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

Towards a dignified death

Eefje Sizoo

VRIJE UNIVERSITEIT

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Eefje Machela Sizoo

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promotoren:	prof.dr. M.J.B. Taphoorn
	prof.dr. L.H.J. Deliens
copromotoren:	dr. H.R.W. Pasman
	dr. J.C. Reijneveld

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Chapter 1.1 General introduction and outline

Introduction

Epidemiology of brain tumours

Primary brain tumours account for approximately 2% of all cancer types[1]. The large majority (85%) of all histologically confirmed primary brain tumours are gliomas[2]. In the Netherlands, the annual incidence is stable with approximately six per 100.000, corresponding with approximately 1000 new cases[2, 3]. Men are more often affected with a male/female ratio of 1.6[2]. Gliomas are classified according cell type and tumour grade using World Health Organization (WHO) criteria (table)[4]. Grade I and II gliomas are denominated low grade, grade III and IV high grade. Most gliomas (70-75%) are high-grade at time of diagnosis[2]. Increasingly, molecular features of glioma cells are important for diagnosis and prognosis[5, 6]. In this thesis, we focus on patients with high-grade glioma (HGG).

Table 1 WHO classification of gliomas

Grading	**Histological characteristics**		
Grade I	Pilocytic astrocytoma		
Grade II	Astrocytoma	Oligodendroglioma	Oligoastrocytoma
Grade III	Anaplastic astrocytoma	Anaplastic oligodendroglioma	Anaplastic oligoastrocytoma
Grade IV	Glioblastoma multiforme		

High-grade glioma

High-grade glioma (HGG) patients present with neurological or cognitive deficits related to the localization of the tumour (motor functioning, speech, personality), with epileptic seizures and/or with signs of increased intracranial pressure (e.g. headache, vomiting, visual disturbance, drowsiness)[4].

Until date, patients with HGG cannot be cured and median survival is poor: approximately 42 months for patients with anaplastic oligodendroglioma[7, 8], 19 months for patients with anaplastic astrocytoma[7] and 5 to 14 months for patients with glioblastoma multiforme[7, 9]. Age, WHO performance status and the need for dexamethasone before the start of treatment are independent prognostic factors[10].

At diagnosis, the main aim of treatment in HGG patients is to prolong life, but since the treatment of primary brain tumours is not curative, morbidity during the remaining survival time is of utmost importance for both the patient and his or her relatives. Thus, the potential

benefit of any treatment should be weighed against the impact on health-related quality of life (HRQOL) of that treatment.

Treatment in HGG patients consists of surgery, followed by radiotherapy, often in combination with chemotherapy. The goal of surgery is histological verification of the tumour and cytoreduction aimed at alleviation of symptoms. Moreover, several (non-randomized) studies suggest that more extensive resection increases overall survival[11]. Surgery may cause neurological deficits and focal cognitive deficits negatively affecting HRQoL short after the operation. However, these deficits are often transient and more extensive resection is associated with improved HRQoL over time[12]. Radiotherapy has long been acknowledged as effective in HGG treatment[13-16], without having a negative effect on HRQoL[16]. The role of chemotherapy was recognized more recently. Chemoradiation (radiotherapy with temozolomide chemotherapy) followed by six adjuvant cycles of chemotherapy has proven to increase median and two year survival in glioblastoma (grade IV) patients in comparison with radiotherapy alone[9]. The addition of concomitant and adjuvant temozolomide in glioblastoma patients in good condition at the start of treatment had no negative effect on health-related quality of life[17]. Whether there is an effect of this combined modality treatment in anaplastic astrocytoma (grade III) patients is currently evaluated in a randomized controlled trial. In patients with recurrent HGG, temozolomide chemotherapy improves time to progression, but not overall survival[18]. In patients with anaplastic oligodendoglioma, the addition of six cycles of procarbazine, lomustine and vincristine (PCV) chemotherapy to radiotherapy has proven to improve both progression free[19] as overall survival[8]. PCV chemotherapy has proven to have a negative effect on health-related quality of life (domains nausea, loss of appetite, drowsiness) during and shortly after treatment, but no long-term effects were reported[20].

During the disease process, the aim of treatment gradually shifts from mainly life-prolonging, to mainly maintaining HRQoL by means of supportive treatment. Towards the end of life (EOL), (nearly) all treatment will be supportive.

End-of-life phase

The EOL phase in HGG is generally referred to as the period when the patient starts to deteriorate and tumour-directed treatment is no longer possible. Furthermore, it is most often confined to the last three months of life. In this EOL phase, symptom burden is generally high and palliative care is of utmost importance[21]. The main goals of palliative care are to improve or maintain the HRQoL of the patients facing a life-threatening illness and their relatives by the prevention and relief of suffering[22] and to facilitate a dignified death[23]. EOL care is aimed at maintaining HRQoL as long as possible, but it also may require medical EOL decisions for the prevention and relief of suffering. In some instances these decisions may hasten death. EOL decisions include the withholding or withdrawing of life-prolonging

treatment, and the administration of drugs with a potential or certain life-shortening effect[24]. Examples of EOL decisions in HGG are withdrawal of chemotherapy or dexamethasone, withholding artificial food and fluid administration, non-admittance to the hospital or intensive care unit for treatment of infections, and palliative sedation. In the Netherlands 57% of deaths are preceded by an EOL decision[24]. In some European countries (The Netherlands, Belgium, Luxemburg and Switzerland), physician-assisted death such as euthanasia or physician-assisted suicide are allowed under strict conditions upon a well-considered request.

In the Netherlands, patients are often no longer seen by the clinical specialist after ending tumour directed treatment and referred to the GP or a palliative care setting (hospice, nursing home) for EOL care. Guidelines for EOL treatment in these patients are lacking and EOL treatment depends on the involved physicians' expert opinion. At the start of this research project in 2008, data about the EOL phase of HGG patients were scarce[21, 25, 26] and it was unknown how long patients live after ending tumour-directed treatment and what EOL care and treatment they receive.

Outline of this thesis

In this thesis, we will focus on the end-of-life phase of HGG patients: what do HGG patients experience, how is their quality of life, do they die with dignity and how is the quality of care and the EOL decision-making process?

We use various methods to answer our questions: *a systematic review* (chapter 1.2), a *chart review* (chapter 3.1) and a *retrospective cohort study* in which we collected data about the EOL phase of deceased HGG patients from physicians (chapter 2.2 and 4) and relatives (chapter 3.2, 4 and 5).

In Chapter 1.2 we review all literature published on the EOL phase of HGG patients before April 2012. Articles are reviewed on: symptoms and signs, HRQoL and quality of dying, caregiver burden, organization and location of palliative care, supportive treatment and EOL decision-making.

Chapter 2 focuses on symptoms and signs of patients in the EOL phase. In chapter 2.1 we report on our first pilot study to explore this EOL phase in which signs and symptoms are summarized. In chapter 2.2, we report on the prevalence and predictors of the development of seizures in the EOL phase. Moreover, we describe the use and (dis)continuation of anti-epileptic drugs in the last week of life according to physicians of a cohort HGG patients.

Chapter 3 focuses on quality of life in HGG patients. In chapter 3.1, we review the current knowledge on quality of life in HGG patients. In particular, we focus on the concept of health-related quality of life (HRQoL), available instruments to measure this HRQoL and the

influence of various treatment modalities on the patients' HRQoL. In chapter 3.2 we describe the development of a proxy-reported questionnaire to measure HRQoL in the EOL phase in retrospect. Furthermore, we describe HRQoL of HGG patients in the EOL phase.

Chapter 4 describes the EOL decision-making process in HGG patients. We assess in physicians and relatives of a cohort deceased HGG patients whether patients express EOL preferences, how often they discuss these preferences with their treating physician, until what time patients are competent to participate in decision-making and how often EOL decisions are taken.

In chapter 5 we address dying with dignity in HGG patients. Dying with dignity can be regarded as an overarching goal of palliative care. We assess how often HGG patients die with dignity as perceived by their relatives and what disease- and care factors correlate to dying with dignity in these patients.

Chapter 1.2

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

Eefje M. Sizoo

H. Roeline W. Pasman

Linda Dirven

Christine Marosi

Wolfgang Grisold

Günther Stockhammer

Jonas Egeter

Robin Grant

Susan Chang

Jan J. Heimans

Luc Deliens

Jaap C. Reijneveld

Martin J.B. Taphoorn

Submitted.

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

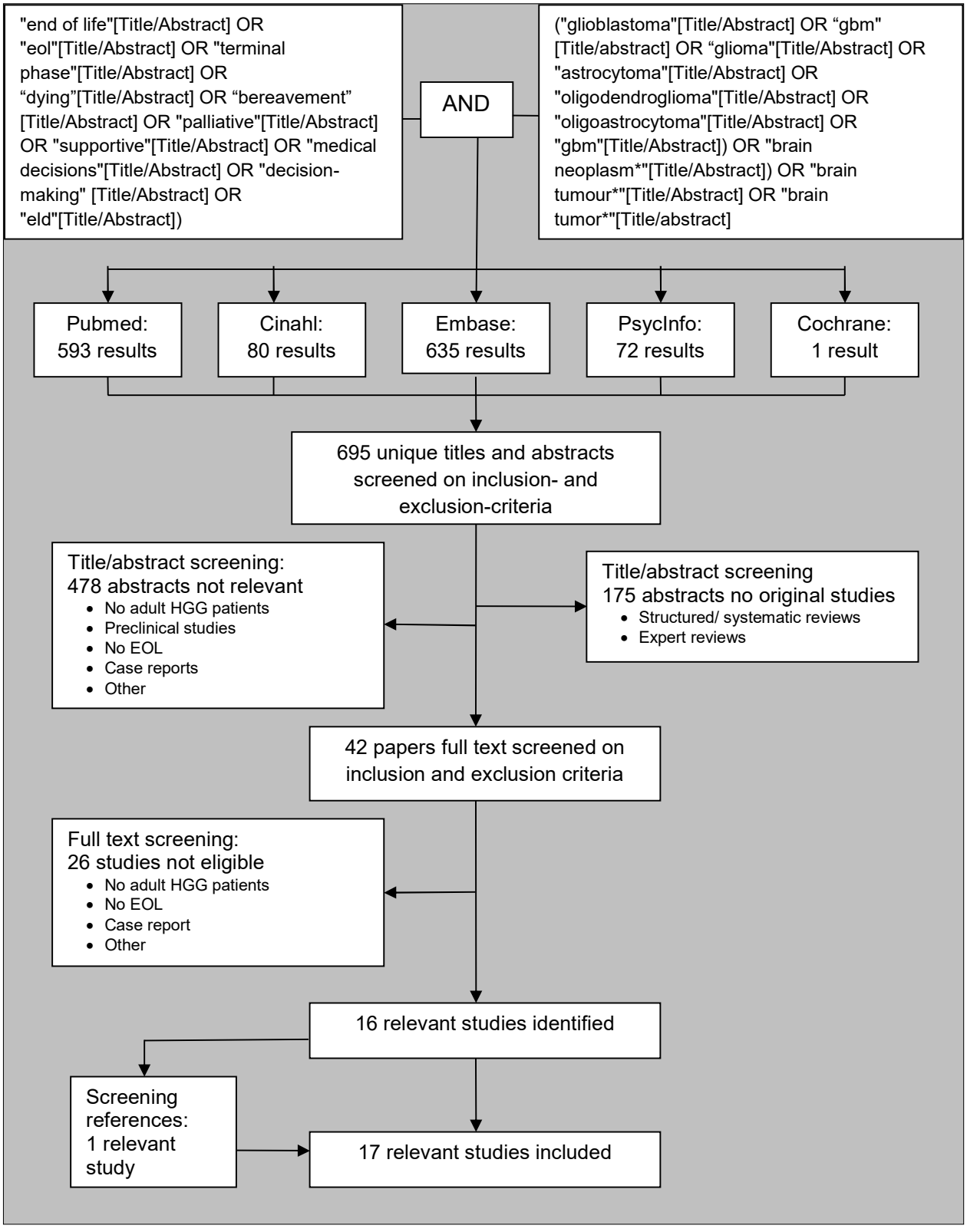

Table 1: Summary of main characteristics of selected articles

	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	A Symptoms and signs in the last stage of disease B Peaceful death E Supportive treatment

			comprehensive program of neuro-oncological home care (n=169)	F Advance directives and EOL decisions
	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

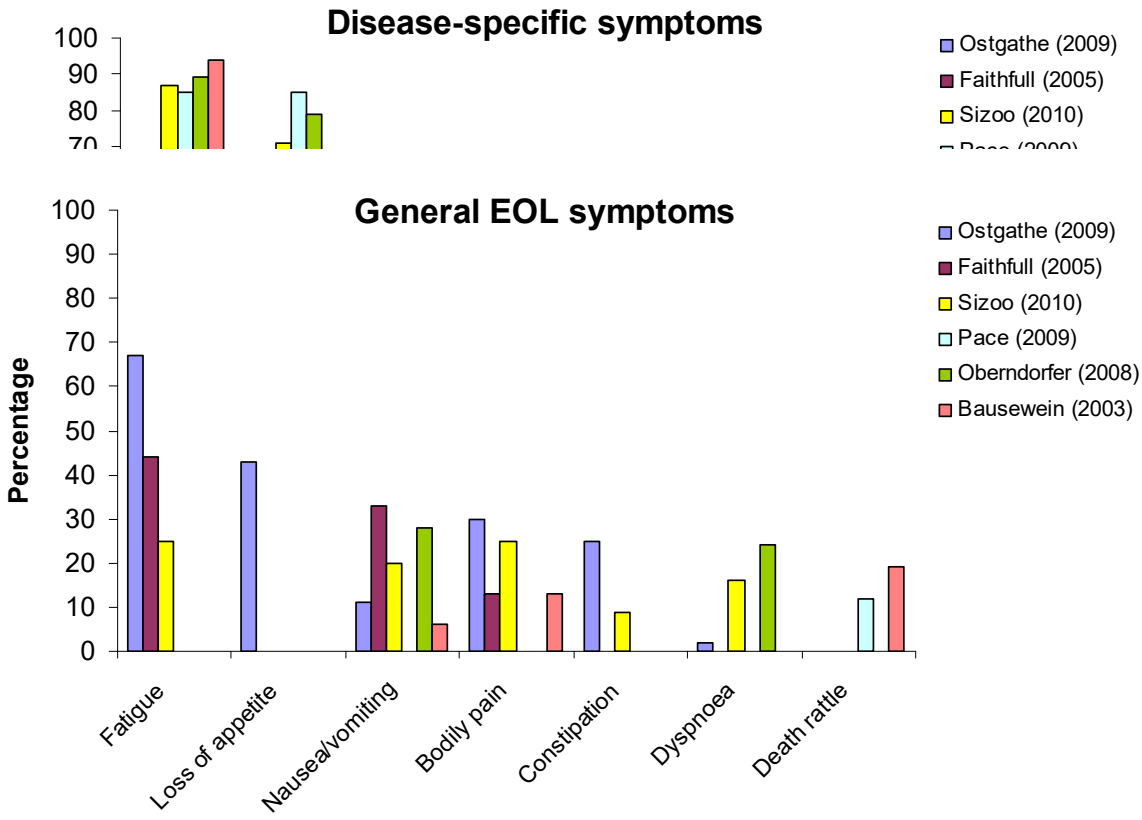

Figure 2b: Prevalence of general end-of-life symptoms

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.

Chapter 2.1

Symptoms and problems in the End-of-Life Phase of High-Grade Glioma Patients

Eefje M. Sizoo

Lies Braam

Tjeerd J. Postma

H. Roeline W. Pasman

Jan J. Heimans

Martin Klein

Jaap C. Reijneveld

Martin J.B. Taphoorn

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Abstract

Despite multimodal treatment, it is not possible to cure high-grade glioma (HGG) patients. Therefore, the aim of treatment is not only to prolong life, but also to prevent deterioration of health-related quality of life (HRQoL) as much as possible. When the patient's condition declines and no further tumour treatment seems realistic, patients in the Netherlands are often referred to a primary care physician for end-of-life (EOL) care. This EOL phase has not been studied adequately yet. The purpose of this study was to explore specific problems and needs experienced in the end-of-life phase of patients with high-grade glioma.

We retrospectively examined the files of 55 patients who received treatment in our outpatients clinic and died between January 2005 and August 2008. The clinical nurse specialist in neuro-oncology maintained contact on a regular base with (relatives of) high-grade glioma patients once tumour treatment for recurrence was no longer given. She systematically asked for signs and symptoms.

The majority of the patients experienced loss of consciousness and difficulty with swallowing, often arising in the week before death. In nearly half of the patients in the end-of-life phase, and in one third of the patients in the week before dying seizures occurred. Other common symptoms reported in the end-of-life phase are progressive neurological deficits, incontinence, progressive cognitive deficits and headache. Our study demonstrates that HGG patients, unlike the general cancer population, have specific symptoms in the EOL phase. Further research is needed in order to develop specific palliative care guidelines for these patients.

Introduction

Patients with high-grade glioma (HGG), the most frequently occurring primary malignant brain tumour, have a poor prognosis and cannot be cured. Despite aggressive multimodality treatment with surgery, radiation therapy and chemotherapy, median survival ranges from less than one year to five years depending on histological subtype, tumour grade, cytogenetic analysis, age and performance status at the time of diagnosis.[9, 73]

Focal neurological deficits, symptoms of increased intracranial pressure, epilepsy and cognitive dysfunction are prominent symptoms in HGG patients which may arise in any stage of the disease.[4, 37, 74] Furthermore, fatigue, mood disturbances and anxiety are often reported.[75] These factors all negatively affect health related quality of life (HRQoL) of patients and their relatives.[76-78] Anti-tumour treatment as well as supportive medication (often steroids and anti-epileptic drugs) may cause side-effects which may further diminish HRQOL.[39, 79] Since HGG patients cannot be cured, the aim of treatment is not only to prolong life, but also to maintain quality of life as long as possible. In this respect, HRQOL is included as a secondary endpoint in a growing number of randomized clinical trials evaluating anti-tumour treatment.[17, 80]

When the patient's condition declines due to tumour progression and further tumour treatment is not an option, the end-of-life (EOL) phase begins. In this phase only supportive treatment is given.[81] In the Netherlands, patients in this phase often no longer visit the neuro-oncology outpatients department, and become dependent on care provided by primary care physicians. Depending on where the patients resides, the general practitioner (GP), the nursing home specialist or the hospice doctor is the coordinating physician. In the Netherlands, only a minority of cancer patients dies in hospital, which probably also holds true for HGG patients.[82, 83]

Patients and their relatives often are anxious about what will happen in the last phase of life. Until now, there are limited data on the EOL phase of these patients. The few existing reports identified symptoms related to increased intracranial pressure (headache, drowsiness), as well as progressive neurological deficits, epileptic seizures, confusion/delirium, fatigue, and dysphagia as the most prominent symptoms.[21, 46, 48]

A better knowledge of the clinical issues for this specific group of patients in the end-of-life phase will improve the information given to future HGG patients and their families as well as the care supplied. We therefore explored the incidence of specific symptoms in the EOL phase in a group of HGG patients.

Patients and Methods

Patients

Adult (> 18 year of age) glioma patients, who had died between January 2005 and August 2008 after being treated for their tumour at the VU University Medical Centre Amsterdam were considered for inclusion in the analysis. Patients with either an initial histological diagnosis of HGG (glioblastoma multiforme, high-grade astrocytoma, high-grade oligodendroglioma or high-grade mixed glioma), or a histological confirmed low-grade glioma (LGG), with clinical and radiological progression suspected for a high-grade tumour following initial treatment were included. According to our definition, the end-of-life phase started once patients presented with progressive disease for which there were no further tumour treatment options, or if patients refused further tumour treatment. Patients who died during tumour treatment were therefore excluded.

Material and Methods

In the EOL phase, patients no longer visited the outpatient clinic on a regular basis. The clinical nurse specialist, however, kept in touch with the patients and/or their families via a telephone-service. Patients and caregivers were invited to call the clinical nurse specialist in case of questions and problems. Otherwise, the clinical nurse specialist contacted the patients and/or their main informal caregiver(s) on a bi-weekly basis and asked for signs, symptoms and problems encountered. In these telephone contacts, using a checklist, the clinical nurse specialist investigated the occurrence of pain, headache, focal neurological deficits, confusion, cognitive disturbances, seizures and incontinence, as well as the level of consciousness, changes in medication (anti-epileptics, steroids) and problems with intake of medication, fluid and food, using a checklist (Figure 1). Furthermore, in the month following death, the course of the disease in the last week before dying was enquired after with the family or the primary care physician.

Figure 1: Checklist used in the telephone interviews

- □ Headache
- □ Pain
- □ Nausea/ vomiting
- □ Cognition
- □ Confusion or agitation
- □ Paresis and mobility
- □ Seizures
- □ Level of consciousness
- □ Intake and problems with intake
- □ Incontinence
- □ Dexamethasone use

Symptoms, signs and treatment in the EOL phase as a whole were retrieved from medical files and the chart of the clinical neuro-oncology nurse specialist. Symptoms and problems arising in the week before death were recorded separately.

Statistical analysis

We used SPSS software 15.0 for statistical analysis.

Results

Demographic and clinical data

Seventy-five consecutive adult HGG patients, who ended all tumour treatment while being treated at our centre, and died between January 2005 and August 2008, were identified. Seventeen (relatives of) patients did not use the telephone service. Nine of these 17 were referred to another institution in the EOL phase and had a contact person over there. The other eight declined the service. Fifty-eight patients were included in this analysis. Of these fifty-eight patients, twelve patients had been diagnosed with a LGG before dedifferentiation to a HGG. Table 1 shows demographic and clinical data.

Table 1 Demographic and clinical data (n = 58)

Sex ○ Male ○ Female	 39 (67%)[a] 19 (33%)[a]	*** clinically and radiological evidenced** **** from diagnosis**
Age at diagnosis, years	52 (18-81)[b]	
Grade ○ Grade III ○ Grade IV ○ Unspecified*	 15 (26%)[a] 41 (71%)[a] 2 (3%)[a]	
History of low grade glioma	12 (21%)[a]	
Survival** in months ○ Grade III ○ Grade IV	 21 (11-86)[b] 12 (0.5-71)[b]	
Length of the end-of-life phase, days	46 (1-294)[b]	
Place of death ○ At home ○ Hospital ○ Hospice ○ Nursing home	 38 (66%)[a] 10 (17%)[a] 5 (8.5%)[a] 5 (8.5%)[a]	

number of patients (percentage) [a] or median (range) [b]

Symptoms and signs in the end-of-life phase

Three of the 58 cases were lost to follow up in the EOL phase and therefore excluded. Two of these patients died in a nursing home, one passed away at home. In Table 2 symptoms and signs occurring anytime in the EOL phase are depicted.

The most frequently reported symptom was decreased consciousness (87% of patients) which, however, was not reported until the last week before death in the majority of patients (73% of these patients). The second most common symptom was dysphagia. This occurred in 71% of cases and often coincided with decreased consciousness. Fifty-two percent of patients experienced progressive neurological deficits (motor deficit, coordination loss and/or aphasia). Seizures were reported in 45% of all patients in the end-of-life phase. Of patients who already had seizures during the course of disease, 53 % also had seizures in the EOL phase. Conversely, of patients who had been free of seizures so far, 11% had their first seizure in the end-of-life phase. Thirteen (52%) of the 25 patients who had seizures in the EOL phase had more than one seizure in this phase. All patients with seizures received antiepileptic drugs. Among the patients who were on anticonvulsive drugs, there were no patients who never had epileptic seizures. In 40% of patients, incontinence was reported to occur before the patient was bed-ridden. Headache, progressive cognitive deficits (memory loss, personality changes, apathy, problems in executive functioning and understanding) and agitation/ confusion all were reported in one third of patients. Next to headache, 25% of patients reported bodily pain, often related to immobilization.

Table 2 Symptoms documented anytime in the EOL phase (n=55)

Symptoms	**Number of patients (percentage)**
Drowsiness/ progressive loss of consciousness	48 (87%)
Dysphagia	39 (71%)
Progressive focal neurological deficits (motor, dysphasia)	28 (51%)
Seizures	25 (45%)
Incontinence*	22 (40%)
Progressive cognitive deficits	18 (33%)
Headache	18 (33%)
Confusion	16 (29%)
Bodily pain	14 (25%)

*before the patient was confined to bed

Additionally reported symptoms

In addition to the symptoms and signs structurally asked for, other symptoms and signs which were additionally reported by the patients and their caregivers are given in Table 3. Twenty-five percent of patients experienced severe fatigue and 20% of patients suffered from nausea or vomiting. Dyspnoea was reported in nine patients (16%): in five cases this was most likely due to pneumonia; in one patient due to pulmonary embolism, while in the remaining three cases the cause of dyspnoea was unclear. Constipation, probably due to morphine use, was severe enough to be reported in five cases. In five patients, symptoms of anxiety and/or depression were mentioned. One patient had severe vertigo due to tumour infiltration in the 8th cranial nerve. Severe side-effects from steroid-use were reported in four cases: two patients suffered from steroid myopathy, one patient developed hyperglycaemia and one patient had a bowel perforation while using steroids. Overall, 44 (80%) patients used steroids in the end-of-life phase.

Table 3 Additionally reported symptoms (n=55)

Symptoms	Number of patients (percentage)
Fatigue	14 (25 %)
Nausea/vomiting	11 (20 %)
Dyspnoea	9 (16 %)
Constipation	5 (9 %)
Anxiety/depressive symptoms	5 (9 %)

Symptoms in the week before dying

Although drowsiness was only present in 13 patients (24%) at the start of the week before dying, this number increased to 48 (87%) of patients during the last week. This also holds true for dysphagia: the number increased from 5 patients (9%) to 39 (71%) patients. In the last week, 28% of all patients experienced at least one seizure.

Cause of death

In 40 patients (73%), the presumed cause of death was brain herniation due to tumour progression. For four other patients, the cause of death was directly tumour-related; these patients died following a seizure (three patients) or a haemorrhage in the tumour (one patient). For eight patients the cause of death was indirectly tumour-related; five patients

died due to an infection (in two cases this concerned an aspiration pneumonia following a seizure), one died from bowel perforation while using steroids, one patient died from pulmonary embolism, and another one suffered traumatic brain damage following an accident and died from urosepsis. In three patients, euthanasia was performed under strict conditions upon a voluntary and well-considered request.

Discussion

The most common reported symptoms in the last phase of our cohort of HGG patients were drowsiness (87%), dysphagia (71%), progressive neurological deficits (51%), seizures (45%), incontinence (40%), progressive cognitive deficits (33%) and headaches (33%) respectively. Of these, drowsiness and dysphagia appeared to occur most frequently in the week before death.

One of the drawbacks of this study is the focus on symptoms specific for brain tumours. The more general EOL symptoms reported in extracranial cancer patients, such as fatigue, mood disturbances, nausea and constipation are probably underreported as these were not structurally asked for.[84, 85] Another restraint is the relatively small number of patients. Despite these limitations, our data are worth reporting, given the lack of studies in this field.

In three earlier studies in patients dying from brain tumours, comparable prevalence rates of increased intracranial pressure symptoms (drowsiness, headaches), neurological deficits, seizures and cognitive deficits were reported.[21, 46, 48] The occurrence of dysphagia, however, differed amongst these studies. Dysphagia was reported in 70% of our cases, more or less comparable to the studies by Oberndorfer[46] and Pace[48], respectively. In contrast, Faithfull described a prevalence of only 10%.[21] This discrepancy in prevalence rates is probably due to the fact that we also denominated patients to be dysphagic if they were unable to swallow due to loss of consciousness. If these patients are excluded, only 14% had (true) dysphagia.

The high prevalence of swallowing difficulties in the last week of life may yield problems in taking medication. The majority of patients used anti-epileptic drugs (AED) and/ or glucocorticoids (dexamethasone) in the last phase of life. About one third of patients suffered from seizures in the last week of life and these may be life-threatening as appeared to be the case in five patients. Since seizures are even a more prominent feature in the end-of-life phase than we had anticipated, continuation of AED's should therefore be recommended, even if oral administration is no longer possible. In view of the fact that most patients stay at home or in a first line care setting, a non-invasive administration route is preferred when patients are unable to swallow at the EOL. Rectal administration of carbamazepine, valproic acid and phenobarbital is available. Otherwise, seizures may be treated with rectal diazepam, intranasal or subcutaneous midazolam or sublingual clonazepam.[65] In the hospital setting, intravenous infusion should be considered.

Urinary incontinence has not been described in former reports concerning the EOL phase of brain tumour patients. In our cohort, it was a relatively early and prominent sign (before the patient was confined to bed) occurring in 41% of cases. Incontinence has often been associated with immobilization, social withdrawal, body image distortion and depression and thus has a major impact on quality of life.[86] Urinary incontinence specifically in brain tumour patients can be caused by the tumour itself, such as may be the case in frontal tumours, or due to impaired cognition and consciousness. Other (reversible) causes may be urinary tract infection, hyperglycaemia and the use of sedatives. In a general cancer population, 29% of patients were incontinent for urine in the EOL phase.[86] Thus, the prevalence of incontinence appears to be relatively high in brain tumour patients.

Of further interest is to compare the prevalence of more 'general' EOL symptoms in HGG patients with other cancer patients. The main symptoms reported in terminally ill cancer patients are fatigue and anorexia, followed by pain, nausea, constipation, delirium and dyspnea.[84, 85] As noted before, these symptoms are probably underreported in our patients, since we did not ask for general symptoms. However, bodily pain was asked for and appeared to occur less frequently in glioma patients (25%) as compared to patients with systemic cancer, where prevalence rates of 60-80% are reported[87]. Despite the fact that we are still unaware of the prevalence of general symptoms in glioma patients in the EOL phase, the disease specific symptoms are prominent. This indicates that the EOL phase of HGG patients cannot be compared simply with a general cancer population. Future studies prospectively exploring the EOL phase of HGG patients are mandatory in order to develop specific palliative care guidelines for these patients and their relatives.

Chapter 2.2

Seizures in high-grade glioma patients: a serious challenge in the end-of-life phase

Eefje M. Sizoo*

Johan A.F. Koekkoek*

Tjeerd J. Postma

Jan J. Heimans

H. Roeline W. Pasman

Luc Deliens

Martin J.B. Taphoorn

Jaap C. Reijneveld

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* equal contribution

Abstract

Background: to analyse the prevalence of seizures and use of anti-epileptic drugs (AEDs) in the end-of-life (EOL) phase of high-grade glioma (HGG) patients and to identify patient characteristics associated with the occurrence of seizures in the last week of life.

Methods: patients were recruited from a cohort of adult HGG patients diagnosed in 2005 and 2006 in three tertiary referral centres for brain tumour patients. Physicians involved in the EOL care for deceased HGG patients were asked to fill in a questionnaire regarding seizures and anti-epileptic treatment both in the last three months and in the last week of life. Data on seizures and use of AEDs before the EOL phase were obtained from medical correspondence and hospital medical charts.

Results: out of 155 deceased patients, data of 92 patients were eligible for analysis. Twenty-nine percent of these 92 patients had seizures during the last week of life; 33% of the patients with and 22% of the patients without a history of seizures. Besides a history of status epilepticus (p=0.047), we identified no other significant risk factors to develop seizures in the last week of life. Seventy percent of all patients used AEDs before the last week of life. In 35% of patients of whom AEDs were tapered, seizures occurred in the last week of life.

Conclusions: our results demonstrate that seizures are a common symptom in HGG patients during the last week of life and emphasize the importance of adequate AED treatment throughout the EOL phase.

Introduction

Epileptic seizures are very common in high-grade glioma (HGG) patients: in 30 - 50% of patients seizures are the presenting symptom and an additional 10-30% will develop seizures during the further course of their disease.[88] Little is known about the occurrence of seizures in the end-of-life (EOL) phase of HGG patients, when the goal of treatment is primarily maintaining quality of life as high as possible. High-grade glioma patients and their relatives fear seizures in the EOL phase[25] and the occurrence of seizures has proven to diminish patients' health-related quality of life.[89, 90] In a pilot study of our group we found that 45% of HGG patients experienced seizures after ending tumour treatment and 28% of patients even had seizures in the last week of life, suggesting seizures to be a serious problem in this disease stage.[47]

During the EOL phase, and particularly in the last week of life, the majority of HGG patients eventually lose consciousness and develop swallowing difficulties, interfering with the intake of oral anti-epileptic drugs (AEDs).[21, 46-48, 65] Since no strict guidelines exist for the anti-epileptic treatment in the EOL phase, currently the decision whether or not to continue AEDs in case of intake problems depends on the doctors' expert opinion. Improved knowledge regarding epilepsy in the EOL phase could contribute to the development of more specific treatment guidelines.

The aims of this study were (1) to systematically evaluate the prevalence of seizures and use of AEDs in the last week of life in a cohort of deceased HGG patients and (2) to identify patient characteristics predictive for development of seizures in the last week of life.

Methods

Subjects

The study population comprised a cohort of adult HGG patients diagnosed in 2005 and 2006 in three Dutch tertiary referral centres for brain tumour patients (VU University Medical Centre, Academic Medical Centre and Medical Centre Haaglanden). Physicians involved in the EOL care of deceased patients (i.e. general practitioners, nursing home physicians, hospice doctors or neurologists) were approached for participation, and asked to fill in a questionnaire regarding the EOL phase of the specific patient. The EOL phase is generally defined as the phase after ending anti-tumour treatment. As the EOL phase ranges widely in duration and the actual beginning is often difficult to determine even in retrospect, questions related to both the last three months and the last week of life. The study protocol was approved by the Ethics Committee of the three participating hospitals.

Study measures

Data regarding seizures *before* the EOL phase were obtained from the medical correspondence and hospital medical charts. We recorded (1) whether a seizure was the presenting symptom, (2) the most severe seizure type (focal, generalized or status epilepticus), (3) the epilepsy burden (one time event, multiple seizures using ≤ one type of AED, multiple seizures using multiple AEDs) and (4) the type of AEDs prescribed.

From the questionnaire filled in by physicians, data were obtained concerning the EOL phase: (1) place of death, (2) the occurrence of seizures in the last week of life and (3) the use and (dis)continuation of AEDs in the EOL phase.

Analysis

SPSS software 15.0 was used for statistical analysis. Descriptive statistics were used to summarise baseline data. Differences between groups were tested using the chi-square test/Fisher's Exact Test for categorical data and either the students T-test or Mann Withney U test for continuous data, depending on the distribution of the tested variable. All tests were two-tailed and $p<0.05$ was considered to be statistically significant.

Results

Subjects

Figure 1 shows the flow chart of patient identification and data collection. Data of seven patients who were reported to use an AED according to the questionnaires could not be confirmed by their hospital medical charts. As there was a gap between the last report in the hospital medical chart and the end of anti-tumour treatment, these cases were excluded from analysis to avoid bias. The median time between patients' death and completion of the questionnaires by the physicians was 27.0 months (range 1.2 - 50.5 months).

Patient and seizure characteristics are outlined in table one. Of the 92 patients, 61 died at home (66%), 13 in a nursing home (14%), 8 in a hospital (9%), 7 in a hospice (8%) and 3 elsewhere (3%). In 38 patients (41%), seizures were the presenting symptom. During anti-tumour treatment, 60 patients (65%) used at least one type of AED: 46 used valproic acid, 27 levetiracetam, 6 phenytoin, 3 lamotrigin, and 1 carbamazepine. No significant differences in sex, age and tumour grade were reported between the 92 patients analysed in this study and the cohort of 155 patients eligible for inclusion (data not shown).

Seizures in the last week of life

Of all evaluated 92 HGG patients, 29% had seizures in the last week of life. No significant differences were identified in baseline characteristics and place of death between patients with and without seizures in the last week of life (table 1). Seizures in the last week of life did not occur more often in patients who experienced seizures before the EOL phase (table 1). Patients with a previous status epilepticus, however, showed a significantly higher seizure incidence in the last week of life (p = 0.047). Seven of the 32 patients without seizures before the EOL phase (22%) had seizures in the last week of life (table 1). In four patients, seizures in the last week were the first seizure ever, and the other three patients had their first seizure ever in the last three months of life after ending all anti-tumour treatment.

Table 1: Patient characteristics and seizure frequency in the last week of life

	Baseline characteristics all patients [a] N (%)	Patients with seizures in the last week of life [b] N (%)
Sex		
▪ Male	68 / 92 (74%)	18 / 68 (27%)
▪ Female	24 / 92 (26%)	9 / 24 (38%)
Age at diagnosis		
▪ < 60 years	51 / 92 (55%)	16 / 51 (31%)
▪ > 60 years	41 / 92 (45%)	11 / 41 (27%)
Tumour grade (WHO)		
▪ Grade 3	12 / 92 (13%)	3 /12 (25%)
▪ Grade 4	80 / 92 (87%)	24 / 80 (30%)
Seizures anytime during disease		
• Yes	60 / 92 (65%)	20 / 60 (33%)
• No	32 / 92 (35%)	7 / 32 (22%)
Seizure burden (before EOL phase)		
• No seizures	32 / 92 (35%)	7 / 32 (22%)
• 1 seizure, ≤ 1 AED	10 / 92 (11%)	3 /10 (30%)
• > 1 seizure, ≤ 1AED	29 / 92 (31%)	10 / 29 (35%)
• > 1 seizure, ≥ 2 AED	21 / 92 (23%)	7 / 21 (33%)
Type of seizures		
• Focal	11 / 92(12%)	1 / 11 (9%)
• Generalized	43 / 92 (47%)	15 / 43 (35%)
• Status epilepticus	6 / 92 (7%)	4 / 6 (67%)*

[a] data obtained from medical chart; [b] data obtained from physician's questionnaire; * p=0.047 (Fischer's' exact)

Anti-epileptic treatment in the EOL phase

According to the questionnaire filled in by the physicians, 64 HGG patients (70%) used AEDs before the last week of life. In 29 cases, AEDs were tapered close before death due to

difficulties with oral intake. In 10 of the 29 patients of whom AEDs were tapered (35%), seizures occurred during the last week of life. In 35 patients whose AEDs were continued until death, 15 patients (43%) still experienced seizures in the last week. None of the patients without seizures before the EOL phase received prophylactic AEDs.

Discussion

To our knowledge, this is one of the first studies on the prevalence of seizures and its anticonvulsant treatment in the EOL phase of HGG patients from a well-defined cohort. The retrospective design, which is a generally acknowledged practice in EOL research, might have caused recall bias of our results and thus requires cautious interpretation of the data. Unfortunately, prospective data collection in this patient population in this disease stage is subjective to substantial bias, as the identification of patients approaching the EOL is often complicated.[91] As a precaution, we excluded patients of whom the information in the medical chart was incomplete.

Our results corroborate with a previous retrospective study which showed a prevalence of 36.9% of seizures in the last month before death and confirms that seizures are a common symptom during the EOL phase.[21, 46-48, 92] Apart from a history of status epilepticus, we were unable to establish predictive factors for the occurrence of seizures in the last week before dying.

Our findings are mainly focused on the last week before dying, as most intake problems develop at this time, requiring an alteration in the administration (routes) of AEDs. [8] About one third of the patients with a history of epilepsy developed seizures in the last week, irrespective whether AEDs were tapered close to death or not, which suggests a relative inefficacy of AEDs in preventing seizures towards the EOL. Almost a quarter of patients without a history of epilepsy had seizures during the last week of life. The pathogenesis of the relatively high seizure frequency in the EOL phase remains unknown. Both tumour progression and the development of metabolic disturbances during the last stage of the disease might cause an elevated seizure risk in the last week of life. Changes in administration routes coinciding with insufficient drug absorption could lead to subtherapeutic AED levels, which might explain the occurrence of seizures in patients whose AEDs were not tapered.

This retrospective cohort study demonstrates the high frequency of seizures in the EOL phase and shows the complexity of effective AED treatment throughout the disease course in HGG patients with a history of seizures. To improve seizure control in the EOL phase, the development of treatment guidelines for both recurrent and *de novo* seizures is warranted. Furthermore, the occurrence of seizures in the EOL phase in patients without a history of epilepsy raises the question whether prophylactic AEDs should be prescribed in all HGG patients. Future studies should focus on the identification of risk factors for the

development of *de novo* seizures in the EOL in glioma patients and on alternative AED administration in the EOL phase, such as buccal or intranasal routes, contributing to an improvement of quality of life in HGG patients.

Chapter 3.1

Health-Related Quality of Life in Patients with High-grade Gliomas

Eefje M Sizoo

Andrew Bottomley

Martin J.B. Taphoorn

Adapted from:

- **Sizoo EM** and Taphoorn MJB. Health-related quality of life in patients with high-grade gliomas. In: M.A. Hayat (ed.), *Tumors of the central nervous system*. Volume 3. DOI 10.1007/978-94-007-1399-4_32, © Springer Science+Business Media B.V. 2011.
- Taphoorn MJB, **Sizoo EM**, Bottomley A. *Review on quality of life issues in patients with primary brain tumours.* The Oncologist 2010; 15:618-626

Abstract

Health-related quality of life (HRQOL) has become an important outcome measure in clinical trials in high-grade glioma patients. HRQOL is assessed using self-reported, validated questionnaires, addressing physical, psychological, emotional, and social issues. In addition to generic HRQOL instruments, disease-specific questionnaires have been developed, including for brain tumour patients. For the analysis and interpretation of HRQOL measurements, low compliance and missing data are methodological challenges. HRQOL in high-grade glioma patients may be negatively affected by the disease itself, as well as by side effects of treatment. But treatment with surgery, radiotherapy and chemotherapy may improve patient functioning and HRQOL, in addition to extending survival. Although HRQOL has prognostic significance, it is not superior to well-known clinical parameters. In clinical practice, assessment of HRQOL improves physician-patient communication and could thereby in turn improve the patient's quality of life. More focused HRQOL questionnaires are needed for common use in daily practice.

Introduction

High-grade gliomas (HGG) are among the most feared diseases. Not only is the patient inflicted by an incurable malignancy, the disease directly involves the brain, thereby threatening the "being" of the patient. Patients diagnosed with a HGG have a poor prognosis and despite intensive treatment with surgery, chemotherapy, radiotherapy, tumour recurrence inevitably occurs. Eventually, patients will die from tumour progression. Thus, in this patient category, the aim of treatment is not only to prolong life, but also to maintain quality of life as long as possible.[80] Combined radiochemotherapy and other new treatment strategies may not only increase the duration of survival, but may also have severe side-effects including a risk of toxicity.[9, 18] Therefore, the benefits of extended survival and/or progression delay have to be carefully balanced against side-effects of treatments and their potential negative impact on functioning and quality of life. Hence, the concept of health-related quality of life (HRQoL) should be included as an outcome measure supplementing traditional end points such as (progression-free) survival time in clinical trials evaluating the effect of treatment. Measuring HRQoL emerged in the early nineties in the medical oncology literature. In brain tumour patients, however, it has long been a neglected issue.[9] Since the beginning of this century, HRQoL has become a secondary outcome measure in a growing number of clinical trials evaluating glioma treatment.[93]

Outcome Measures in Glioma Research

Next to the classic outcome measures such as progression free survival and overall survival, the effect of a brain tumour and its treatment on the patient's functioning and well-being should be assessed. It is important to make a distinction between impairment, disability, and handicap.[94] Impairments are the direct consequences of disease demonstrated by physical examination. Disability is the impact of the impairment on a patients' ability to carry out activities. Finally, handicap is the consequence of disability on the patients' well-being. Impairment is considered to be a "hard" measure compared to disability and handicap, which are more relevant for the patient's functioning. Impairment in a brain tumour patient can be evaluated using neurological and neuropsychological examination. Disability can be determined by using scales, such as the Barthel index (BI), an instrument on a persons' ability for selfcare[95], or the Karnofsky Performance Scale (KPS), an assessment tool to measure a patient's ability to carry out activities of daily living.[96] The Modified Ranking Handicap Scale (MRHS) is frequently used to measure handicap. This is a six-point scale ranging from 0 (no symptoms) to 5 (severe handicap/ totally dependent; requiring attention day and night)[97]. It should be noted that there are no specific disability or handicap scales for brain tumour patients, besides the Spitzer scale[98] which is hardly used.

Although these outcome measures provide information on the influence of the tumour on a patient's functioning in daily life, they do not fully reflect the effect of the tumour on the patient's HRQoL.

Assessing Health-Related Quality of Life: A Patient-Reported Outcome Measure

To measure quality of life, the concept of HRQoL was developed. HRQoL is defined as a person's self-assessed ability to function in the physical, psychological, emotional, and social domains of day-to-day life.[99] This complex patient-reported outcome (PRO) measure demands a multidimensional instrument, and preferably should be assessed using a self-reported questionnaire. As an alternative, a (semi)-structured interview could be undertaken with the patient. At present, no single gold standard tool exists to measure HRQoL. Both generic and disease specific tools have been developed and validated to assess HRQoL, both for cancer patients and in the non-cancer population. For cancer patients, the most common tool in use was developed by the European Organisation for Treatment and Research of Cancer (EORTC) quality of life group: the EORTC QLQ-C30.[100] This is a 30-item measure designed to assess HRQOL of cancer patients. Table 1 shows the construction of this measure.

Table 1 Content of the EORTC QLQ c30 version 3.0

	Number of items	Range item scores	Item numbers	Scale scores
Global health status/QOL				
Global health status/QOL	2	1-7	29,30	0-100
Functioning scales				
Physical	5	1-4	1-5	0-100
Role	2	1-4	6, 7	0-100
Emotional	4	1-4	21–24	0-100
Cognitive	2	1-4	20, 25	0-100
Social	2	1-4	26, 27	0-100
Symptom scales				
Fatigue	3	1–4	10, 12, 18	0–100
Nausea/vomiting	2	1–4	14, 15	0–100
Pain	2	1–4	9, 19	0–100
Single-item scales				
Dyspnoea	1	1–4	8	0–100
Sleep disturbance	1	1–4	11	0–100
Appetite loss	1	1–4	13	0–100
Constipation	1	1–4	16	0–100
Diarrhoea	1	1–4	17	0–100
Financial impact	1	1–4	28	0–100

The EORTC BN20 was specifically developed and validated for patients with brain cancer.[101] It includes 20 items and assesses visual disorder, motor dysfunction, various disease symptoms, treatment toxicity, and future uncertainty (Table 2). This tool should be used in combination with the EORTC QLQ C30 and is often used in clinical trials in glioma patients undergoing chemotherapy and radiation therapy. The items on both the EORTC QLQC30 as well as the EORTC BN20 measures are scaled, scored, and transformed to a linear scale (0–100). Differences of at least 10 points are classified as a clinically meaningful changes in a HRQoL parameter. Changes over 20 points are classed as large effects.

Table 2 Content of the EORTC BN20

	Number of items	Range item scores	Item numbers	Scale scores
Subscales				
Future uncertainty	4	1–4	1-3, 5	0-100
Motor dysfunction Communication	3	1–4	10, 15, 19	0-100
deficits	3	1–4	11-13	0-100
Visual disorder	3	1–4	6-8	0-100
Single-item scales				
Headaches	1	1–4	4	0-100
Seizures	1	1–4	9	0-100
Drowsiness	1	1–4	14	0-100
Bothered by hair loss	1	1–4	16	0-100
Bothered by itching skin	1	1–4	17	0-100
Weakness of legs	1	1–4	18	0-100
Difficulty controlling bladder	1	1–4	20	0-100

Another widely used (brain) cancer specific HRQoL tool is the Functional Assessment of Cancer Therapy (FACT). Next to a general FACT module (FACT-G), a brain cancer specific module was developed (FACT-Br) by Weitzner et al., combining the FACT-G with a brain subscale.[102] Table 3 shows the construction of this measure. Compared to the EORTC questionnaires, the FACT modules are more focused on psychosocial aspects and less on symptoms.

Table 3 Content of the FACT-Br Version 4

	Number of items	Range item scores	Item numbers	Range scale scores
FACT-G subscales:				
Physical well-being	7	0-4	GP1-GP7	0-28
Social well-being	7	0-4	GS1-GS7	0-28
Emotional well-being	6	0-4	GE1-GE6	0-28
Functional well-being	7	0-4	GF1-GF7	0-28
Brain subscale	19	0-4	Br1-Br18	0-76

An alternative recently developed PRO measure for brain tumour patients is the MD Anderson Symptom Inventory Brain Tumour Module (MDASI-BT), which has been validated for both primary brain tumour patients and patients with brain metastases.[103, 104] Given that this questionnaire addresses symptoms, it has similarities with the EORTC QLQ-BN20. The MDASI-BT might be useful to describe symptom occurrence throughout the disease trajectory and to evaluate interventions designed for symptom management.

When patients are unable to self-report, for example due to cognitive disturbances, one might consider using proxies or health care professionals to rate the patient's quality of life. In the past, this method was regarded far from optimal. However, a recent review found moderate to good agreement in various studies evaluating the concordance between patient and proxy measures.[105] Mixed results have been reported for patients and health care providers. Proxies and health care providers tend to report more HRQoL problems than do patients themselves, and proxy ratings tend to be more in agreement with the patients' physical HRQoL domains compared to the psychological domains. Also, the agreement between

patients, and proxy HRQoL reports was evaluated specifically in brain tumour patients. The EORTC QLQ-C30, EORTC-BN20, and the FACT-Br showed moderate agreement between the patients' and proxies assessment of HRQoL, provided cognitive functioning was not severely affected.[106, 107] The use of a nonpatient-based report should, therefore, only be used when patients are incapable of self-report.

One may anticipate that patients with more severe clinical symptomatology and quality of life difficulties are less likely to complete questionnaires because it is too burdensome. Because these patients (noncompliers) will be excluded from the analysis, this may lead to an overestimation of the actual quality of life.[107] Indeed, the interpretation of serial measurements of HRQOL is affected by missing data.[108] Apart from the selection bias due to the clinical condition, in both patients and observers compliance with filling out questionnaires decreases over time. The main cause of missing data, however, is administrative failure. Administrative failure arises, for example, when questionnaires are not distributed by the doctor or nurse, distributed at the wrong moment or handed out without instructions. Methodological and patient-related factors can also lead to missing data. Methodological problems may arise due to the study design, for example, using HRQoL instruments unknown to the clinicians who are supposed to hand these out. Other patient-related factors than the clinical situation encompass lack of motivation on the part of the patient, misunderstanding instructions, and/or filling out questionnaires incorrectly. Several approaches can be undertaken to minimize avoidable loss of data on HRQoL.[108] Of the utmost importance is that research staff and patients understand the relevance of these data to be collected. While writing a research protocol, HRQoL assessment should be explicitly defined as a trial endpoint, the way of data collection should be specified, and the analysis of HRQoL parameters should be described in order to prevent methodological problems. Administrative problems can be challenged by the training staff in charge of data

collection to check for completeness of assessments at submission, document reasons for missing data, and structurally contact patients who miss appointments. To reduce patient-related missing data, it is important to motivate patients. At trial entry, patients should be fully informed regarding the importance of HRQoL assessments, how they will be done, and when they will be done. Multiple questionnaires addressing similar issues in a different format and/or a high frequency of assessments will result in a low overall compliance.

Cognitive functioning versus HRQoL

Cognition encompasses functions such as language, memory, attention, and executive functioning – core functions of the human brain. Cognitive disturbances can be caused not only by the tumour itself or by tumour-related epilepsy, but also by the tumour treatment (surgery, radiotherapy, chemotherapy) as well as by supportive treatment (anti-epileptic drugs, corticosteroids).[109] Cognitive disturbances can cause burdensome symptoms for patients; therefore, it is assumed that impaired cognitive function reduces quality of life. The direct relation between cognitive functioning and HRQoL in glioma patients was only demonstrated in one study.[110]

Health-Related Quality of Life in Patients with High-grade Glioma

As one would expect, the majority of newly diagnosed HGG patients have a significant impaired level of HRQoL compared to healthy controls.[111, 112] In patients with a reduced level of HRQoL at the time of diagnosis, the quality of life will further decrease over time, while in patients not significantly distressed, the HRQoL scores may improve.[12] In comparison to other neurological diseases of the central and peripheral nervous system, patients with HGG experience the same level of HRQoL.[113] When comparing HGG patients to other cancer patients, such as lung cancer patients, again similar quality of life results were found in both patient groups.[112]

Several tumour-related factors in HGG patients can have an impact on perceived quality of life. Patients with HGGs experience worse quality of life than patients who have a low grade glioma.[114] However, between patients diagnosed with glioblastoma multiforme (grade IV) and patients diagnosed with anaplastic astrocytoma (grade III), no differences in HRQoL scores exist at the time of diagnosis.[111] Next to the grade, the size of the tumour and the location in the brain correlate with HRQoL. Large tumours, tumours in the nondominant hemisphere, and tumours located anteriorly in the brain are associated with poorer HRQoL scores.[114]

Disease-specific signs and symptoms have a major impact on quality of life. Neurological signs and symptoms as seizure frequency[90], motor deficits[106] and functional status [110] have proven to diminish HRQoL. Surprisingly, no deleterious effect of dysphasia on HRQOL has

been established.[106] As to nonspecific signs and symptoms in patients with systemic cancers, fatigue and depression are identified as the leading factors diminishing HRQoL.[115] Also, in high-grade glioma patients, fatigue is one of the most common symptoms and, therefore, one of the leading symptoms of decreasing quality of life.[75] Clinically significant symptoms of depression have shown to be present in a significant portion of HGG patients, and are probably higher than the prevalence in the general cancer population. Thus, depressive symptoms are a serious clinical issue negatively affecting HRQoL in these patients.[75] Disease recurrence has a significantly deleterious impact on a patients' life. Patients carry a significant symptom burden and neurological deficits are more severe at the time of recurrence compared to the initial presentation.[110] Not surprisingly, HRQoL of patients with tumour recurrence is more comprised compared to patients without recurrence at the same time from diagnosis.[116, 117]

Effect of (Tumour) Treatment on Health-Related Quality of Life

Effect of Surgery on HRQoL

Reduction of tumour mass may alleviate neurological symptoms and cognitive deficits; thereby, improving quality of life. On the other hand, surgery and perioperative injuries may cause neurological deficits and focal cognitive deficits as a result of damage to normal surrounding tissue.[109] Although these deficits are often transient, they may result in a temporarily lower perceived quality of life. In a nonrandomized study, patients who had undergone a gross-total resection had both a longer survival and a better HRQoL than patients who only had a biopsy.[12] Clearly, these results have been biased because the selection of patients for resection versus biopsy depends on factors as tumour size, tumour location, multi-focality, and performance status. Finally, the HRQOL in patients who had undergone a gross-total resection increased over time. Therefore, it appeared from this study that the benefit of resection in terms of quality of life outweigh the early side-effects of surgery.

Effect of Radiotherapy on HRQoL

The benefit of radiotherapy is well-established in the treatment of HGG patients, because tumour progression is postponed and overall survival extended. By stabilizing disease and delay progression, quality of life can be maintained for a longer period than without radiation. Side-effects of cranial radiotherapy, however, of which cognitive deterioration is most feared, may negatively affect HRQoL. Radiation side-effects in the brain can be divided in acute radiation encephalopathy, early-delayed radiation encephalopathy and late-delayed encephalopathy. Acute and early-delayed radiation encephalopathy, occurring during or

shortly following radiotherapy, may result in drowsiness and fatigue. Because these side-effects are nearly always completely reversible, they may only temporarily affect HRQoL. By contrast, late-delayed radiation encephalopathy which occurs months to years after radiotherapy, may result in progressive cognitive decline.[109] Two randomized studies evaluating the combination of chemotherapy and radiation versus radiation therapy alone included HRQoL as an outcome measure.[17, 20] No negative effects of radiotherapy on quality of life were observed in anaplastic oligodendroglioma patients and patients with glioblastoma multiforme with a good performance status. On longer follow-up, >1.5 year after completion of radiotherapy, HRQoL scores of HGG patients without progression even improved compared to scores at the start of the treatment. In long term (i.e., >2 years from initial treatment) HGG survivors without disease progression who all had initial radiotherapy, even HRQoL scores were observed meeting the level of healthy controls, which may partly be explained by response shift, i.e., that patients over time more readily accept their situation.[117] Specifically in the elderly population (age >70 years), a moderate survival benefit from radiotherapy has been established for patients who had a good performance status at the start of the treatment. More importantly, HRQoL, performance status and cognitive functions did not further deteriorate compared to the observation arm of this study, in which patients only received supportive care.[16]
Reirradiation in HGG patients is increasingly applied because patients live longer following their initial treatment. Reirradiation should be considered in patients with an adequate performance status (KPS ≥70) applying focal radiation treatment after an interval from initial treatment of at least 6 months.[118] The effect of reirradiation, specifically on HRQoL, was only evaluated in one small study[119] with a median follow-up of 9 months. The majority of patients (80%) judged their general health status after reirradiation to be stable or even improved compared to before treatment; in 20% of patients, their perceived general health status declined. Scores for physical functioning, cognitive functioning and fatigue remained stable in nearly all patients.

Effect of Chemotherapy on HRQoL

In 2005, a large randomized controlled EORTC trial showed that the combination of temozolomide chemotherapy and radiotherapy significantly prolonged survival in patients with newly diagnosed glioblastoma multiforme compared to patients treated with radiotherapy alone.[9] The effect of this new treatment modality on HRQoL was evaluated separately.[17] During treatment and follow-up, in both treatment groups changes over time in 7 preselected HRQoL domains were not substantial during the first year of follow-up, provided there was no progression of disease. For several scales, scores even improved over time. However, during treatment, the patients in the combination treatment group reported more side effects (nausea, vomiting, appetite loss and constipation) compared to the radiotherapy only group, which can be attributed to the use of temozolomide and

antiemetics. Furthermore, during adjuvant temozolomide treatment, social functioning was worse in the intensive treatment group. Overall, it can be concluded that the addition of temozolomide during and after radiotherapy significantly improved survival without a long-lasting negative effect on quality of life.

As for treatment of patients with anaplastic oligodendroglioma, adjuvant treatment with combined procarbazine, CCNU (lomustine), and vincristine (PCV) chemotherapy after radiotherapy significantly prolongs progression-free survival, but not overall survival[19]. With respect to HRQoL, patients receiving PCV chemotherapy show a significant increase in nausea/vomiting and appetite loss during and shortly following treatment compared to patients only receiving radiotherapy. Furthermore, patients on PCV chemotherapy report more drowsiness. These differences, however, resolve over time: after 1 year follow up, no longer differences were observed in HRQoL between treatment groups.[20] Overall, there is a short-lasting negative impact of PCV chemotherapy on HRQoL during and shortly after treatment, but no long term effects or HRQoL have been established. More importantly, because PCV chemotherapy postpones tumour progression, the impact of progression on well-being and HRQoL should be evaluated in future studies.

In recurrent glioma, the median survival is short and treatment so far is only modestly effective. Because HRQoL measurements encompass assessment of both functioning ability and toxicity from therapy, HRQoL outcomes are of equal importance as survival in this patient group.[116, 120] Patients with recurrent anaplastic astrocytoma or glioblastoma multiforme successfully treated with temozolomide achieve a statistically significant improvement in a portion of the HRQoL domains while patients with disease progression reported statistically significant deterioration in most HRQoL domains.[116, 120] Thus, there is HRQoL benefit from temozolomide treatment for the period of stable disease due to treatment before disease progression occurs. The effect of temozolomide on HRQoL in recurrent glioblastoma has been compared with the effect of procarbazine in a randomized study. Patients receiving procarbazine showed deterioration in most HRQoL domains during treatment, whereas patients treated with temozolomide improved while on treatment.[116] Although temozolomide chemotherapy has largely replaced PCV chemotherapy in glioma patients due to fewer side effects and improved tolerability, HRQoL data on chemotherapy in elderly HGG patients with poor performance status, as well as in the recurrent setting are scarce.[18]

Effect of Supportive Treatment on HRQoL

Symptomatic medications prescribed for glioma patients often include anti-epileptic drugs (AED) and steroids (dexamethasone). Because the occurrence of seizures can diminish HRQOL, it can be assumed that treatment with AEDs would improve quality of life. Conversely, an adverse effect of AED on cognition has been demonstrated.[121] This, in turn, can have a negative effect on the quality of life. A study examining the impact of seizures

and AED on cognition and quality of life showed both cognitive functions as well as HRQOL to deteriorate. The cognitive deficits could primarily be ascribed to the use of antiepileptic drugs, whereas the low HRQOL scores were mainly related to poor seizure control. [90] Dexamethasone reduces peritumoural oedema and is prescribed to alleviate neurological symptoms, thereby improving quality of life. On the other hand, common side-effects are myopathy, gastro-intestinal complications, hyperglycaemia, and psychiatric complications (mainly agitation or depression). Because these side-effects are related to the prescribed dosage, steroids should be tapered or maintained at the lowest effective dose.[122]

Health-Related Quality of Life in Clinical Practice

Old age and low functional status (Karnofsky Performance Status <70) have proven to be poor prognostic factors for survival in patients with HGGs. In daily practice, these prognostic factors are used to select patients who will probably benefit from aggressive treatment and patients who will probably not. HRQoL parameters have shown to be independent prognostic factors in various types of cancers.[123] At present, the prognostic value of baseline HRQoL data in predicting survival of HGG patients is questionable. Hitherto, four relatively large studies have been published about this subject. Two analyses using FACT scores for prognosis were performed. The first analysis has demonstrated patients with high scores on the FACT-G to have an enhanced survival compared to patients with low scores.[124] The second one, using the FACT-Br in combination with a five-item linear analogue scale assessment (LASA) also found a relation between high HRQoL scores and improved survival in univariate analysis. However, HRQOL was closely related to functional status and after correction for this in a multivariate analysis, no prognostic significance of HRQoL scores remained. [111] Two EORTC brain tumour studies regarding this issue were analysed by Mauer et al. [123] Classical analysis of EORTC-QLQ C30 subscores, controlled for major prognostic factors as age and performance status, identified cognitive functioning, global health status, and social functioning as statistically significant prognostic factors for survival in glioblastoma patients. In patients with anaplastic oligodendrogliomas, emotional functioning, communication deficit, future uncertainty, and weakness of legs were found to be significant prognostic factors. [125] In a more sophisticated boot-strap analysis, HRQoL scales were added to other predictive factors in a prognostic model. It came out that the HRQoL scales did not improve the prognostic value of known clinical factors. More importantly, fewer parameters are required in the prognostic model using clinical factors compared to the model using HRQoL data. From these analyses it can be concluded that, although various HRQoL scales have prognostic value, they have no additional value over already known clinical factors.

However, HRQoL data may have value in daily clinical practice. Routine HRQoL measurements in oncology patients visiting the outpatient department, with information provided to physicians, have shown to have a positive effect on physician-patient

communication. In some patients, these measurements improved HRQoL and emotional functioning. However, measurement of HRQoL, symptoms, and functioning are still far from being implemented in daily practice. In the future a core set of standard and disease specific questions repeated at key points of the disease trajectory (beginning of treatment, midtreatment, during follow up, at relapse) should be implemented to allow comparison over time. A small set of focused HRQoL questions could be used at each visit (for example, during treatment the focus could be on side effects). Furthermore, clear interpretation of scores is important and decision guidelines should be provided to the clinicians [126].

Chapter 3.2

Measuring health-related quality of life at the end of life in high-grade glioma patients using a proxy-reported retrospective questionnaire

Eefje Sizoo*

Linda Dirven*

Jaap Reijneveld

Tjeerd Postma

Jan Heimans

Luc Deliens

Roeline Pasman

Martin Taphoorn

In preparation

* Equal contribution

Abstract

Objective

To develop, validate, and report on use of a retrospective proxy-reported questionnaire measuring health-related quality of life (HRQoL) in the end-of-life (EOL) phase of high-grade glioma (HGG) patients.

Methods

Items relevant for the defined construct were selected using existing questionnaires, topics identified as important in literature, and expert opinion. Psychometric properties, content validity and internal consistency, were determined and the questionnaire was subsequently adapted. Proxy-reported HRQoL data of HGG patients in the EOL, including changes over time, were analysed.

Results

Twenty-nine items were selected covering seven domains; physical comfort, physical and cognitive functioning, psychological, social and spiritual well-being, and overall quality of life. Relatives of 83 deceased HGG patients completed the questionnaire. Content validity was assessed to be adequate. Internal consistency in the domains varied from reasonable to good. Two items were excluded due to poor psychometric properties.

Symptom burden increased (p<0.01), except for nausea (p=0.058), as death approached. Cognitive, physical and psychological functioning deteriorated over time (all p<0.01). Acceptance of disease seemed to increase slightly towards death, but this was not significant (p=0.058). Scores for social activities and family life were low (≤50), whereas scores for support and dignity were high (>50). Moreover, overall quality of life was rated as poor, mean(SD) of 29(26).

Conclusion

Measuring HRQoL at the EOL of HGG patients with a retrospective, proxy-reported questionnaire was feasible, yielding a validated instrument. HRQoL was poor and deteriorated as death approached.

Introduction

Despite aggressive anti-tumour treatment, patients with high-grade glioma (HGG) have a poor prognosis and cannot be cured from their disease.[4, 9] Inevitably, the end-of-life (EOL) phase will commence when tumour directed treatment is no longer possible and the condition of the patient deteriorates. Palliative care in this stage becomes of paramount importance, aiming to preserve or improve health-related quality of life (HRQoL) of patients and their families.[127]
The EOL phase of HGG patients is distinctive from the EOL phase of the general cancer population.[49] Patients with HGG not only have cancer, but also a progressive brain disease. Several studies have reported on the EOL phase of HGG patients demonstrating that the symptom burden of HGG patients is high and that disease-specific symptoms such as cognitive dysfunction, seizures and progressive neurological deficits are common.[25, 46-49, 92] It is suggested that especially these disease-specific factors contribute to a lower HRQoL in the EOL phase[25, 26, 45], but data are lacking so far.

HRQoL is considered as a multidimensional construct covering physical, psychological, social and spiritual aspects.[99, 128] Numerous HRQoL instruments are available, differing considerably. There is no consensus on the number of relevant domains to measure HRQoL nor on the content of these domains.[128] Generic HRQoL instruments generally do not capture experiences unique to the dying process, such as comfort, dignity and spiritual well-being.[128-131]

Several instruments have been developed to measure HRQoL in the EOL phase or in the palliative care setting specifically [132-135], but there is no measure that includes all domains that are thought to be relevant for HGG patients. In addition, these instruments are patient-reported outcome measures and therefore only suitable for prospective research. However, prospective studies on EOL in HGG patients applying patient-reported measures are difficult if not impossible, since these patients not only have a poor health status but are often cognitively impaired or incompetent, therefore not being able to complete questionnaires. In EOL research, retrospective studies relying on reports by formal and informal caregivers (proxies) are therefore widely accepted. [91]

To date, no questionnaire exists to retrospectively measure HRQoL in the EOL phase of HGG patients. Therefore, we developed a new proxy-reported questionnaire, to retrospectively measure HRQoL in HGG patients in the EOL, and here report on the construction, validation and first results of this questionnaire.

Methods

I. Development of the HRQoL questionnaire

Construct

The demarcated subject of measurement (so-called construct) for this study is HRQoL of HGG patients in the EOL phase, measured retrospectively by proxies. Individuals confronting death define HRQoL differently from those not facing imminent death.[136] In the literature, seven domains are identified as important aspects of HRQoL in the EOL phase and include (1) physical comfort, (2) physical functioning, (3) cognitive functioning, (4) psychological well-being, (5) social well-being, (6) spiritual well-being and (7) overall quality of life.[128, 130]

Development of the questionnaire (item selection)

In order to reduce the response burden for proxies, it was decided not to include complete questionnaires covering a specific domain, but only relevant items. Items relevant for the defined construct were selected using existing questionnaires in HRQoL and EOL research.[100-102, 137, 138] In addition, aspects relevant for the seven predefined domains which were previously identified as important for HGG patients in the EOL phase [21, 25, 46, 47], and clinical observation and expert opinion of experienced neuro-oncologists (JCR, TJP, JJH and MJB) and EOL experts (LDe and HRWP) were used to construct items. Items were related to the last three months before death and/or the last week before death.

Similar to the generic EORTC QLQ-C30 questionnaire, an adjectival scale was chosen for most HRQoL items; responses ranged from 'not at all', 'a little', 'quite a bit' to 'very much' or from 'no', 'more or less' to 'yes'. Items formulated using an adjectival scale are easily understood and quantified, and force respondents to give a meaningful reply. Overall quality of life was evaluated on a 7-point Likert scale, ranging from 'very poor' to 'excellent'. To reduce the amount of missing data and to prevent proxies from randomly filling in items, most items included the response option 'unknown'.

Psychometric properties of the questionnaire

First, the content validity was determined. Content validity is 'the degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured'.[139] One aspect of content validity is face validity, defined as 'the degree to which a measurement instrument, indeed, looks as though it is an adequate reflection of the construct to be measured'.[139] The purpose of the content validation is to assess whether the questionnaire represents the construct under study; the HRQoL in the EOL phase of HGG

patients. Content validation is a qualitative assessment, by definition subjective in nature and assessed based on expert opinion.

Next, the internal consistency of multi-item scales was assessed. Internal consistency is defined as 'the degree of relatedness among the items' [139] and is a measure of the extent to which items assess the same construct. To do so, Cronbach's alphas(α) were determined as well as inter-item correlations (Spearman's rho (r_s)). The optimal value for Cronbach's alpha is between 0.7 and 0.9. Inter-item correlations should range between 0.2 and 0.9: items that are not correlated with any of the other items (<0.2) could be omitted immediately, whereas items that are correlated highly are likely to measure the same.

Based on this psychometric evaluation and the results of an analysis of missing data (to determine how often the proxy opted 'unknown' for a specific item), the questionnaire was adapted. See the appendix for the final questionnaire.

II. HRQoL in the EOL phase of HGG patients

Subjects

Proxies of deceased patients from a cohort of adult patients diagnosed with HGG in 2005 and 2006 in three tertiary referral centres for brain tumour patients (VU University Medical Centre Amsterdam, Academic Medical Centre Amsterdam, and Medical Centre Haaglanden The Hague, the Netherlands) were approached for participation. Proxies were identified through information retrieved from the medical charts or by the physician who was involved in the EOL care of the deceased patient.[56]

Proxies were approached by mail with information on the study and a reply form and envelope. Proxies were requested to indicate if the researchers could contact them for further information on the study or if they declined any interest in participation. If proxies indicated they wanted to participate in the study, questionnaires on HRQoL in the EOL phase were sent to them.

The Medical Ethics Committees of each participating centre approved the study protocol and all proxies provided written informed consent.

HRQoL measurements

Data on HRQoL of the patients were collected retrospectively. Proxies completed the questionnaire after death of the patient and the scales referred to the last three months and/or the last week before death.

All ordinal items and/or scales in the HRQoL questionnaire were converted to 0-100 scales using the EORTC QLQ-C30 algorithm.[140] On symptom scales (physical comfort domain), a higher score represents *worse* HRQoL, whereas on functional and well-being scales (physical, cognitive, psychological, social and spiritual domains) and the quality of life scale, a higher score represents *better* HRQoL. Items with a nominal character are reported separately. Moreover, scores >50 were classified as 'high' and scores ≤50 as 'low'.

Statistical analysis HRQoL

Demographic and clinical baseline characteristics for patients and proxies were described using descriptive statistics. For HGG patients, HRQoL in the last three months and/or the last week before death were described.

To determine if the HRQoL scores of the patients on the different domains significantly changed over time, HRQoL scores three months before death and one week before death were compared using a Wilcoxon Signed Rank Test. To reduce the amount of missing items, last observation carried forward was used for items for which no sudden improvement/deterioration was expected in the last week of life.

To analyse the data, SPSS version 20.0 software (SPSS, Chicago, IL, USA) was used. All tests were two-tailed and $p < 0.05$ was considered to be statistically significant.

Results

Subjects

A total of 223 patients diagnosed with HGG in 2005 and 2006 were identified in the participating centres. Of these, 39 patients were still alive, 4 were emigrated and 25 were not traceable. Proxies of the remaining 155 deceased patients were considered eligible for inclusion. Proxies of 131 patients could be identified and approached for participation. Forty-eight of these proxies either did not respond or declined participation. Thus, a total of 83 proxies participated in this study. The proxies completes the questionnaire about 27 (18-34) months (median, interquartile range) after the patient died.

Proxies were mostly female (64%) with a median (range) age of 60 (30-86) years. Proxies were the partner of the deceased patient in 80% of patient-proxy dyads, and the parent, child and sibling, in 11%, 7% and 2% respectively. Patients were on average 62 years at the time of diagnosis and mostly male (64%). Further patient and proxy characteristics are outlined in table 1. Of notice, respondent burden for completing the questionnaire was found to be limited.

I. Development of the HRQoL questionnaire

Twenty-nine items were selected to be relevant for the construct to be measured, covering seven domains including physical comfort, physical functioning, cognitive functioning, psychological well-being, social well-being, spiritual well-being and overall quality of life (table 2). The selected items were qualitatively assessed on content validity by experts and found to be an adequate reflection of the construct to be measured.
Next, in domains with multi-item scales (cognitive and physical functioning, and psychological well-being), the internal consistency was assessed using Cronbach's alpha and inter-item correlations (table 3).

Table 1. Baseline characteristics of the HGG patients and their proxies.

Variable	**Proxies (n=83)**	**Patients (n=83)**
Age at diagnosis, median (range) years	60 (30-86)	62 (20-86)
Gender, no. (%)		
Male	30 (36)	53 (64)
Female	53 (64)	30 (36)
Religious, no. (%)		
No	45 (55)	45 (55)
Yes, not important	8 (10)	13 (15)
Yes, important	29 (35)	25 (30)
Educational level, no. (%)		
Low	31 (37)	37 (45)
Intermediate	26 (31)	21 (25)
High	26 (31)	25 (30)
Relation to patient, no. (%)		
Partner	66 (80)	
Parent	9 (11)	
Child	6 (7)	
Sibling	2 (2)	
Intensity contact patient, no. (%)		
Lived together	59 (71)	
Daily	22 (27)	
Weekly	2 (2)	
Tumour grade, no. (%)		
Grade III		11 (13)
Grade IV		72 (87)
Survival in months, median (range)		
Grade III		13 (0.5-38)
Grade IV		12 (0-43)
Place of death, no. (%)		
At home		48 (58)
Hospital		8 (10)
Hospice		14 (17)
Nursing home		10 (12)
Other		3 (3)

Table 2. All domains that are covered in the HRQoL questionnaire for HGG patients in the EOL phase as well as the content of these domains and the corresponding scales.

Domain	**Content**	**Scales**
Physical comfort	- Pain - Specific symptoms	Single item: headache, pain Single item: nausea, *visual deficits**, motor dysfunction, fatigue, drowsiness, bladder control, seizures, dyspnoea, dysphagia, communication deficits
Psychological well-being	- Emotional well-being	Domain emotional functioning: anxiety, sadness, irritability, *loss of interest**
Social well-being	- Social connection	Single items: family life, social activities, support
Spiritual well-being	- Acceptance of death - Dignity	Single item: acceptance Single item: dying with dignity
Physical functioning	- Mobility - Ability to care for self	Domain physical functioning: mobility, self-care
Cognitive functioning	- Ability to think, comprehension, attention - Avoiding confusion	Domain cognitive functioning: memory, concentration, understanding, confusion, behavioural change
Overall quality of life	- Overall rating quality of life	Single item: general quality of life

** Items excluded after validation*

Table 3. Internal consistency (Cronbach's alpha and inter-item correlation (r_s)) of the three multi-item scales for patients, and the items that are retained in the questionnaire.

Domain	**Cronbach's alpha**	**Correlation (r_s) (range)**	**Items retained**
Cognitive functioning 3 months before death 1 week before death	 0.88 0.86	 0.47 – 0.70 0.40 – 0.67	Memory, concentration, understanding, confusion, behaviour change
Physical functioning 3 months before death 1 week before death	 0.79 0.43	 0.69 0.29	Mobility, self-care
Psychological well-being 3 months before death 1 week before death	 0.64 0.67	 0.26 – 0.46 0.29 – 0.52	Anxiety, sadness, irritability

For the domain cognitive functioning in the last three months before death, a Cronbach's alpha (α) of 0.88 was found, inter-item correlations (r_s) ranged from 0.47 to 0.70. Similar results were found for cognitive functioning in the last week before death: α=0.86 and r_s=0.39-0.68. It was concluded that this domain has a good internal consistency and therefore all items were retained.
Likewise, a good internal consistency was found in the domain physical functioning in the last three months before death: α=0.79 and r_s=0.69. However, for physical functioning in the last week before death,α=0.43 and r_s= 0.29. Although the internal consistency for the items in the last week before death cannot be considered as optimal, we decided to have these items included because of good internal consistency measuring physical functioning in the last three months before death.
For the domain psychological well-being in the last three months before death, α=0.63 and r_s=0.14-0.46. Similar results were found for psychological well-being in the last week before death: α=0.67 and r_s=0.21-0.52. The item 'loss of interest' had low correlations with the other items in the scale and was therefore omitted. After removal of this item, α=0.64 and α=0.67 and r_s=0.26-0.46 and r_s=0.29-0.52 in the last three months and last week before death, respectively. Internal consistency in this domain is reasonable, with Cronbach's alpha's slightly below <0.7, and it was therefore decided to keep the items anxiety, sadness and irritability in the questionnaire.
Furthermore, the analysis of missingness (data not shown) revealed that proxies often (>10%) opted 'unknown' for the item 'visual deficit'. Therefore, this item was removed from the questionnaire. After exclusion of the items 'loss of interest' and 'visual deficit', twenty-seven items were retained in the final questionnaire (table 2).

II. HRQoL in the EOL phase of HGG patients

Mean scores on the different scales of the HRQoL questionnaire are shown in table 4. Symptom burden of HGG patients, according to their proxies, increased significantly on all scales (all *p*-values < 0.01) except for nausea (p = 0.058), as death approached. Furthermore, proxies reported seizures in the last three months of life as well as in the last week of life in 32% of the patients. In addition, 4% of patients developed de novo seizures in the last week before death, 21% of patients had seizures in the last three months before death but not in the last week, and 43% of patients did not have any seizures in the EOL phase.
Cognitive, physical and psychological functioning deteriorated significantly as death approached (all *p*-values <0.01). Although not significant (p=0.058), acceptance of disease increased slightly towards death. Within the domain social well-being, mean (standard deviation (SD)) scores for social activities and family life were low (17 (26) and 45 (39), respectively), whereas the mean (SD) scores for support and dignity were high (81 (27) and 71 (28)). Moreover, overall quality of life of the patients was rated as poor, with a mean (SD)

of 29 (26). Place of death (at home versus not at home) did not affect perceived overall quality of life or dying with dignity (*p*=0.761 and *p*=0.182, respectively).

Table 4. Mean (SD) scores of the different single and multi-item scales of the HRQoL questionnaire for HGG patients, measured in the last three months and/or the last week before death or in the total EOL phase.

Domain Single item scales	**Last three months** **Mean (SD)**	**Last week** **Mean (SD)**	***p*-value**
Physical comfort (symptoms)			
Headache	31 (35)	42 (41)	<0.01
Pain	29 (33)	48 (41)	<0.001
Nausea	20 (27)	24 (32)	0.058
Motor dysfunction	62 (37)	77 (36)	<0.001
Fatigue	72 (27)	88 (21)	<0.001
Drowsiness	51 (32)	84 (27)	<0.001
Bladder control	36 (41)	69 (41)	<0.001
Dyspnoea	17 (25)	43 (41)	<0.001
Dysphagia	23 (32)	54 (42)	<0.001
Communication deficit	40 (34)	71 (38)	<0.001
Psychological well-being	70 (24)	63 (27)	<0.01
Physical functioning	50 (33)	7 (15)	<0.001
Cognitive functioning	54 (28)	34 (29)	<0.001
Spiritual well-being			
Acceptance	57 (33)	64 (33)	0.058
	Total EOL phase **Mean (SD)**		
Dying with dignity	71 (28)		
Social well-being			
Family life	45 (39)		
Social activities	17 (26)		
Support	81 (27)		
Overall quality of life	29 (26)		

Discussion

Up to now, no questionnaire exists to adequately measure HRQoL in the EOL phase of HGG patients in retrospect by their proxies. Therefore, a new HRQoL questionnaire to measure this construct was developed and validated. The content validity of this questionnaire was

found to be adequate and the internal consistency of the multi-item scales varied from reasonable to good. Furthermore, HRQoL of HGG patients as reported by their proxies was poor and deteriorated as death approached.

Recently, the COSMIN taxonomy was presented, showing all measurement properties that should be considered in the validation of a questionnaire[139]. Measurement properties can be divided into three categories, each including different parameters; validity (content, construct and criterion validity), reliability (test-retest, internal consistency and measurement error) and responsiveness. In this study, the content validity and internal consistency were assessed. However, since validation is an ongoing process, validation can be improved over time if this questionnaire (including 27 items) will be used in future studies.

Although patients are the best source to rate their HRQoL [141], patient-by-proxy ratings should be considered as an appropriate alternative in situations where patients are cognitively impaired, incompetent, have a poor health status or have died. Applying patient-reported measures to HGG patients in the EOL phase is difficult if not impossible, and patient-by-proxy ratings may be considered an appropriate alternative to substitute patient ratings. Although retrospective studies relying on reports by proxies are widely accepted in EOL research[91], the reliability of these patient-by-proxy ratings remains debatable. Some studies have shown moderate to good agreement between patient and patient-by-proxy ratings [107, 142-144], whereas others revealed that patient-by-proxy and patient ratings are not always consistent. Patients and proxies often agree on symptom scales, but less on the psychosocial scales[145, 146]. Moreover, proxies tend to underestimate the patients' HRQoL[147].However, differences between patient and patient-by-proxy ratings do not necessarily reflect inaccuracy [105]. Appreciation of aspects of the patients' HRQoL by proxies however, may be influenced by feelings such as depression and anxiety, which are frequently reported in proxies,[42] although the relatively long interval in our study between the patient's death and the report by the proxy will decrease the chance for this.

Despite the methodological limitations, data generated from this questionnaire provide valuable information on relevant HRQoL aspects in the EOL phase of HGG patients. HRQoL of HGG patients as reported by their proxies was poor and deteriorated over time. With the symptom burden increasing towards death, a concomitant decrease was reported for cognitive, physical, social and psychological functioning. In several other studies, that applied different questionnaires on various aspects of HRQoL, symptom burden was also found to be high in the EOL phase with disease-specific symptoms prevailing[25, 46-49, 92]. A decline in mental, physical, social and existential well-being has also been reported previously [45], with a higher rate of poor functional status and a higher need for social support in HGG patients compared to a general palliative care population[49]. This emphasizes that HGG patients are a unique population with specific supportive care needs[42].

Overall quality of life was classified as poor in 86% of the patients, which comes as no surprise. Previously, poor or unacceptable quality of life was reported in 61% of the HGG patients[26], and was explained by severe disability restricting activities of daily living, personality changes and physical deterioration. At the same time, acceptance of disease increased as death approached and most proxies reported that the patient died with dignity. We have previously demonstrated that being able to communicate, the absence of transitions between health care settings and satisfaction with the EOL care provided by the physician are predictive for a dignified death[148].

In conclusion, this study yields a questionnaire to retrospectively measure all HRQoL aspects that are relevant in the EOL phase of HGG patients. This study demonstrates that the questionnaire is a feasible and potentially useful instrument for future retrospective clinical studies, and not yet for use in daily clinical practice, in this unique population. However, further validation in a separate cohort is warranted. Ideally, the questionnaire should be helpful to determine if enhanced (organization of) palliative care for HGG patients goes along with preservation or improvement of HRQoL in the EOL phase. Vice versa, identification of specific problems in HRQoL may possibly direct future treatment and subsequently the organization of care for HGG patients.

Chapter 4

Decision-making in the end-of-life phase of high-grade glioma patients

Eefje M. Sizoo

H. Roeline W. Pasman

Janine Buttolo

Jan J. Heimans

Martin Klein

Luc Deliens

Jaap C. Reijneveld

Martin J.B. Taphoorn

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Abstract

Background

During the disease course of high-grade glioma (HGG) patients, the goal of therapy eventually shifts from primarily life-prolongation to primarily sustaining quality of life as good as possible. End-of-life care is aimed at prolongation of life with good quality, but inevitably also may require medical decisions for prevention and relief of suffering with a potential life shortening effect. Few data are available on this end-of-life decision (ELD) making process in HGG patients, with decreased consciousness, confusion or cognitive deficits preventing them to participate. In this study the ELD-making process in HGG patients is described.

Methods

Physicians and relatives of a cohort of 155 deceased HGG patients were identified to fill in a questionnaire regarding the end-of-life conditions (patients´ ELD preferences, patients´ competence) and ELD-making (forgoing treatment and the administration of drugs with a potential life-shortening effect) for their patient or relative. Data were analysed with descriptive statistics.

Findings

Of 101 patients, physicians completed surveys including questions about ELDs (62% response rate). More than half of the patients became relatively early incompetent to make decisions due to delirium, cognitive deficits and / or decreasing consciousness. In 40% of patients the physician did not discuss ELD preferences with his/her patient. At least one ELD was made in 73% of patients, most often this comprised the withdrawal of dexamethasone. Palliative sedation was performed in 30% of patients and physician assisted death in 7%.

Interpretation

ELDs are common practises amongst HGG patients, although their preferences towards ELDs are frequently unknown to the physician. Because the majority of patients becomes incompetent towards death, participation in ELD-making is only possible with advance care planning. Hence, timely discussion of ELD preferences is encouraged.

Introduction

High-grade gliomas (HGG) are the most frequently occurring primary malignant brain tumours. Despite intensive treatment with surgery, radiotherapy and chemotherapy, patients with HGG cannot be cured from this disease and the prognosis is poor. Median survival ranges from less than one to more than five years depending on histological subtype, tumour grade, age and performance status at time of diagnosis[9, 73].

Inevitably, the end-of-life phase will come when tumour directed treatment is no longer possible and the patient's condition declines. During this end-of-life phase, symptom burden will increase and in the end become high. Disease specific symptoms such as focal neurological deficits, headache, epileptic seizures, confusion and cognitive deficits prevail[21, 46-48]. In most patients, intracranial pressure gradually increases towards death resulting in headache and progressive loss of consciousness[46, 47]. End-of-life care is aimed at maintaining quality of life as long as possible, but also may require medical end-of-life decisions (ELDs) for the prevention and relief of suffering: in some instances these decisions may hasten death.

In our definition, ELDs include the withholding or withdrawing of life-prolonging treatment, and the administration of drugs with a potential or certain life-shortening effect. Examples of ELDs in HGG patients are withdrawal of chemotherapy or dexamethasone, withholding artificial food and fluid administration, non-admittance to the hospital or intensive care unit for treatment of infections, and palliative sedation[149]. A large European study revealed that 23-51% of all deaths are preceded by an ELD depending on the cultural and legal background[150]. In the Netherlands 44% of deaths are preceded by an ELD[35]. In some European countries (The Netherlands, Belgium, and Luxemburg), physician-assisted death such as euthanasia or physician-assisted suicide are allowed under strict conditions upon a well-considered request.

Until date, little data are available on ELD decision-making in HGG patients. It can be hypothesized that discussing end-of-life issues with HGG patients becomes progressively more difficult during the course of their disease because of cognitive disturbances, confusion, and decreasing consciousness[25]. Therefore, it has been suggested that advance care planning (ACP) should be encouraged early in the course of the disease[25, 151].

The aim of this study is to document to what extent HGG patients expressed wishes regarding end-of-life treatment, whether these wishes were lived up to, and to what extent patients were able to participate in ELD-making. In addition, we specifically focused on the patients' competence in cases were euthanasia was discussed, a procedure restricted to fully competent patients. Finally, the nature and frequency of ELDs made in HGG patients are described.

Patients and Methods

Subjects

A retrospective descriptive study was performed sending questionnaires to physicians and relatives of deceased HGG patients from a cohort of adult HGG patients diagnosed in 2005 and 2006 in three tertiary referral centres for brain tumour patients (VU University Medical Centre and Academic Medical Centre Amsterdam Amsterdam, Medical Centre Haaglanden The Hague, The Netherlands). The physicians involved in end-of-life care of deceased patients of the cohort were approached for participation in the study. Participating physicians were asked to fill in a questionnaire regarding the end-of-life phase of the specific patient. If more than one physician was involved in end-of-life care for a specific patient (for example due to a transition in health care setting close before death), all physicians were approached for participation in the study. The closest relative of the deceased patient was identified by the physician who was involved in the end-of-life care or was retrieved from the medical chart. Identified relatives received a letter shortly explaining the aim of the study and were asked to send back a response form either allowing the researchers to further inform and contact him/her or declining any interest in participation. Relatives who allowed to be further informed received a questionnaire about the end-of-life phase of the deceased patient. The study protocol was approved by the Ethics Committee of the three participating hospitals and informed consent was obtained from all participating relatives.

Development of questionnaires

The questionnaire for physicians was developed using existing questionnaires in end-of-life research[35, 149, 152] and comprised both open-ended and discrete questions. Questions were related to the last three months before death, and more specifically to the last week before death. The questionnaire was piloted in interviews with eight physicians: five general practitioners (GP), two nursing home doctors, and one neurologist. We adjusted the questionnaire according to the feedback gained in these interviews.

The questionnaire for relatives was developed along existing questionnaires regarding quality of life and advance care planning[138, 153] . The questionnaire was piloted in five relatives with face-to-face interviews (two partners, one parent, and two children of the deceased patients).The questionnaire was adjusted according to the feedback gained in these interviews. Questions were related to both the last three months and the last week before death.

Content of the questionnaires

The questionnaire for physicians comprised both open-ended and discrete questions and addressed to whether the physician discussed end-of-life preferences with the patient and what these preferences were; until what moment the patient was competent to decide on care and treatment and - if the patient was incompetent to decide - what the reason for this incompetence was. Furthermore, ELDs were enquired after via four core questions: (1) whether the physician had withheld any life-sustaining treatment, (2) had withdrawn any life-sustaining treatment , (3) had performed palliative sedation (defined as continuous and deep sedated or kept in coma), (4) had carried out euthanasia or physician-assisted–suicide. Whether the physician judged the patient's life to be shortened as a result of the previously described ELD was enquired after separately.

The questionnaire for relatives comprised both open-ended and discrete questions and addressed whether the patient had an advance directive (AD) regarding ELDs, and whether the patient had ever expressed a wish for euthanasia. The relative should also indicate if any decisions were made in contradiction with the patient's or relative's wishes.

Statistical analysis

SPSS software 15.0 was used for statistical analysis. Baseline characteristics and incidences were analysed by means of descriptive statistics. Chi square tests and T-tests were used to test differences in baseline characteristics between the studied patients and other patients in the cohort.

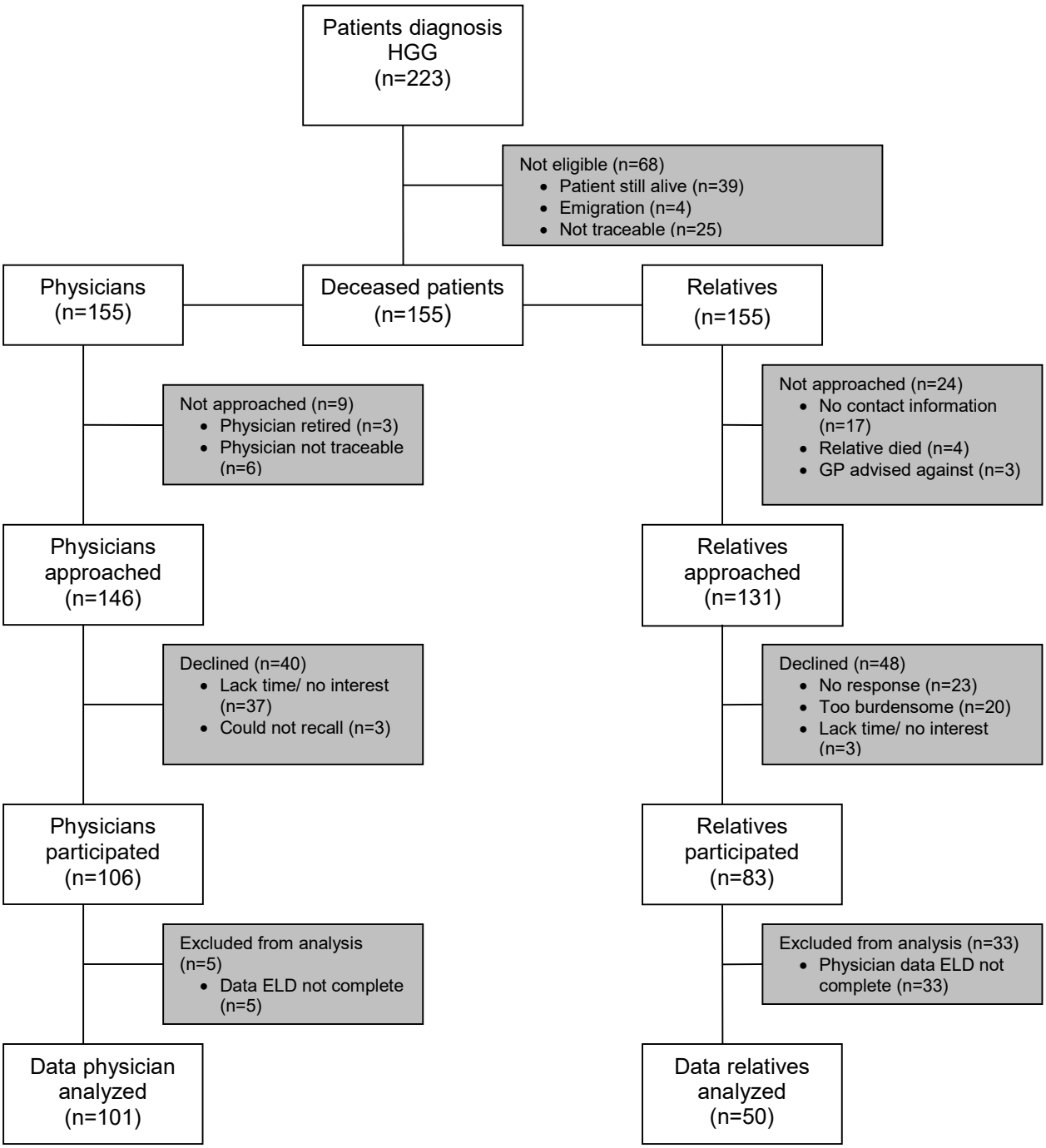
Results

Subjects

Figure one shows the flow chart of patient identification and data collection. Of 101 patients, data on ELDs provided by the physician were complete (62% response rate). Additionally, of 50 of these 101 patients data from relatives were available.

The physician responsible in the last week of life was a GP in 71 cases (70%), a nursing home specialist in 21 cases (21%) and a clinical specialist in nine cases (9%). As stated before, in 50 of these 101 patients, a relative participated in the study as well. The relatives' relation to the deceased patient was partner in 41 cases (82%), parent in three cases (6%), child in five cases (10%), and sibling in one case (2%).

Figure 1: Identification of subjects



Patient characteristics of our cohort are outlined in table 1. The 155 patients eligible for inclusion in the study were significantly more often diagnosed with a grade 4 tumour (p=0.023) as compared to all 223 patients of the cohort. There were no significant differences in patient characteristics between the 101 patients analysed in this study and the 155 patients eligible for inclusion, nor between the 50 patients of whom the relative participated in the study and the 51 patients in whom no relatives' data were obtained.

Table 1 Patient characteristics

Patient characteristics	Cohort (n = 223)				
	Overall (n=223)	Eligible for inclusion (n = 155)			
		All patients eligible for inclusion (n=155)	Included in analysis (n=101)		
			Overall (n=101)	Physician data only (n=51)	Physician and relatives data (n=50)
Sex					
▪ Male	63%	68%	72%	70%	75%
▪ Female	37%	32%	28%	30%	25%
Age at diagnosis, years [a]	57	60	60	58	59
Tumour grade					
▪ Grade 3	20%*	11%*	12%	10%	14%
▪ Grade 4	80%*	89%*	88%	90%	86%
Place of death					
▪ At home	NA	64%	66%	72%	60%
▪ Nursing home	NA	16%	15%	16%	14%
▪ Hospital	NA	7%	8%	4%	12%
▪ Hospice	NA	10%	8%	6%	10%
▪ Other	NA	3%	3%	2%	4%

[a] mean

** significant difference, p = 0·023*

End-of-life preferences and competence

The physicians of 61 patients (60%) were aware that their patient had ELD preferences. In 58 patients, the physician discussed these wishes with the patient and in three patients, the physician had been informed in another way. In three other patients (3%), the physician initiated a discussion regarding ELD preferences, but the patient did not express preferences or declined to discuss ELD preferences. In table two, the specific ELD preferences known by the physician are displayed.

Table 2 Type of end-of-life preferences expressed by the patient according to physician (n=101)

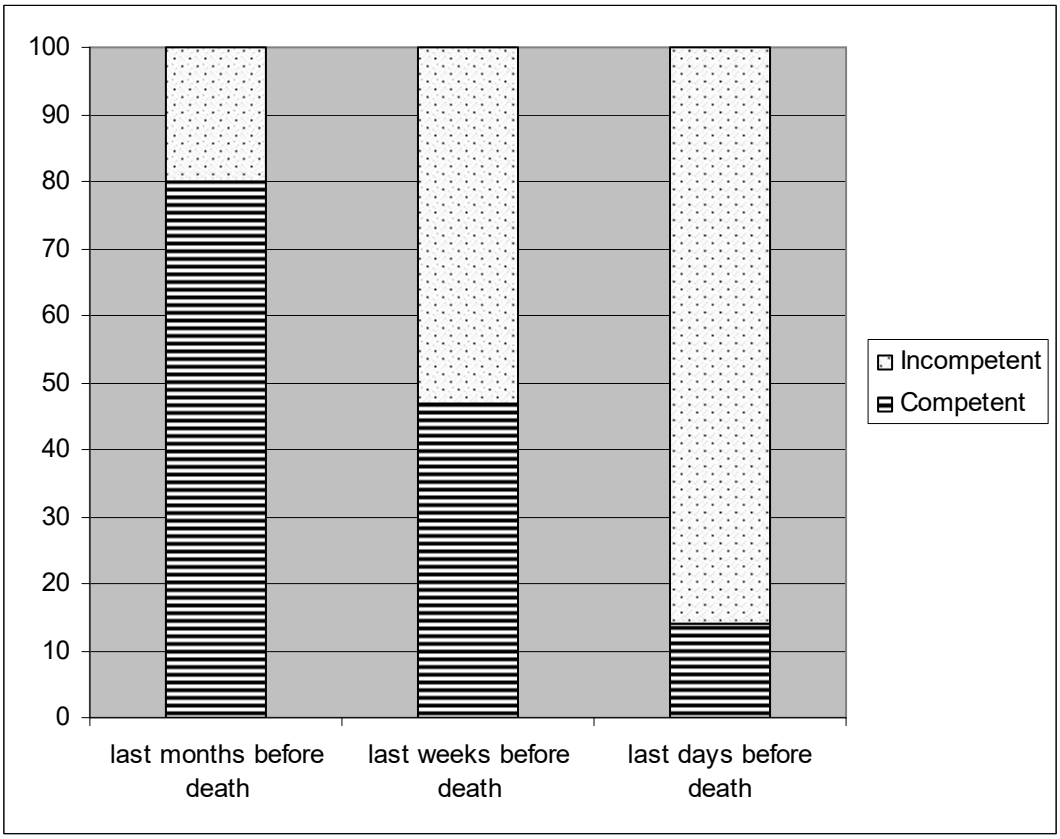
Any wishes expressed	60%
Specific wishes*:	
Life prolonging treatment	
▪ In favour	2%
▪ Opposed	36%
▪ No opinion/ not discussed	62%
Admission to hospital	
▪ In favour	4%
▪ Opposed to	45%
▪ Not discussed/ no opinion/ not applicable	51%
Palliative sedation	
▪ In favour	24%
▪ Opposed to	5%
▪ Not discussed / no opinion	71%
Euthanasia	
▪ In favour	18%
▪ Opposed to	20%
▪ Not discussed / no opinion	62%

**Multiple wishes per patient possible*

GPs more frequently discussed ELD preferences with the patient in comparison to physicians working in an institution: 73% of GPs compared to 40% of nursing home specialists and 22% of clinical specialists respectively (p = 0·001).

Figure 2 displays until what time point before death the patient was deemed competent to participate in decision-making. According to the physicians 53 patients (52%) were incompetent to assess their own situation in the last weeks of life due to: cognitive disturbances in 31 patients, somnolence in 26, aphasia in 16, and/or delirium in 12 patients. Another 33 (33%) patients lost their competence during the last week of life, most often as a result of decreasing consciousness. Patients who died in an institution were incompetent in an earlier stage than the patients who died at home.

Figure 2: Proportion of patients competent to participate in end-of-life decision-making at various time points before death (n =101; physician data).



End-of-life decisions (ELDs)

From 72% of patients, the physician indicated that at least one ELD was made (table 3). Withholding treatment was decided on in 29 patients (29%) and concerned the withholding of: (a) antibiotic treatment for an infection (11 patients), (b) artificial administration of food and fluids (nine patients), (c) admission to the hospital for treatment (six patients), (d) administration of dexamethasone (three patients), (e) planned radiotherapy (two patients), and (f) placement of a ventricular drain (one patient). In 56 patients (55%), one or several treatments were withdrawn in the end-of-life phase. This comprised the withdrawal of: (a) dexamethasone (51 patients), (b) temozolomide chemotherapy (two patients), (c) antibiotic drugs (one patient), (d) insulin (one patient), (e) the artificial administration of fluids (one patient).

For thirty patients (30%), the physician indicated that palliative sedation had been carried out. In 27 of these patients, benzodiapines were administered and three patients were sedated with opioids. The start of sedation ranged from several days to several hours before death.

According to the physician, ten patients requested euthanasia. In seven cases, this request was granted and euthanasia was performed in a stage of the disease where the patient was completely able to judge his own situation. In two of the ten patients, the request was not granted because the patient was unable to decide as a result of cognitive deficits and delirium. In one of these patients, palliative sedation was started, in the other patient no ELDs were applied. In one patient, euthanasia was not carried out as the patient withdrew the request for euthanasia. In this patient, palliative sedation was eventually started close before death.

In 30 patients (30%), the physician indicated the patient's life was probably shortened because of ELDs made (table 3).

Table 3 End-of-life decisions in the cohort (n=101; physician data)

	Number of patients (%)
No ELDs	27 (27%)
Any ELD	74 (73%)
Specific ELDs*	
▪ Withhold treatment	29 (29%)
▪ Withdraw treatment	58 (57%)
▪ Palliative sedation	30 (30%)
▪ Physician assisted death	7 (7%)
Life shortening effect of ELDs	
▪ Not applicable	27 (27%)
▪ No	44 (44%)
▪ Hours	10 (10%)
▪ Days	12 (12%)
▪ Week or more	8 (8%)

**Multiple ELDs per patient possible*

End-of-life preferences according to relatives

Of the 50 patients of whom data of both their physician and relatives was available, data regarding expressed preferences were correlated. According to their relatives, 21 patients (42%) had an advance directive (AD). Physicians of 12 of these patients were aware of the AD, five other physicians discussed wishes with the patient, but were unaware of the AD, and four physicians were unaware of any preferences of the patient. In 13 of the 21 patients, the AD concerned a wish for euthanasia.

According to the answers of the relatives, 19 of the 50 patients (38%) ever expressed a wish for euthanasia to be carried out under certain circumstances. In 11 of these 19 patients, the

wish never became active or the patient died before the procedure could be discussed. In the other eight cases, euthanasia was discussed in the end-of-life phase. According to the physician, four of these eight patients eventually requested euthanasia, which was granted. In the other four patients, the patient's wish was discussed, but could not be granted as the patient had become incompetent due to cognitive deficits (three patients) and decreased consciousness (one patient). In these four patients other ELDs were made: in two patients, the physician withdrew dexamethasone treatment and started palliative sedation, in one patient the physician withdrew dexamethasone treatment and withheld artificial administration of fluids, and in the remaining patient, the physician withheld antibiotic treatment whilst the patient had a pneumonia.

Relatives of six patients were dissatisfied because decisions were made against the patient's wishes. In two cases, this concerned not performing euthanasia because the patient had become incompetent (in one of these patients, the patient had a written AD requesting euthanasia in case of a declining condition), in two cases the patient had to be admitted to an institution in the end-of-life phase, in one case, the physician started artificial administration of fluids and nutrients despite a refusal of treatment, and in one case, the physician had withdrawn all medication including anti-epileptic drugs, causing seizures in the end-of-life phase.

Discussion

In this study, end-of-life data were obtained from a representative sample physicians and relatives of a cohort HGG patients. We have shown that in 40% of patients, physicians were unaware of the patients' end-of-life preferences, even though several patients had an AD according to their relatives. About half of the patients had become incompetent to participate in ELD-making before the last week of life. In approximately three quarters of HGG patients ELDs were carried out. Palliative sedation was performed in 30% of all patients and euthanasia in 7%.

To our knowledge, this is the first study systematically evaluating decision-making and end-of-life practices in HGG patients. The response rate was high in comparison to ELD studies in other diseases and the eligible patients are largely representative for the HGG population. Furthermore, exploring both the physicians´ and the relatives´ perspective adds on to the strength of our study.

Physicians discussed ELD preferences with HGG patients less often than reported in other cancer patients[154]. Probably physicians postpone discussing ELDs until the last week before death[154]. By that time, however, the large majority of HGG patients has become incompetent to participate in ELD discussions. Moreover, the physicians' estimation that 20% of patients are incompetent in the last months before death is probably an underestimation. A previous study evaluating competence in high-grade glioma patients

median 4 months after diagnosis found that 15-23% of patients were incapable to decide[43]. Since most cancer patients wish to be involved in decision-making at the end-of-life[155], our results underscore that ELD-making for HGG patients warrants improvement. Timely organization of ACP could contribute to improve ELD-making[25]. The aim of ACP is to reach consensus about possible ELDs between all participants, respecting both patients' and families' values[156]. Given the fact that in the large majority of HGG patients ELD-making becomes an issue, ACP should become standard for HGG patients. Physicians should discuss the patients' preferences relatively soon after diagnosis, and repeat this discussion subsequently.

A study evaluating ACP in HGG patients during treatment showed that the majority of patients is willing to discuss potential end-of-life scenarios and – once the various treatment options are clear – the majority preferred comfort care over life-prolonging treatment[71].

Unfortunately, according to this study, ACP is not always effective. In 40% of patients the physicians were unaware of the patients' AD and not all expressed wishes can be lived up to. Clear communication with patients and – especially when the patient has become incompetent – their relatives is of major importance[156].

A minority of patients, however, is unwilling to discuss ELD. In our cohort, at least 3% and in the previously mentioned study into ACP, 12% of patients were unwilling to discuss this topic. [71]

The most frequently reported ELD in our study was withdrawal of dexamethasone close before death, as has been reported in previous studies on this issue[46, 48]. The incidence of palliative sedation as ELD in our study is high: 30% of patients received palliative sedation with sedative drugs, which is more than twice as high as has been reported in an Italian HGG population[48]. In comparison, in the general Dutch mortality figures, 13% of non-sudden deaths was preceded by palliative sedation[35]. The main reason for palliative sedation in terminal patients is delirium and agitation[157]. We hypothesize that the high incidence of palliative sedation in our study may be explained by the high incidence of confusion in HGG patients. Unfortunately, however, we did not specifically explore the reason for starting palliative sedation.

Euthanasia had eventually been carried out in 7% of patients. This percentage appears to be relatively high in comparison with non-sudden deaths in the general Dutch population (2·7%)[35] and compared with Belgian cancer patients (4·6%) [158](a country with comparable legislation). In patients with amyotrophic lateral sclerosis (ALS), a neurological condition with a similar poor prognosis as HGG patients, however, the proportion of patients in whom euthanasia is performed is far higher (16·8%)[159, 160]. In at least six of our cases, the patient explicitly expressed a wish for euthanasia which could not be granted because the patient had become incompetent. It can be implied that the procedure for euthanasia is relatively often hampered in HGG patients due to the patients' incompetence to assess the own

situation towards death as a result of cognitive disturbances, delirium and decreasing consciousness, which is generally not the case in ALS patients.

Our study has some limitations. As we selected deceased patients after a prefixed interval from a cohort diagnosed within a two-year frame there is a bias towards patients with a relatively short disease duration, i.e., glioblastoma patients. Another limitation is the fact that patients' physicians and relatives answered the questions regarding the patients retrospectively with a relatively long interval since the patients´ death, possibly causing recall bias. Although this is a common and generally acknowledged practice in end-of-life research[91], the results should be interpreted with caution. Furthermore, the estimation of how long a patient might have lived if ELDs had not been carried out is a subjective measure as this is difficult to estimate in any circumstance. Studies have shown that survival of patients receiving palliative sedation is not significantly different from patients who were not given sedatives and one study even found a longer survival in patients receiving sedation[161].

Overall, it can be concluded that ELDs are very common practices in HGG patients. As most patients become incompetent as death approaches, the decision-making process is not always straightforward. Physicians caring for HGG patients in the end-of-life phase should discuss the full spectrum of ELD preferences before the patient becomes incompetent. Guidelines should be developed to facilitate timely discussion of ACP in HGG patients. Furthermore, as cultural and legal aspects of ELDs vary among countries and cultures, it would be very interesting to compare ELD practices in HGG patients between various countries and cultures.

Chapter 5

The End-of-life Phase of High-Grade Glioma patients: Dying with dignity?

Eefje M. Sizoo

Martin J.B. Taphoorn

Bernard Uitdehaag

Jan J. Heimans

Luc Deliens

Jaap C. Reijneveld

H. Roeline W. Pasman

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Abstract

Background:

In the end-of-life (EOL) phase, high-grade glioma (HGG) patients have a high symptom burden and often lose independence due to physical and cognitive dysfunction. This might affect the patients' personal dignity. We aimed to (1) assess the proportion of HGG patients dying with dignity as perceived by their relatives and (2) identify disease- and care factors correlated to dying with dignity in HGG patients.

Methods:

We approached relatives of a cohort of 155 deceased HGG patients for the study. Participants completed a questionnaire concerning the EOL phase of the patient, covering several subthemes: (1) symptoms and signs (2) health-related quality of life, (3) decision-making, (4) place and quality of EOL care and (5) dying with dignity.

Results:

Relatives of 81 patients participated and 75% indicated the patient died with dignity. These patients had less communication deficits, experienced less transitions between health care settings in the EOL phase, and more frequently died at their preferred place of death. Relatives were more satisfied with the physician providing EOL care and reported that this physician adequately explained treatment options. Multivariate analysis identified satisfaction with the physician, the ability to communicate, and the absence of transitions between settings as most predictive for a dignified death.

Conclusions:

Physicians caring for HGG patients in the EOL phase should timely focus on explaining possible treatment options, since patients experience communication deficits towards death. Physicians should strive to allow patients to die at their preferred place and avoid transitions during the last month of life

Introduction

High-grade glioma (HGG) is an incurable disease with a poor prognosis. Median survival ranges from one to five years[4]. Thus, all HGG patients will sooner or later be confronted with the end-of-life (EOL) phase due to their disease. During this EOL phase symptom burden becomes high and patients are often troubled by seizures and deficits in cognition, communication, motor function [21, 46-49] . Furthermore, loss of consciousness, cognitive disturbances, communicate on deficits and confusion often hamper the patients' competence to participate in EOL decision-making[43, 56]. To date, little is known about the quality of life in the EOL phase or quality of death in HGG patients[42].

Preserving dignity is often mentioned as a point of great concern by patients when considering the EOL[162] and dying with dignity is emerging as an overarching goal of EOL care[23]. Two types of dignity can be distinguished: basic dignity and personal dignity. Basic dignity is the intrinsic dignity of every human being, which nothing can take away. Personal dignity, on the other hand is an individual concept. It refers to a personal sense of worth, associated with personal goals and social circumstances. Personal dignity is frequently invoked in reference to death and dying[163]. Chochinov stated that a patient's personal dignity may be influenced by (1) direct illness-related concerns such as level of independence and symptom distress, (2) dignity conserving repertoire such as autonomy, role preservation, acceptance of disease and spiritual well-being, and (3) social factors such as social support and care tenor[164]. Later studies reporting on personal dignity additionally identified communication, care-related factors [165] and the ability to make choices as important issues[166, 167].

Personal dignity in HGG patients has not been reported on so far. It can be hypothesized that personal dignity is often threatened in the EOL phase of HGG patients. High symptom burden combined with communication deficits, loss of independence due to physical and cognitive dysfunction, and the inability to participate in EOL decision-making are all factors that potentially decrease the patients' perception of dying with dignity . Furthermore, environmental aspects of care and care characteristics might influence dignified dying.

In this study we aimed to establish the proportion of HGG patients who died with dignity as perceived by their relatives. Furthermore, we aimed to explore whether subjective dying with dignity was correlated to (1) disease-related factors, (2) psychological and spiritual well-being, (3) decision-making, and (4) quality of care.

Materials and Methods

Subjects

In 2009, we surveyed the relatives of deceased HGG patients from a cohort of all adult HGG patients diagnosed in 2005 and 2006 in three tertiary referral centres for brain tumour patients (VU University Medical Centre and Academic Medical Centre Amsterdam, Medical Centre Haaglanden The Hague, The Netherlands). Either the treating physician or information from the medical chart identified the relative closest to the deceased patient. These relatives received a letter explaining the aim of the study and were asked to send back a response form, either allowing the researchers to further inform and contact him/her, or declining interest in participation. Relatives who agreed to be further informed received a questionnaire about the EOL phase of the deceased patient. The study protocol was approved by the Ethics Committee of the three participating hospitals and informed consent was obtained from all participating relatives.

Data collection

The questionnaire for relatives was developed in accordance with existing questionnaires in quality of life and EOL research.[101, 138]. Five relatives (two partners, one parent and two children of different deceased patients) provided feedback in face-to-face interviews and the questionnaire was adapted using their comments. In its final version, the questionnaire covered several subthemes: (1) (disease-related) symptoms and signs (2) health-related quality of life, (3) decision-making, (4) place and quality of EOL care and (5) dying with dignity. If applicable, we distinguished in the questions the situation in the last 3 months before death (the whole EOL phase) and specifically the situation in the last week before death (the actual EOL). The questionnaire consisted of two parts; in the first part, relatives were asked to respond as how they think the patient would have replied. Most questions in this part of the questionnaire included an option 'unknown' to prevent relatives from not answering questions or random filling in answers. In the second part, relatives were asked about their own experience with decision-making in the particular case and their own opinion on the quality of EOL care that had been provided to their beloved one.

Dying with dignity was enquired after in the first part of the questionnaire (i.e. the relative estimated how the patient would have answered). No specific definition was provided for dignity and no specifications or criteria were given on the basis of which the respondents could base their rating. Relatives were asked to rate the dignity of the patients' death on a 5 point Likert scale (1 = very undignified, 2 = undignified, 3 = not dignified, not undignified, 4 = dignified, 5 = very dignified)..

Furthermore, items suggested to be of potential importance for personal dignity were selected from the questionnaire. Regarding *disease-related factors*, we included pain, seizures, communication deficits, cognitive functioning and physical functioning using items and scales derived from prospective health-related quality of life (HRQOL) instruments designed for brain tumour patients[101]. Furthermore, we included general (not disease-specific) domains of HRQOL which might be important in the EOL phase such as psychological well-being and spiritual well-being [101, 128-130]. With regard to *decision-making*, the following items were addressed (1) patients' competence to participate in EOL decision-making in the last week (2) whether possible treatment options were discussed, and (3) whether decisions were made against the patients' or relatives' wishes. Concerning *quality of EOL care*, we incorporated (1) whether the patient deceased at the preferred place of death (2) whether transitions between health care settings took place during the last 3 months of life (3) whether the relative was satisfied with the physician providing EOL care, and (4) overall quality of care (Likert scale 1-7).

Data analysis

SPSS software 15.0 was used for statistical analysis.

We divided subjects into two subsets: patients who died with dignity (scoring ≥ 4 on the dignity scale) and patients who did not die with dignity (scoring ≤ 3 on the dignity scale) as perceived by their relatives.

All disease related factors and QOL domains derived from prospective HRQoL instruments were converted to 0-100 scales using the EORTC QLQ-c30 algorithm[100, 168]. On symptom scales, a higher score represents *worse* QOL whereas on functioning scales, the overall QOL scale and the dignity scale, a higher score represents *better* QOL or dignity. The symptom/functioning score in the last week of life was used for data-analysis. If possible, missing data in the last week were imputed using a 'last observation carried forward' method, filling in the score of 3 months before death. Not normally distributed scores were dichotomously analysed. For symptoms and QOL scores, a score > 50 was classified as 'high' and a score ≤ 50 represents 'low'. Questions regarding decision-making and quality of care were dichotomized if applicable.

We compared data of patients who died with dignity and patients who did not die with dignity as perceived by their relative with t-tests, Chi-square test and Fisher's Exact tests, as appropriate. All tests were done on a two-tailed basis and a *p-value < 0.05* was considered significant. The predictive value of the individual variables that were significantly (*p<0.05*) associated with dignity was examined in a manual stepwise multiple logistic regression analysis using a backward selection procedure. At each step, we evaluated whether the model changed by removing the least significant factor. A p-value of <0.05 was considered statistically significant.

Results

Subjects

We identified 223 patients diagnosed with a HGG in 2005 and 2006 in our three participating hospitals. Of these 223 patients, 39 patients were still alive, 4 emigrated and 25 were not traceable. The 155 patients who were known to have died were considered eligible for inclusion in our study. We were able to identify relatives from 131 patients and these relatives were approached median 27 months(interquartile range 18 – 34 months) after death of the patient. Eighty-three relatives participated (response rate 63%). Two relatives did not fill in the questions concerning dignity, and these cases were thus excluded from analysis. Patient characteristics of the 81 patients analysed in this study are outlined in table 1. No significant differences in patient characteristics (sex, age at diagnosis, tumour grade) were reported between the 81 patients analysed in this study and the cohort of 155 patients eligible for inclusion (data not shown).

Table 1 Characteristics of the studied HGG patients

Sex (male), *n* (%)		52 (64)
Age at death, mean (range)		61 (20-86)
Religious (yes), *n* (%)		37 (46)
Relationship status (with partner), *n* (%)		68 (84)
Education, *n* (%)	Low	17 (21)
	Intermediate	39 (48)
	High	25 (31)
Participating relative, *n* (%)	Partner	64 (79)
	Parent	6 (7)
	Child	9 (11)
	Sibling	2 (3)
Sex of relative (male), *n* (%)		29 (36)
Age of relative at time of the patient's death, mean (range)		58 (30-86)
Place of death, *n* (%)	At home	46 (57)
	Hospice	14 (17)
	Nursing home	10 (12)
	Hospital	8 (10)

	Other	3 (4)

Dying with dignity

Figure 1 shows to what extent the patients' death was dignified according to the relative. The relatives of 61 patients (75%) reported that the patient died with dignity (scoring ≥ 4 on the dignity scale) whereas the relatives of 20 patients (25%) reported the patient did not (scoring ≤ 3 on the dignity scale).

Figure 1 Dignified dying in HGG patients according to relatives (N=81)

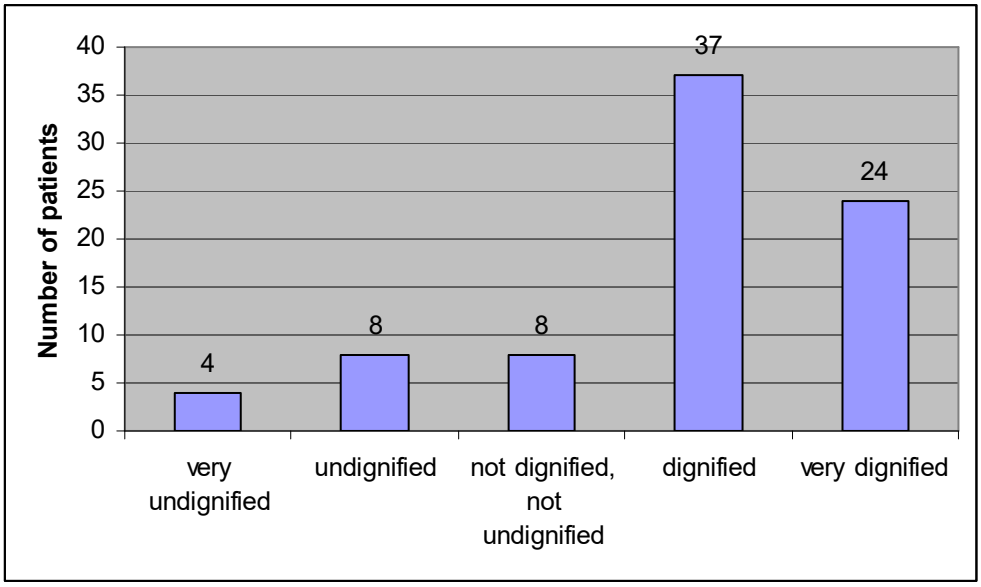


Table 2 shows the correlation between a dignified death and patient characteristics, disease-specific factors, psychological and spiritual well-being, decision-making aspects and quality of care. We found that patients who died with dignity significantly less often had communication deficits and were more frequently at peace to die. Furthermore, in patients who died with dignity, EOL decisions were more often explicitly discussed and relatives were more satisfied with the physician(s) providing EOL care. Patients who died with dignity more often died at their preferred place of death and experienced less transitions between health care settings in the last month. As to place of death, patients who died at home died most often with dignity (83%), followed by hospice (71%), hospital (63%) and nursing home patients (50%) (*p=0.255*).

Table 2 Determinants of dying with dignity, univariate analysis

	Dignified n/N (%)	**Not dignified n/N (%)**	**OR (CI)**	***P-value***
Patient characteristics				
Sex, male (n=52)	77%	23%	1.27 (0.45- 3.58)	0.652
Age of death, > 60 years (n=51)	77%	23%	1.18 (0.42-3.33)	0.752
Disease-related concerns				
Pain, low score (n=35)	83%	17%	2.62 (0.86-7.94)	0.083
Seizures, no (n=47)	72%	28%	0.68 (0.24 – 1.93)	0.466
Communication Deficit, low score (n=24)	92%	8%	**5.08 (1.08-23.81)**	**0.031**
Cognitive functioning, high score (n=20)	85%	15%	6.30 (0.77-51.63)	0.201
Physical functioning, high score (n=2)	50%	50%	3.00 (0.18- 50.0)	0.450
Psychological and spiritual well-being				
Emotional functioning, high score (n=52)	81%	19%	2.58 (0.84-7.91)	0.090
Acceptance disease, yes (n=51)	87%	13%	1.39 (0.44-4.42)	0.561
At peace for death, yes/ unaware (n=63)	81%	19%	**6.03 (1.65-22.05)**	**0.008**
Decision-making aspects				
Able to make decisions last week, yes (n=23)	83%	17%	1.81 (0.53 -6.14)	0.337
Decisions against patients' will, no (n=67)	87%	13%	2.48 (0.69-8.92)	0.168
Decisions against relatives' will, no (n=69)	80%	20%	3.92 (0.997- 15.38)	0.055
Decisions against any will, no (n=65)	78%	22%	2.18 (0.68-7.04)	0.206
EOL decisions explained, yes (n=66)	80%	20%	**3.57 (1.09 -11.63)**	**0.045**
Quality of EOL care				
Satisfied with physician last week, yes (n=59)	86%	14%	**7.65 (2.49 – 23.50)**	**<0.001**
Quality of Care, high (n=59)	78%	22%	1.91 (0.63 – 5.76)	0.249
Deceased at preferred place of death , yes (n=60)	82%	18%	**3.34 (1.13 -9.88)**	**0.025**
Transition in health care setting last month, no (n=52)	85%	15%	**3.88 (1.35 – 11.1)**	**0.009**

All patients	**75%**	**25%**		

OR = Odds Ratio; CI = confidence interval

In the univariate analysis, six variables were identified as predictive for a dignified death. Due to our study sample, we were limited in the number of variables we could add to the multivariate model predicting a dignified death. As the absence of transitions in the last month of life was strongly correlated with dying at the preferred place of death, we decided only to include the most significant factor of these two (i.e., transitions). Furthermore, we included the strongest predictors based on the p-values. We started with a model with four factors (communication deficits, being at peace for death, being satisfied with the physician providing EOL care, transitions) These four factors were evaluated in a stepwise logistic regression analysis using a backward selection procedure. The final model is presented in table 3. The three most important factors predicting dying with dignity in HGG patients are (1) being satisfied with the physician providing EOL care, (2) the absence of transitions between health care settings in the last month of life and (3) being able to communicate.

Table 3 Determinants of dying with dignity, multivariate analysis.

	Corrected OR (CI)	***P-value***
Communication Deficit, low score	4.55 (0.87 -23.67)	0.072
Satisfied with physician last week, yes	**6.13 (1.80 - 20.83)**	**0.004**
Transition in health care setting last month, no	3.09 (0.925-10.31)	0.067

OR = Odds Ratio; CI = confidence interval

Discussion

Our study showed that a quarter of HGG patients die with reduced dignity as perceived by their relatives. No previous study has addressed this important issue. The relatives were systematically selected from a well-defined cohort of deceased HGG patients, which adds up to the strength of our study.

The percentage of patients that not died dignified that we found is relatively high as compared to other cancer cohorts: in a study prospectively examining dignity in incurable general cancer patients in the EOL phase, only 7% of patients had a disturbed sense of dignity[169].

We identified several disease-, decision-making and care-related factors that correlated with dignified dying. With respect to disease-related factors, we found a significant association between the severity of communication deficits and not dying with dignity. This finding is in

accordance with Albers et al[165], who identified that communication is an important issue for dignity at the EOL. Concerning decision-making, neither the patients' inability to participate in decision-making close before death, nor decisions taken against the patients' will appeared to decrease dignity. Previously, both the ability to choose as well as wishes being carried out have been identified as important for dignity at the EOL. This contradiction might be explained by the fact that these items were mainly selected as important from the perception of medical staff[170], while our study focused on the patient's perspective (as perceived by their relative). According to our results, it proved to be important that the physician explained possible treatment options at the EOL. Although we found no studies relating EOL discussions to dignity, a large, prospective study previously demonstrated that discussing EOL preferences with advanced cancer patients and their proxies reduces distress and improves quality of life of both the patient and the relative at the EOL[171, 172]. EOL care-related aspects appeared to be very important. The strongest independent predictor we identified was being satisfied with the physician providing EOL care. The importance of health care providers was previously demonstrated by Hall et al, who identified the importance of home staff in nursing homes for the patients' sense of dignity[173]. Furthermore, in accordance with previous studies, we found that dying at the preferred place of death was important[165] and that transitions between health care settings in the last month of life decreased dignity.

Our study has several limitations. First, due to the retrospective nature, we were dependent on the relatives' information. Nevertheless, proxy ratings are considered a feasible strategy to gain information if the patient is not able to provide information himself [145] and using proxy ratings is a common and generally acknowledged practice in EOL research[91, 129, 145]. Although the relatives were asked to answer the questions for the patient, relatives may have used their own perception of dignity as a reference to estimate the patient's dignity and their overall satisfaction with the dying process may also have influenced this perception. Second, a persons' sense of dignity and the factors that have impact on dignity change towards death[165, 169, 174]. Since dying with dignity was evaluated applying a single question, these issues were not further explored. Third, our outcome measure has not been validated in previous studies. Fourth, our sample sizes is relatively small. The final limitation is the fact that relatives answered the questions regarding the patients retrospectively with a relatively long interval since the patients´ death, possibly causing recall bias.

In conclusion, our results suggest that in HGG patients, satisfaction with the physician providing EOL care and the patients' ability to communicate at the EOL are very important for a dignified death. Usually, the latter item cannot be affected by medical intervention in patients with brain tumours. But it is important to realize that physicians caring for HGG patients in the EOL phase should explain possible treatment options at the EOL to patients and their involved relatives. Previous studies suggest these discussions should be initiated by the physician[175, 176]. As the majority of patients experience communication deficits towards death, we advocate timely discussion of EOL preferences as we did previously[56]. Physicians

should strive to letting the patients die at the preferred place of death and –if possible- should avoid transitions in the last month of life. If the patient prefers to die at home, specialized palliative home care should be considered as this has proven to be effective in reducing the number of hospital admissions at the EOL[44]. Future studies should focus on systematically incorporating EOL discussions into clinical practice by active advance care planning.

Chapter 6

Summary, discussion and future prospects

6.1 Summary

Patients with high-grade glioma (HGG), the most frequently occurring and most malignant primary brain tumour, have a poor prognosis. Despite intensive treatment with surgery, radiotherapy and chemotherapy, patients cannot be cured. Hence, throughout the disease process, the goal of treatment shifts from primarily life-prolongation to primarily quality of life. For all patients inevitably the moment will come when the disease progresses and life-prolonging tumour treatment is no longer an option. At this moment, the end-of-life (EOL) phase begins. At the start of this research project, little was known about this EOL phase in HGG. In the studies described in this thesis, we explored what happens to HGG patients after ending tumour treatment.

In Chapter 1.2 we present a systematic overview of current (until April 2012) knowledge on the EOL phase of HGG patients with respect to symptoms and signs, quality of life and quality of dying, caregiver burden, organization and location of palliative care, supportive treatment and EOL decision-making. In the past few years, the EOL phase of HGG patients is receiving increasing attention. Nevertheless, nearly all studies concerning the EOL phase of HGG patients were observational and there is a lack of high-quality intervention studies. Furthermore, an important conclusion that can be drawn from our overview is that the EOL phase of HGG patients is different from other cancerpatients.

In the following chapters, we largely report on original data collected in two types of studies. First, a *chart review* in which we examined the files of 55 HGG patients who maintained contact on a regular basis with the clinical nurse specialist in neuro-oncology after ending tumour-directed treatment. The clinical nurse specialist used a checklist, systematically asking for specific symptoms and signs. Second, a r*etrospective cohort study* in which we identified a cohort of HGG patients diagnosed with HGG in 2005 and 2006 in three Dutch tertiary referral centres for neuro-oncology. In 2009, we approached physicians and relatives of deceased patients from this cohort and invited them to fill in a questionnaire about the EOL phase of the specific patient.

Chapter 2 focuses on symptoms and signs of patients in the EOL phase. In chapter 2.1 we report on the above mentioned chart review. Common symptoms after ending tumour-directed treatment were progressive neurological deficit, incontinence, progressive cognitive deficit, and headache. Loss of consciousness and difficulty with swallowing occurred in particular in the week before death. Nearly half of the patients in the EOL phase, and one third of the patients in the week before dying, had seizures. Given the high prevalence of seizures found in this pilot study, we further report on seizure prevalence in chapter 2.2, using data collected in our cohort study (physician data). Next to providing descriptive statistics on seizure prevalence, we aimed to identify predictors for the development of seizures in the last week of life. We report on 92 patients, of whom 29% had seizures in the

last week before death. A history of status epilepticus was the only significant predictor we identified. Anti-epileptic drugs were reported to be frequently tapered before death. We conclude that epileptic treatment throughout the EOL phase warrants improvement.

Chapter 3 focuses on the quality of life in HGG patients. In chapter 3.1, we review the current knowledge on the quality of life in HGG patients. In particular, we focus on the concept of health-related quality of life (HRQoL) and available instruments to measure this outcome. Since all available instruments to measure HRQoL in HGG patients are patient-reported outcomes to be used in prospective studies, we developed a proxy-reported questionnaire to measure HRQoL of HGG patients in the EOL phase in retrospect. In chapter 3.2 we describe the development and first validation of this questionnaire. The content validity was found to be adequate and the internal consistency of the multi-item scales varied from reasonable to good. Furthermore, we report on the patient's HRQoL in the EOL phase, which was poor and deteriorated over time. While the symptom burden increased towards death, a concomitant decrease was observed for cognitive, physical, social and psychological functioning.

In chapter 4, we describe the EOL decision-making process in HGG patients from both the physician's and relatives' perspective. We found that more than half of the patients became incompetent to make decisions relatively early, due to delirium, cognitive deficits and / or decreasing consciousness. EOL decisions were common in HGG patients and the majority of patients were prepared to discuss EOL preferences. This is in contrast to the fact that the patients' preferences towards EOL treatment and decisions were frequently unknown to the physician. We suggest that given the high occurrence of incompetent patients close before death, patients' preferences regarding the EOL should be discussed timely.

Chapter 5 focuses on dying with dignity, a relatively new outcome measure emerging as an overarching goal of palliative care. The majority of HGG patients in our cohort died with dignity (75%) according to their relatives. Multivariate analysis identified satisfaction with the physician, the ability to communicate, and the absence of transitions between health care settings as most predictive for a dignified death. Since communication deficits increase towards death, we recommend physicians caring for HGG patients to explain possible treatment options and preferences in an early stage. If at all possible, patients should die at their preferred place of death, and undesirable transitions between health care settings at the EOL should be avoided.

6.2 General discussion

Introduction

At the start of this research project in 2008, only few data were available on the end-of-life (EOL) phase of HGG patients; this field had yet to be explored. Therefore, the central question we needed to answer was "what happens to HGG patients in the EOL phase". In the previous chapters, we subsequently reported on symptoms and signs, health-related quality of life (HRQOL), EOL decision-making, and dying with dignity. In this chapter, methodological considerations are presented and the results described in the previous chapters are discussed from an overarching view.

Methodological considerations

Retrospective design

The results presented in this thesis are all based on retrospective studies. The optimal way to study the EOL of HGG patients would be to assemble a cohort of all patients diagnosed with a HGG, regardless of clinical condition, and prospectively collect data on their symptoms, signs, HRQoL, care, and EOL decision-making until all patients have died. This study design would provide an "unbiased" look at the EOL phase. Since all patients with HGG will sooner or later be confronted with the EOL phase of their disease, this might be feasible. However, such a study would be very demanding for both patients and doctors, as they will have to comply with repeated measures. Particularly in the EOL phase, patients are less likely to comply with measures as their condition is declining. Moreover, at this point, they often suffer from severe cognitive deficits yielding them unable to provide information[43, 56]. Furthermore, it would take years before results are available and repeated HRQoL are prone to missing data[108]. Another prospective approach could be to include patients who are entering the terminal phase. This approach is prone to substantial selection bias as only patients whose physician recognises the approaching EOL phase and whose physician is willing to discuss this with the patient, will be approached for the study[91]. And even if they are approached, it is still hard to include patients as they are by definition very ill.

In EOL research, retrospective designs therefore not only are widely accepted, but also might have several advantages over prospective designs[91]. First, it is far less intensive and complex[177]. Second, it allows for more easy identification of a cohort of relevant patients. Third, the selection of the cohort is less prone to selection bias (introduced by the treating physician), thereby making the results more generalizable to other patients[91].

Potential sources of bias

There are several potential sources of bias in our studies. In our explorative retrospective chart review described in chapter 3.1, patients were only included if they and/ or their proxies stayed in touch with the nurse specialist until death. Although the nurse specialist actively offered to contact patients and their relatives on a regular basis after ending tumour treatment, not all patients used this service. Thus, selection bias (towards patients who stayed at home) is likely in this study. In the retrospective cohort study reported on in chapter 2.2, chapter 3.2, chapter 4 and chapter 5, we selected patients after a prefixed interval from a cohort diagnosed within a two-years frame. This caused a selection bias towards patients with a relatively short disease duration, i.e., patients with glioblastoma multiforme over other HGG patients. Furthermore, physicians and relatives filled in the questionnaires after a relatively long interval since the patient's death, possibly introducing recall bias.

Questionnaire for relatives

We aimed to evaluate several topics important in the EOL phase: HRQoL of patients and proxies in the EOL phase, dying with dignity, and provided EOL care, for which we constructed a questionnaire for relatives (Appendix A).

Preferably, we should have selected an existing, validated instrument to measure HRQoL. Several instruments had been developed before to measure HRQoL in the EOL phase or in the palliative care setting[132-135] , but no measure includes all domains that are relevant for brain tumour patients. Vice versa, available brain tumour specific instruments [100-102, 137] do not capture all experiences unique to the dying process[128-130]. Moreover, both available palliative care-specific and brain tumour-specific instruments are patient-reported outcome measures to be used in prospective research. Hence, we developed a retrospective, proxy-based HRQoL questionnaire adapted from existing questionnaires in quality of life research [100-102, 137]. As described in chapter 3.2, we evaluated several psychometric properties of the domains of our proxy-based questionnaire. The questions about dying with dignity and decision-making were adapted from questionnaires previously used in EOL research [138].

Although patients are generally considered to be the best source to rate their quality of life [178], proxy ratings are regarded an appropriate alternative in situations where patients are cognitively impaired, incompetent, have a poor health status or are deceased. Given the fact that the majority of HGG patients develop cognitive deficits towards death[43, 56], proxy ratings are warranted for EOL research in these patients. Using proxy ratings is a generally acknowledged and commonly applied practice in EOL research [179].

Several studies have shown moderate to good agreement between patient and proxy ratings of the patients' HRQoL[107, 142, 144, 145, 180]. However, patient and proxy ratings tend to be more in agreement on symptom scales than on psychosocial scales [145, 146, 181], in particular in patients with cognitive impairment[107]. Furthermore, proxies tend to report more HRQOL problems than do patients themselves [105, 147]. Differences in responses do not necessary mean that proxy-reports are inaccurate. For example, in screening for major depression disorder in glioma patients, proxies appeared more reliable than patients in reporting objective behavioural symptoms of depression[182]Bereaved relatives may alter their assessments during bereavement [181] and ratings on the presence and severity of pain and depressive symptoms appear to decrease over time[183]. Probably, mood and mourning stage of the bereaved relative will affect the responses[181]. These considerations should be taken into account when interpreting our results.

Questionnaire for physicians

The information about the occurrence and treatment of seizures in the EOL phase we described in chapter 2.2 was derived from the questions about symptoms, signs and treatment of our questionnaire for physicians (Appendix B). One could argue that these questions are not detailed enough. For example, we did not ask for seizure frequency. Given the relatively long median interval between the patients' death and the completion of the questionnaire by the physician, more detailed questions would probably have been hard to answer for physicians. More detailed information about seizure frequency close before death should in future studies be obtained in a retrospective evaluation shortly after death.

The part of the questionnaire for physicians concerning EOL decisions (referred to as ELDs in chapter 4) was obtained from a repeated nation-wide death certificate study [24, 35, 149, 152]. In the original death certificate questionnaires, all questions about EOL decision-making include the phrase "taking into account the probable or certain life-shortening effect". In our pilot of the questionnaire, the questions were interpreted differently by physicians (unpublished data) as insights in EOL care and treatment evolved over the years. When the original questionnaire for the death certificate study [149] was developed in the early nineties, it was generally assumed that the admission of opioids and sedatives at the EOL had a potential life-shortening effect. More recent findings do not confirm these assumptions [161, 184, 185]. To this respect we slightly adapted our questionnaire by assessing whether the physician believed there was a life-shortening effect in a separate question. This approach makes our study not completely comparable with the national death certificate study. As our main aim was to gain insight into EOL practices, and not whether these decisions did or did not hasten death, we believe this is an appropriate approach. Probably, this adaptation resulted in a higher number of non-treatment decisions reported.

In the studies reported on in this thesis, we defined the EOL phase of HGG patient as 1) the time period starting from the moment the patient deteriorates while tumour-directed treatment is no longer possible or 2) the last three months of life. The main aim of treatment in this EOL phase is palliative or comfort-oriented treatment. This approach resembles the traditional "transition" model of care[186] as shown in figure 1, suggesting that there is a strict line between life-prolonging care and palliative care. However, in most patients with incurable diseases (including patients with HGG) this distinction is unclear. Early in the disease trajectory, the main aim of treatment is life-prolongation, but most patients need 'palliative' care aimed at treating symptoms as well, whereas near the EOL, some treatment options might still delay disease progression, while at the same time treatment is aimed at relieving symptoms and providing support. This approach is depicted in the "trajectory" model of care (figure 2), which was originally developed for frail elderly [186], and will apply for HGG patients as well.

A good example of (early) involvement of palliative care in current practice for HGG patients is the clinical nurse specialist in neuro-oncology. One of his/her main tasks is providing continuous supportive treatment and care to HGG patients and their relatives from diagnosis until bereavement which is valued highly[26, 187, 188]. Furthermore, early structural involvement of palliative care consultation in HGG patients should be considered. In patients with incurable lung cancer, this was found to have a positive impact on HRQoL, mood and EOL decision-making[189, 190].

Figure 1: Traditional "transition"model of care, showing an acute transition from life-prolonging treatment into symptomatic treatment. This figure illustrates the current care for high-grade glioma patients. Adapted from Lynn et al, 2003[186]

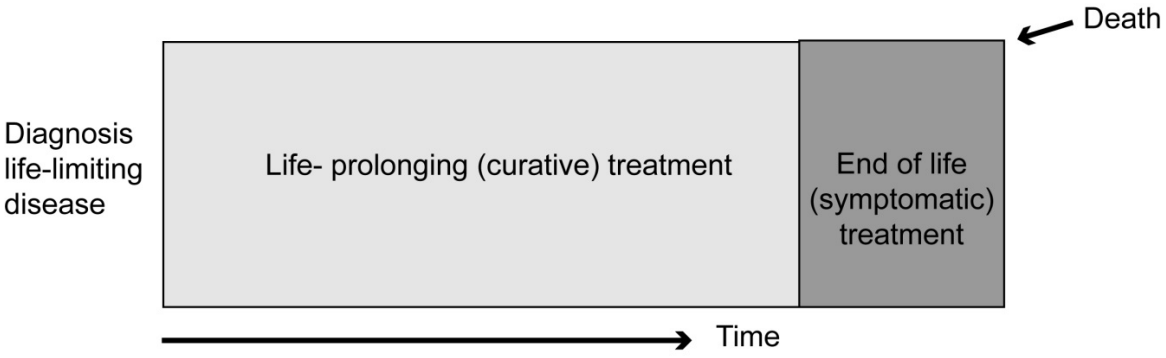
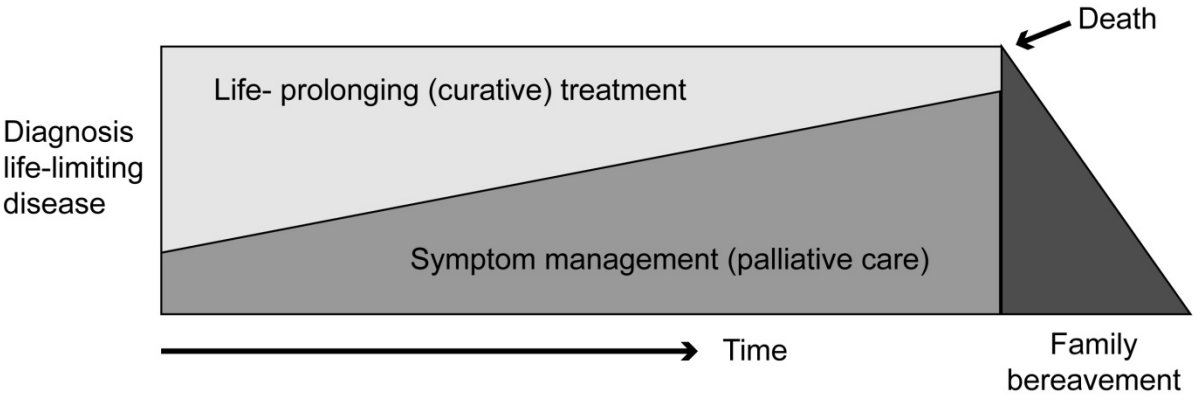


Figure 2 Trajectory model of care: palliative care is started from diagnosis along with life-prolonging treatment, and becomes increasingly important over time. This model of care may be more appropriate for HGG patients. Adapted from Lynn et al. 2003)[186]



Symptoms, signs and quality of life

We have shown that in the EOL phase of HGG patients, disease-specific symptoms as cognitive decline, progressive neurological deficits and seizures are prominent which is in accordance with the growing body of literature in this field[21, 25, 46, 48, 191]. This underlines the unique character of the EOL phase of HGG patients compared to general cancer patients[49]. Not only did disease-specific symptoms occur more often, the more generally acknowledged EOL symptoms such as dyspnoea, pain and anorexia occurred less often than in other patient groups.

Motor disability

In chapter 2.1, we have shown that half of the patients experience progressive neurological deficits. Furthermore, in chapter 3.2 we described that in both the last three months and in the last week of life, mean scores for motor disability are high and, probably consequently, low for physical functioning.

Tumour progression is probably the main cause of motor disability at the end-of-life and often refractory to steroids[122]. Steroid myopathy induced by long-term use is another potential source of immobility[192]. Patients and their relatives will thus have to cope with increasing handicap. In this context, there may be a role for palliative rehabilitation (i.e. physiotherapy, occupational therapy, provision of appliances and aids) to improve or maintain functional status, independency and participation as long as possible thereby maintaining HRQoL[193]. In patients with amyotrophic lateral sclerosis, rehabilitation plays an

important role in the symptomatic and palliative management[194, 195]. Multidisciplinary rehabilitation in these patients has shown to improve mental HRQoL[196].

A few studies have focused on rehabilitation in HGG patients demonstrating that rehabilitation may increase a brain tumour patient's functional status within a relatively short time[197, 198]. A rehabilitation intervention in the home care setting is feasible and probably effective as demonstrated in an Italian study: HRQoL of patients participating in the intervention improved over 3 months[57]. Moreover, patients participating in the home-rehabilitation programme were less often hospitalized in the last month of life than patients receiving usual care[44]. (Home) rehabilitation interventions should therefore be evaluated in a clinical trial with outcome measures such as HRQoL, quality of death, caregiver burden, caregiver mastery and cost-effectiveness.

Cognition, confusion and emotional well-being

In chapter 2.1 we reported that both cognitive deficits and confusion are present in approximately one third of patients and mean scores on proxy-reported cognitive functioning and emotional well-being decrease towards deaths as presented in chapter 3.2. Furthermore, in chapter 4 we have shown that cognitive disturbances and confusion are common reasons for decreased decision-making capacity.

Psychostimulants as modafinil and methylphenidate are suggested to have a potential beneficial effect on neurocognitive functioning, fatigue and quality of life of brain tumour patients [199]. However, a recent randomized controlled trial evaluating the effect of modafinil on fatigue, neurocognitive functioning and quality of life found that modafinil did not exceed the effect of placebo for symptom control[200]. Cognitive rehabilitation has proven to have a positive effect on short-term cognitive complaints and long-term cognitive functioning in patients with low-grade glioma and anaplastic glioma patients with favourable prognosis[201]. Cognitive rehabilitation in HGG glioma patients with poor prognosis is, however, less relevant.

Confusion at the EOL could be the result of delirium or behavioural disturbances and may alter the peaceful process of dying for patients and relatives[202-207]. Studies in various palliative care populations yielded recommendations concerning treatment and care of delirious patients in the end-of-life phase[203-205, 207-209]. When symptoms are refractory, the medication of first choice is usually a neuroleptic drug such as haloperidol[207, 208, 210-213]. However, neuroleptics might lower seizure threshold and should be prescribed with caution in patients with frequent seizures[209]. To this respect sedative drugs (midazolam, lorazepam) seem to be good treatment options in patients with confusion at the EOL[208, 210]. As evidence concerning the optimal treatment of confusion at the EOL is lacking, this could be a subject of evaluation in future studies.

Decreased emotional well-being could be a sign of major depressive disorder. In the treatment phase, approximately one in five patients develop major depressive disorder [214]. As there is a strong correlation between depression and decreased functional status[214, 215], it can be hypothesized that the prevalence of depression increases towards the EOL. Studies focusing on depression and its management in glioma patients should incorporate the EOL phase.

Seizures

As we have shown in both our retrospective chart study (chapter 2.1) as our retrospective cohort study (chapter 2.2), seizures are a serious problem in the EOL phase of HGG patients. We found that 45 % of patients have seizures after ending tumour treatment [47] and 29 % in the last week of life[216]. These results corroborate evidence from other retrospective studies published in the last 10 years[21, 25, 46, 48, 92, 191].

It remains unknown what pathophysiological processes induce seizures in the EOL phase. Several causes can be hypothesized. First, it can be the result of the progressing tumour or increasing oedema disturbing the local architecture. Second, it can be the consequence of metabolic change. Third, due to swallowing difficulties, AEDs are often tapered close before death thereby lowering the threshold for seizures to develop. However, our results do not support this final hypothesis since the patients in whom AEDs were continued until death more frequently experienced seizures than patients whose AEDs were tapered [216]. Nevertheless, since tapering occurred not random, we cannot draw any conclusions from these observations.

Guidelines for the prevention and treatment of seizures at the EOL are warranted. Given the fact that the majority of HGG patients develop swallowing difficulties and the apparent ineffectiveness of AEDs in the EOL phase, the focus should be on alternative AED administration routes, such as buccal or intranasal routes[67]. Besides, if we would be able to identify patients at risk for seizures in the last week of life, preventive treatment protocols could be specifically aimed at patients at risk. In our cohort study, we tried to identify predictors for the development of seizures in the last week of life. Apart from a history of status epilepticus, however, we found no significant predictors[216].

End-of-life decision-making

Practice of decision-making

In chapter 4, we discussed the decision-making process and reported that 60% of physicians were aware of the patients' ELD preferences, with only 3% of patients unwilling to discuss ELD preferences. Moreover, 42% of HGG patients had an advance directive according to

their relatives, but not all physicians were aware of this. These results suggest that the decision-making process in HGG patients could be improved. Most cancer patients wish to be involved in decision-making at the EOL[155] and it proved very important that physicians discuss EOL preferences with patients and their caregivers[148, 171, 172].

A Dutch study among GPs found that physicians tend to postpone EOL discussion until the last week of life[154]. As we have shown in our study, the large majority of HGG patients are incompetent to decide by that time. Preferences should thus be discussed early in the disease trajectory by means of advance care planning (ACP), thereby taking into account that the patients' decision-making capacity could be comprised relatively soon after diagnosis[43]. In ACP, one aims to reach consensus about how to act in possible EOL scenario's respecting both patients' and families' values[156]. A randomized controlled trial evaluating a video support tool to facilitate ACP in HGG patients found that the majority of patients is willing to discuss potential EOL scenarios[71]. Future studies should focus on effective interventions in ACP in HGG patients. For example, a facilitated ACP intervention has shown promising results in improving EOL care in elderly patients[217].

End-of-life decisions

We have shown that EOL practices occurred in approximately three quarter of HGG patients. Particularly, and specific for brain tumour patients, the withdrawal of dexamethasone at the EOL occurred frequently (45%). Furthermore, the prevalence of palliative sedation in our cohort of HGG patients (30%) is high; in the general Dutch population, only 12% of deaths are preceded by palliative sedation[24]. Although we did not explore for what refractory symptoms palliative sedation was started in our cohort, it is likely that there is a correlation with the high prevalence of confusion at the EOL as this is the most commonly reported reason for palliative sedation in terminal patients[157, 218]. Furthermore, one can imagine that physicians apply palliative sedation in patients with intractable seizures. Physician assisted death (i.e. euthanasia or physician assisted suicide) occurred in 7% of patients in our cohort, similar to the prevalence in all Dutch cancer patients (7.6%)[24].

The practice of EOL decision-making varies among countries and cultures[150]. Pace reported on EOL practices in an Italian population[48]: the prevalence of steroid tapering is similar whereas palliative sedation occurred more than twice as often in our population. Further insight in EOL practices in HGG patients among various countries and cultures are important in order to develop international applicable guidelines for palliative care in HGG patients.

<u>Dying with dignity</u>

In chapter 5, we addressed “dying with dignity”, an important outcome measure emerging as an overarching goal of palliative care. We found that one quarter of HGG patients did not die with dignity. This percentage is high as compared to general cancer patients where only 7% of patients reported they had a disturbed sense of dignity[169].

In line with previous studies[165], being able to communicate appeared to one of the most important factors for dignified death in HGG patients. Furthermore, satisfaction with the physician providing EOL care and whether the physicians explained possible treatment options were identified as important. A recent study evaluating dying with dignity in elderly patients confirmed these findings[219]. Since communication disturbances at the EOL are often irreversible, this underlines our above mentioned suggestion that EOL preferences and treatment should be discussed early in the disease process by means of ACP. Moreover, communication between different involved physicians about known preferences is important. Next to EOL treatment preferences, another important issue to discuss in ACP is preferred place of death. Dying with dignity was more common in patients who experienced no transitions in place of care at the EOL and who deceased at their preferred place of death. Clearly, if the physician is unaware of the patient’s preferred place of death, transitions in the last month of life, most often to the hospital, will increase[220]. As described above, home rehabilitation has proven to be effective in reducing the number of hospital admissions at the EOL[44].

Caregiver burden

Last, but definitely not least, caring for a patient with HGG puts a huge burden on informal caregivers as we discussed in chapter 1.2 In providing good palliative care to brain tumour patients, support for these caregivers is equally important. Discussing EOL preferences with both patient and relative by the physician decreases distress at the EOL and reduces the risk on major depressive disorder of the bereaved caregiver after death[171, 172]. Furthermore, a recent study showed that caregivers could benefit from a psychological intervention providing psychoeducation regarding disease-specific symptoms and the resulting problems, as well as cognitive behavioural therapy to increase the ability to cope with the demands of providing care to the patient[221].

6.3 Future prospects

In this thesis, we specifically explored the end-of-life (EOL) phase of high-grade glioma (HGG) patients. We identified several disease-specific topics which warrant improvement. Palliative care in HGG patients should not just be confined to the EOL phase, but be initiated relatively early in the disease process. The following suggestions for future research emerged from our findings so far.

First, we have shown that towards death, many HGG patients experience progressive neurological deficits. Consequently, both physical and cognitive functioning decrease and patients and their proxies will have to cope with the increasing handicap. Rehabilitation could help patients to maintain functional status, independency and participation as long as possible and prevent hospitalization in the last month of life[44]. This is highly relevant since - as we discussed in chapter 5 - transitions in the last month of life may hamper dying with dignity. Furthermore, less handicap and dependency of the patient will have a positive effect on informal caregivers. In the future, (home) rehabilitation interventions should be evaluated in (randomized) controlled studies. Outcome measures should include prospective evaluations of physical functioning of the patient, HRQoL of both patient and caregiver, dying with dignity, transitions in the last month of life, caregiver burden and caregiver mastery.

Second, we have established that seizures are a serious problem in the EOL phase, in particular in the last week of life. Future studies should be aimed at the identification of risk factors for the development of seizures at the EOL and the development of treatment protocols for patients at risk for seizures at the EOL. Since the majority of HGG patients have swallowing difficulties in the last week of life, alternative administration routes of anti-epileptic drugs are necessary to prevent acute withdrawal of medication.

Third, several findings from this thesis suggest that the EOL decision-making process warrants improvement. Physicians often did not discuss EOL preferences with the patients, possibly due to reluctancy to discuss this topic not until closely before dying when the patient is often no longer competent to make decisions. Furthermore, dying with dignity was correlated to decisions at the EOL being discussed. This argues for advance care planning (ACP), where one aims to explore the patients' and relatives' wishes in relation to end-of-life scenarios. In a study evaluating ACP in HGG patients it was demonstrated that the majority of patients is willing to discuss potential end-of-life scenarios and – once the various treatment options are clear – the majority prefers comfort care over life-prolonging treatment[71]. A facilitated ACP intervention has generated promising results in improving EOL care, achieving patient and caregiver satisfaction and reduce stress, anxiety and depression in surviving caregivers of elderly patients [217]. Whether such an intervention is applicable and useful in HGG patient and caregiver dyads should be evaluated in a prospective clinical trial.

Fourth, guidelines for the organization of health care around HGG patients at the EOL are lacking. Currently, EOL care depends on the involved health care providers. In further research, it is important to establish to what extent palliative care is embedded in providing care for HGG patients, at what time it is started and whether it is effective in improving HRQOL of the patients and proxies. Furthermore, in future studies, the value of early involvement of palliative care consultation in HGG patients should be evaluated as this could improve HRQOL, mood and the definition of treatment goals at the EOL[190].

Finally, as both medical-ethical values and legal aspects of EOL decision-making vary widely among countries and cultures, our results concerning EOL decisions in HGG patients cannot be generalized to patients outside the Netherlands. The organisation and facilities for palliative care will differ between countries and cultures. Comparison of palliative care, the decision-making process and EOL decisions in HGG patients amongst various countries and cultures will be useful to identify consistencies and differences. In this respect, our questionnaires were translated in English and German and sent to physicians and relatives of cohorts deceased HGG patients in Scotland and Austria. The results from this international comparison will be helpful in the development of internationally applicable guidelines.

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