms were prominent in the EOL phase. Figure 2 summarizes the prevalence of

Figure 1: Systematic search

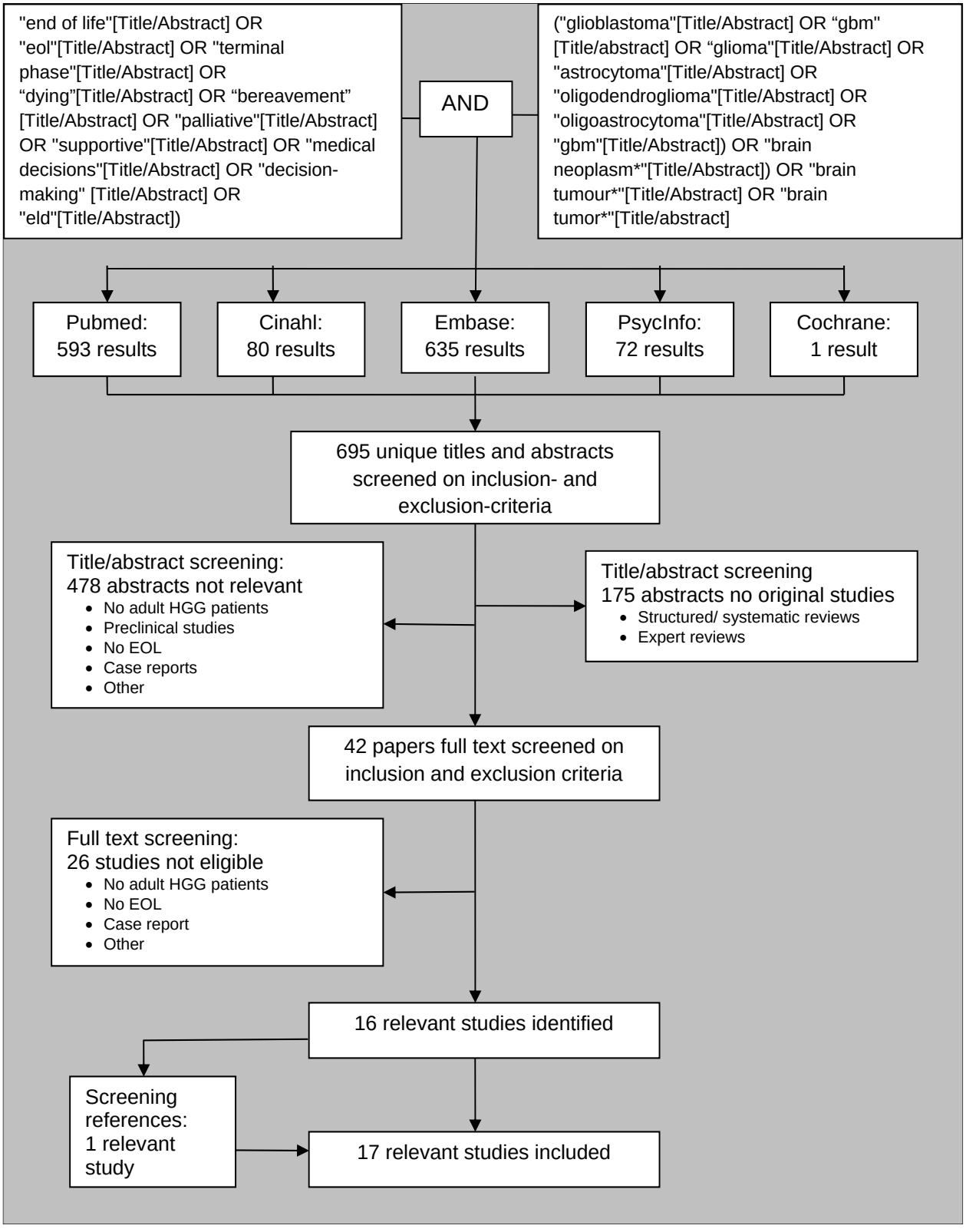


Table 1: Summary of main characteristics of selected articles

	Region of origin	Study type	Population	Themes covered
Addington-Hall 2000	United Kingdom	Retrospective study, semi-structured interviews	Patients with various cancer types, subpopulation brain tumour patients (n=268)	D Use of specialist palliative care services
Arber 2010	United Kingdom	Retrospective study, chart review	Patients with primary malignant brain tumours referred to specialist palliative care setting (n=70), majority of patients deceased (n = 55)	C Caregiver need for support D Access to health services, place of death
Bausewein 2003	Germany	Retrospective study, chart review	Patients with a primary brain tumour (n=31)	A Symptoms and signs in the last 72 hours of life B Peaceful death E Supportive medical treatment F Decision-making capacity
Cavers 2012	United Kingdom	Prospective study, interviews	HGG patients and their proxies, longitudinal interviews including interviews with bereaved proxies (n=9) Interviews with general physicians of HGG patients (n = 19)	A Symptom burden towards death B Social, psychosocial and existential well-being of patients towards death D Physicians' opinion on perceived role in EOL care.
Davies 2005	United Kingdom	Retrospective study, semi-structured interviews	Bereaved relatives of malignant glioma patients (N=56)	B Quality of life after ending tumour treatment
Faithfull 2005	United Kingdom	Retrospective study, chart review	Patients with primary malignant brain tumours referred to specialist palliative care setting (n=39)	A Symptoms during palliative stages of illness D Referral to palliative care, use of palliative care service and place of death
Gofton 2012	United States of America	Retrospective study, chart review	Patients admitted to the inpatient neurology or neurosurgery services, subpopulation HGG patients deceased within 6 months after admission (n=43)	D Place of death F DNR discussions, health care proxies, hospice discussions.
Horowitz 1996	United States of America	Prospective study, observations	Spouses participating in a psycho-educational intervention for spouses caring for brain tumour patients (n±20)	C Spouses coping with the end of life, dying and bereavement
Oberndorfer 2008	Austria	Retrospective study, chart review	Glioblastoma patients admitted to the hospital (n=29)	A Symptoms in the last two weeks of life E Supportive treatment at the end of life
Ostgathe (2010)	Germany	Cross-sectional survey, questionnaires (multiple choice)	All patients admitted to different palliative care settings in Germany, subset of patients with primary brain tumours (n= 151)	A Symptoms in patients referred to palliative care B Emotional and social well-being at the EOL C Overburden of family caregivers D Nursing levels, reason for admission to palliative care
Pace 2009	Italy	Retrospective study, chart review	Brain tumour patients (80% HGG) deceased at home selected from a cohort of patients admitted to a comprehensive program of neuro-oncological home care	A Symptoms and signs in the last stage of disease B Peaceful death E Supportive treatment F Advance directives and EOL decisions

			(n=169)	
	Region of origin	**Study type**	**Population**	**Themes covered**
Pace 2012	Italy	Retrospective observational comparative study	Patients of a cohort brain tumour patients admitted to a home care program (N=72) and a control group of brain tumour patients from another hospital not admitted to this home care program (n=71)	D Hospitalization rate in the last month of life between the two groups.
Salander 2002	Sweden	Prospective study, interviews	Patients and spouses of malignant glioma patients (n=25), spouses interviewed after death of the patient (n=20)	C Spouses coping with approaching death of the brain tumour patient
Schubart 2008	United States of America	Cross-sectional study, interviews	Caregivers of primary brain tumour patients, subpopulation of bereaved caregivers (n=6). Five of these deceased patients had a HGG.	C Caregiver burden
Sherwood 2004	United States of America	Retrospective study, self-report questionnaires	Bereaved caregivers of HGG patients (n = 43)	C Caregiver tasks at the EOL and bereavement
Sizoo 2010	The Netherlands	Retrospective study, chart review	High-grade glioma patients (n=55)	A Symptoms and signs after ending tumour treatment D Place of death E Supportive treatment
Sizoo 2012	The Netherlands	Retrospective study, questionnaires (multiple choice and open ended)	Physicians (n=101) and informal caregivers (n=50) of a cohort deceased HGG patients	D Place of death F Advance directives, decision-making, EOL decisions

Themes: A symptoms and signs B quality of life in the EOL phase or quality of dying, C Informal caregiver burden, D palliative care and place of care, E supportive treatment and F end-of-life decisions-making

the most common disease-specific symptoms (figure 2A) and general symptoms (figure 2B) reported in the various papers. In most studies patients' consciousness gradually decreased as death approached. In the majority of cases, this was considered to be the result of increasing intracranial pressure.[25] The prevalence of dysphagia varied from 10% to 85%. Headache was reported in 36 to 62 % of the patients, and 10 to 56% of the patients had seizures.[21, 25, 46-48] Focal neurological signs were present in half of the patients (51%), and often worsened as the tumour progressed.[47] The same applied for cognitive disturbances, such as forgetfulness, problems in concentration, and behaviour. The prevalence of confusion varied substantially in the different studies; in the study by Pace et al. 15% of patients dying at home were confused or agitated[48], compared to half of the patients in two other studies[21, 49].

Ostgathe et al. compared the prevalence of EOL symptoms in brain tumour patients with a general palliative care population. The frequency of disorientation or confusion was significantly higher in primary brain tumour patients (50%) compared to patients with brain metastases (35%), or a general palliative care population (14%). The prevalence of general EOL symptoms such as dyspnoea, nausea, vomiting, anorexia, constipation, and pain was significantly lower in primary brain tumour patients, while the occurrence of fatigue in

primary brain tumour patients did not differ significantly from the general palliative care population.[49] Two other studies reported on symptoms, but not specifically in the EOL phase.[50, 51]

Figure 2a: Prevalence of disease-specific symptoms

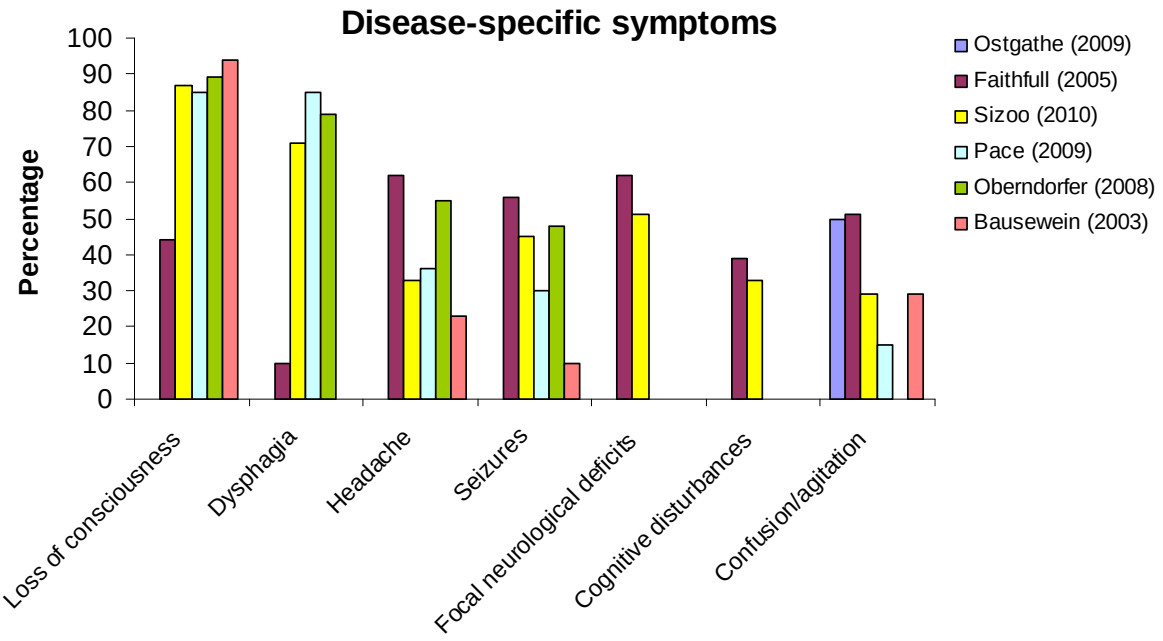
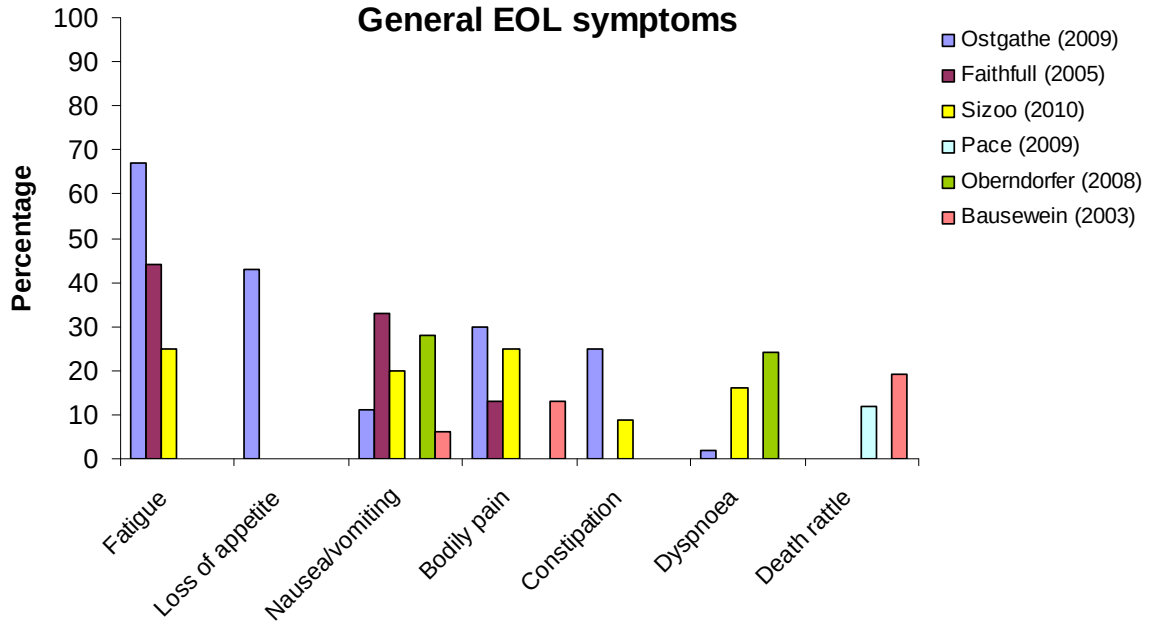


Figure 2b: Prevalence of general end-of-life symptoms



B. Quality of life and quality of dying

Three studies addressed quality of life in the EOL phase[26, 45]; two discussed peaceful dying of HGG patients[25, 48].

Interviewing relatives of deceased glioma patients revealed that 40% of HGG patients had a relatively good or acceptable quality of life in the EOL phase. These patients were described as being 'fit' and having 'a normal life', meaning they kept their interests, were able to carry out the things they used to do, and could enjoy close relationships. Sixty per cent of patients were considered to be severely disabled leading to dependence, distress, loss of normal personality and interactions, or even existence in a state worse than death. Factors associated with a poor quality of life in the EOL phase were the presence of disability at the time of diagnosis, moderate to marked cognitive or personality change, and a high level of stress at initial diagnosis.[26] Cavers et al. reported on mental, social, and existential well-being in the EOL phase. The realization of disease-progression often resulted in a decline in mental well-being. Several interviewed patients indicated that knowing the dismal prognosis from the start prepared them for the moment of disease progression. Patients' social lives in the EOL phase worsened alongside their physical and cognitive decline. Towards death, patients became more house- and bedbound and lost the ability to communicate. Existential sadness and distress were expressed, along with finding meaning and peace in the process towards death.[45]

Ostgathe et al. reported the prevalence of psychological problems in primary brain tumour patients and compared these to a general palliative care population. Feelings of depression were reported in one third of patients, and anxiety or emotional strain in about 40%. The prevalence of both symptoms did not differ between patients with primary brain tumours and other palliative care patients. Ninety per cent of the patients with primary brain tumours were reported to have a poor functional status, which was significantly more often than in a general palliative care population (72%). The need for social support was identified in about 55% of the brain tumour patients and was significantly higher compared to a general palliative care population.[49]

As to quality of dying, the majority (82%) of brain tumour patients that died at home, died peacefully with a progressive loss of consciousness and adequate control of symptoms. A non-peaceful death was described in 13% to 16% of the patients due to poor symptom control (pain, refractory seizures), or agitation.[25, 48]

C. Caregiver burden

Psychosocial burden of the caregiver at the EOL was often underappreciated by health care professionals and overshadowed by the patient's increasing disability, and physical decline. As the patient became progressively disabled, stress increased for caregivers. This was

attributed to a change in the relationship with the patient, adaptation of new roles, and the addition of new responsibilities. Caregivers emphasized the need for information and support, especially after a transition from the hospital to the home care setting. Schubart et al. found that bereaved caregivers felt unprepared for the EOL phase and regretted not being able to manage symptoms as the patient's condition declined, and not having accepted hospice care earlier.[52] Sherwood et al. paradoxically reported that in their study most caregivers emphasized they preferred to keep the patient at home, thereby facilitating a peaceful transition to death.[53]

Caregivers reported that they prepared themselves for the patients' death by making funeral arrangements, seeking information on what to expect in the final days, and preparing for their life after death of the patients. Communicating with the terminally ill patient about these issues was experienced as helpful.[53] These findings are supported by Salander et al. (specifically reporting on spouses), who found that being unable to share thoughts and feelings with the patient was very distressing for caregivers. Reasons for a patient's inability to share were found to be cognitive deficits including aphasia, personality change, deep despair, and premorbid characteristics of the relationship. In cases where the patient's comprehension of the situation was limited, spouses often acknowledged the changed mutuality in the relationship and adopted a caring role.[54] Sharing with peers was suggested to be helpful as well. Observations from a psycho-educational support group for spouses caring for brain tumour patients revealed that discussing the later stages of disease and death with peer spouses was appreciated by participating spouses.[34]

Regarding bereavement, caregivers of deceased HGG patients felt that the loss of the patient occurred stepwise, and the bereavement process thus already had started while the patient was still alive.[34, 53] Specifically, the transition from being an active caregiver to a grieving family member was very difficult.[53]

The quantitatively analysed studies of caregivers of HGG patients referred to a specialist palliative care unit, revealed that significant caregiver burden and feelings of stress were present in approximately 50%, and severe caregiver distress in 10%.[21, 50] In the cohort described by Ostgathe et al., 74% of the family members of primary brain tumour patients rated themselves overburdened in the EOL phase. The number of overburdened relatives was significantly higher in brain tumour patients than in a general palliative care population. This was supposed to be (partly) related to a high prevalence of cognitive or communicative changes, and confusion in this patient category.[49]

D. Organization and location of palliative care

The organization of palliative care differed between countries making interpretation of results difficult. In a US cohort, palliative care consultation was initiated in 12% of patients.[51] In a UK cohort, 19% of the brain tumour patients received community specialist outpatient

palliative care.[55] Another study originating from the UK reported on a population of brain tumour patients referred to specialist palliative care settings. Community specialist palliative care was provided in about half of these patients; other palliative care facilities used were hospice inpatient units (28%), other acute inpatient services (15%), social services (36%), hospice day care (24%), and voluntary-based services (7%).[50] Referral to palliative care occurred at a median of eight weeks before death.[50] Reasons for admission to inpatient palliative care units were inadequate symptom control, functional deficits, cognitive impairment, social issues/crises, specific terminal care such as palliative sedation, and respite for the caregiver.[21, 49]

The required level of nursing support was high in primary brain tumour patients as compared to a general palliative care population with 12% per cent of HGG patients needing nursing support around the clock, and an additional 14% requiring support at least three times a day. A need for assistance in activities of daily living was reported in 93% of brain tumour patients.[49]

The place of death varied among countries, reflecting differences in feasibility of home care, use of hospices, and accessibility of institutions. In studies originating from continental Europe (Italy, The Netherlands), most patients (64-70%) died at home[47, 48, 56] as compared to 21% in the USA[51] and 16-33% in the UK[21, 50]. Hospice facilities are more commonly used in the USA (68%)[51] and in the UK (30-33%)[21, 50] than in continental Europe (9-10%)[47]. In all four countries, only a minority of the patients (7-20%) died in the hospital.[21, 47, 48, 50, 51, 56]

Pace et al. reported on an intervention using a palliative home care program for neuro-oncological patients, originally set up as a home-rehabilitation program.[57] Part of the patients participating in the intervention had a follow-up until death. The authors retrospectively investigated whether the home care program decreased hospitalization rate at the EOL. A well-defined subset of 72 deceased patients participating in the program was compared with a control group of 71 patients from another hospital receiving standard care. Of the patients receiving standard care, 26·8% were hospitalized in the last month of life compared to 8·3% in the home-care program group (corrected OR 0·29). Mean hospitalization duration was shorter in patients of the home-care program (0·8 vs. 2·5 days).[44] No information was provided on the effect of the home care intervention on outcome measures such as quality of life, quality of death, and caregiver burden.

E. Supportive treatment

The use of supportive drug treatment generally increased towards death[46], but at the same time dysphagia and decreasing consciousness hampered the use of oral medication, particularly in the home care setting.[47]

More than 80% of the HGG patients were taking steroid treatment in the EOL phase.[25, 47] The use of steroids initially increased in the EOL phase[46], whereas in the last two weeks of life, steroids were tapered or discontinued in 23-45% of patients.[25, 46, 48] Almost two thirds of patients received anti-epileptic drugs (AED) in the EOL phase[25] and the use of AED increased towards death in the hospital setting.[46] None of these four studies addressed the policy towards (dis)continuation of AEDs, once patients became unable to swallow. As to other supportive treatment, the large majority of HGG patients received painkillers in the last two weeks before death: non-steroid anti-inflammatory drugs (NSAID) were prescribed in 85%, while 93% of patients used opioids.[46] Confusion and agitation required the use of psychopharmacological (neuroleptic) or sedative drugs in 12-45% of brain tumour patients in the EOL phase.[46, 48]

F. EOL Decision-making

Three studies reported on decision-making capacity towards death, emphasizing the lack of competence in participating in decision-making as death approached, due to cognitive disturbances, somnolence, aphasia, and/or delirium.[25, 48, 56] In the last month of life, the majority of brain tumour patients lacked capacity to make treatment decisions.[48, 56]

Gofton et al. reported on the timing and content of EOL discussions in HGG patients who were admitted to the hospital within six months of death. Of 43 deceased HGG patients, potential admission to a hospice was discussed in 38 patients (88%), a healthy care proxy was appointed in 33 patients (77%), and 28 patients (65%) had a Do-Not-Resuscitate (DNR) order. Hospice discussions were initiated at a median of 39 days before death and DNR orders were filled in at a median of 41 days before death.[51]

Sizoo et al. reported a retrospective analysis of physicians and carers EOL decisions in the terminal phase of care in HGG patients in a Dutch cohort. Sixty per cent of physicians were aware of the patient's preferences regarding treatment at the EOL. Usually, the physician discussed the preferences with the patients (60%). The patient declined to discuss EOL decision-making in only 3% of cases. According to the relatives of a subset of the same cohort deceased HGG patients, 42% of patients had an advance directive (AD). The physicians were not always aware of this AD.[56] In a similar Italian population, only 6% of patients were reported to have an AD.[48]

Two studies addressed the actual EOL decisions. Pace et al. described EOL decisions in 169 Italian brain tumour patients receiving home care. In this population, tube feeding was installed in 13% of the patients, steroids were tapered in 45% of the patients, and palliative sedation was applied in 13% of the patients.[48] Sizoo et al. found that at least one EOL decision was made in 73% of the patients in the Netherlands. Most often this concerned the withdrawal of life-prolonging treatment and specifically dexamethasone was withdrawn in half of the patients, similar to the Italian cohort. On the other hand, both palliative sedation

and withholding life-prolonging treatment were reported more often in the Dutch than in the Italian population: both were carried out in almost a third of the cases. Euthanasia, legislated in the Netherlands but not in Italy, was requested in 10% of the Dutch patients. Due to incompetence in part of the patients, the request could not be granted in all. Ultimately, euthanasia was proceeded in 7% of all cases.[56]

Discussion

With this review, we identified only seventeen studies specifically reporting on the EOL phase of HGG patients. The search identified only two intervention studies, which were non-randomized controlled studies.[34, 44] Most studies were descriptive of nature, often chart reviews or interview studies. Consequently, the level of evidence of the studies this review is based on is low according to classifications used in evidence-based medicine.

The lack of controlled studies into the EOL phase is not restricted to patients with HGG; the same holds true for EOL research in other neurological patient groups[58] such as patients with dementia[59], or patients with amyotrophic lateral sclerosis (ALS)[60]. The majority of studies regarding these neurological diseases are descriptive as well. By contrast, for patients with systemic malignancies various (intervention) studies are available with regard to symptom management at the EOL[61, 62], the practice of artificial nutrition and hydration at the EOL[63], and EOL care[64].

By performing a systematic search strategy conducted by two authors separately using strict criteria and various data resources, we have provided a focused overview about the EOL phase of HGG patients. Trying to be as complete as possible, we may still have missed data, e.g., by excluding studies in which patients with HGG represented a minority or were not reported on separately with potentially additional relevant information on the EOL of HGG patients.

Despite the limited currently available evidence, a recurring and pivotal topic emerging from the studies we reviewed is that the EOL phase of HGG patients is unique, and that the course of disease differs from that of a general cancer population.[49] Disease-specific symptoms such as seizures, cognitive decline and progressive neurological deficits are prominent and, except for fatigue, the more generally acknowledged cancer EOL symptoms such as dyspnoea, pain, and anorexia occur less often than in other groups of palliative patients.[49] In particular, increasing motor disability and cognitive decline were reported to be disturbing the patient's quality of life and social well-being in the EOL phase. These factors also put a huge burden on informal caregivers. Confusion and seizures are symptoms that prevent patients from dying peacefully.[25]

Given the specificity of the described problems, we conclude that most general guidelines for EOL care and treatment are apparently not sufficient or incomplete for treating HGG

patients. Further systematic studies on problems and needs of HGG patients and their caregivers during the EOL phase are needed. From the currently available evidence, several important areas have been identified where evidence-based guidelines are required.

First, the need of supportive drugs increases towards death, but this increasing need may be hindered by problems with drug administration. For painkillers and sedative drugs, alternative administration routes (e.g. rectal, subcutaneous) are commonly used, and guidelines on administration of these drugs at the EOL can be shared with those for other (cancer) populations.[62] For administration of anti-epileptic drugs (AEDs) at the EOL phase, however, no guidelines are available. In 2000, Krouwer et al. published an expert review providing suggestions for alternative administration routes of AEDs when patients become unable to swallow.[65] Unfortunately, the effectiveness and feasibility of the suggestions provided in this paper have never been systematically evaluated. Moreover, since publication of this review, several new AEDs that are potentially useful for the prevention and treatment of seizures in patients unable to swallow at the EOL, have become available.[66, 67] Development and validation of treatment guidelines regarding AED in the EOL phase would be relevant.

Second, discussions about treatment restrictions in HGG patients were often initiated relatively close to death[51], and several authors advocated advance care planning (ACP) (more) early in the disease course[56, 58, 68]. ACP refers to a broad process of communication and aims at timely involvement of patients and their proxies in decision-making with respect to their EOL care.[69] Completion of an AD may be part of this ACP process. In ALS patients such treatment restrictions are discussed with the patient in a much earlier stage. When compared to cancer patients, and probably also to HGG patients, ALS patients are more adequately prepared for EOL decision-making.[70] This difference in approach is surprising since the median survival in HGG patients is similar, or even worse, to ALS patients. Moreover, in contrast to ALS patients, decision-making capacity is comprised relatively early in HGG. More than 50% of the HGG patients are marginally capable or incapable for decision-making at a median of four months after diagnosis[43], and decision-making capacity will undoubtedly further decline towards death. In a randomized controlled trial, El Jawahri et al. showed the feasibility of interventions regarding ACP through studying the effect of a video decision support tool facilitating ACP in HGG patients. This video support tool proved effective in promoting comfort care and gaining confidence in decision-making, but the effect of the intervention on quality of life and care at the EOL was not reported on.[71]

Third, the only intervention study in brain tumour patients in the EOL phase focused on the impact of a palliative home care program on hospitalization rate at the EOL.[44] Hospitalization rate was lower in the intervention group. Unfortunately, the impact of the palliative home care program on quality of life, quality of dying, or caregiver burden was not studied. Nevertheless, as hospitalization at the EOL is known to be distressing for patients and their informal caregivers, further research into this and other interventions will be valuable,

keeping in mind that organization of care and location of care varies among countries and cultures.[72]

In conclusion, there is a need for high-quality studies focusing on (1) the prevalence of problems and needs of HGG patients in the EOL phase, as well as on (2) development of treatment guidelines for HGG-specific EOL symptoms and problems, in particular seizures, (3) active and early ACP, and (4) interventions aimed at organization of care at the EOL. Given the high burden on caregivers of HGG patients, interventions to be developed should also aim at decreasing caregiver burden.