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Chapter 4

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

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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 sedation¹⁴⁹. A large European study revealed that 23-51% of all deaths are preceded by an ELD depending on the cultural and legal background¹⁵⁰. In the Netherlands 44% of deaths are preceded by an ELD³⁵. 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 consciousness²⁵. 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 where 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.

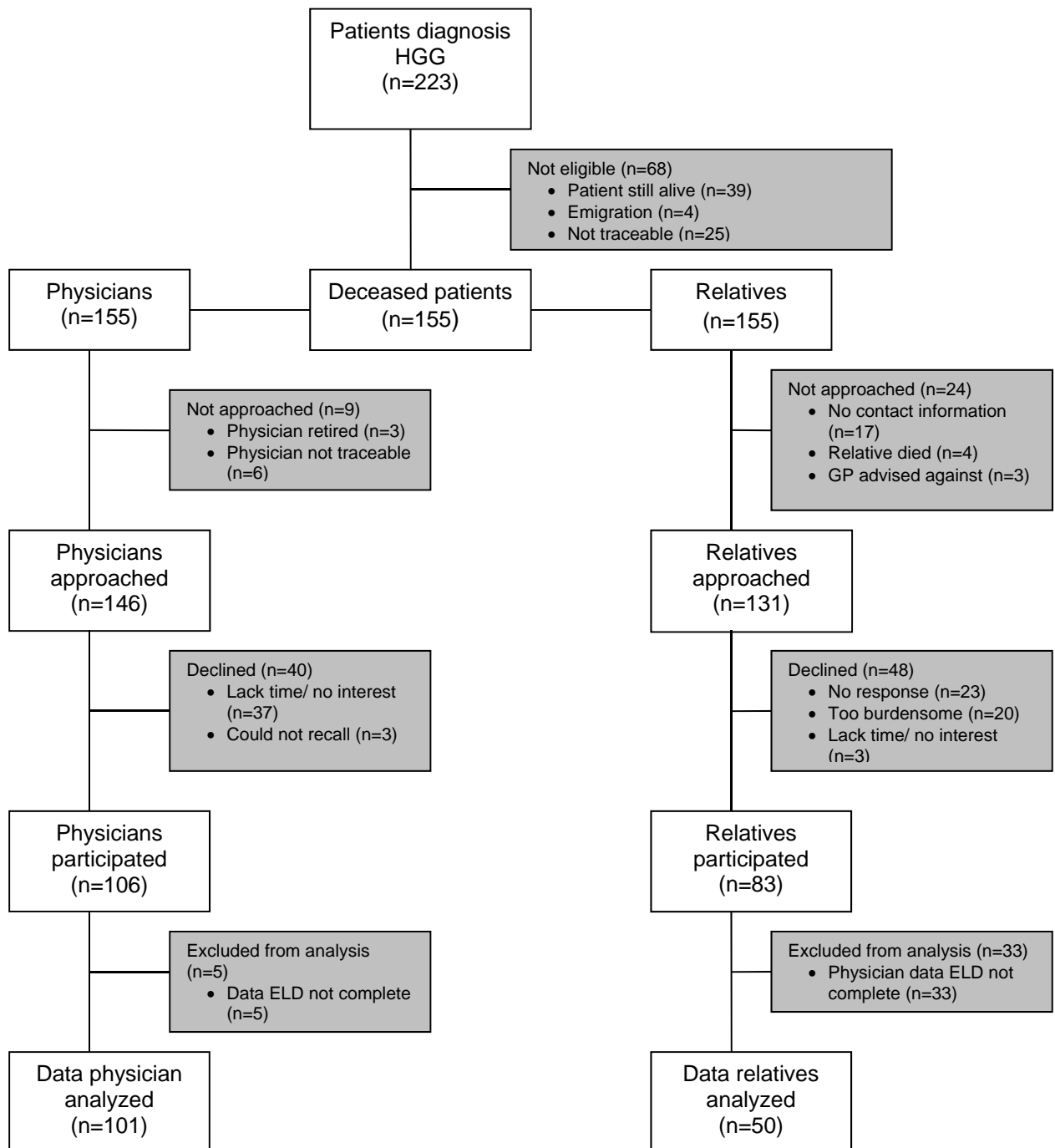
Results

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)

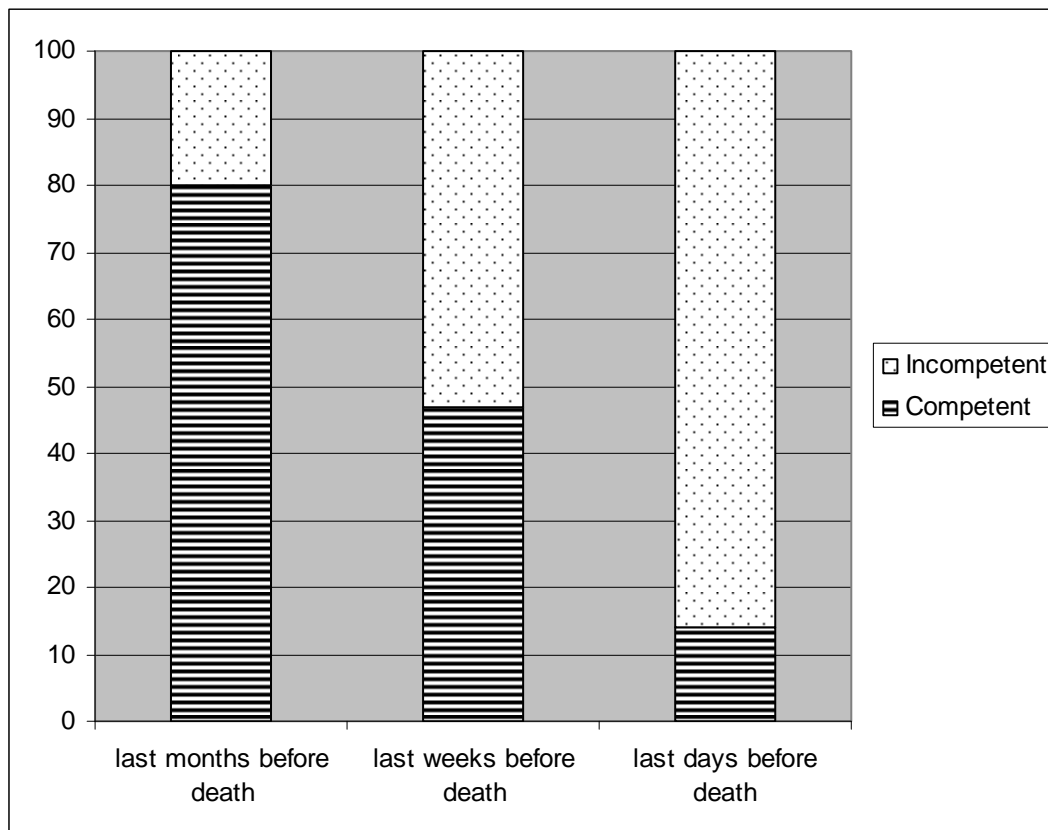
Any wishes expressed	60%
Specific wishes*:	
<i>Life prolonging treatment</i>	
▪ In favour	2%
▪ Opposed	36%
▪ No opinion/ not discussed	62%
<i>Admission to hospital</i>	
▪ In favour	4%
▪ Opposed to	45%
▪ Not discussed/ no opinion/ not applicable	51%
<i>Palliative sedation</i>	
▪ In favour	24%
▪ Opposed to	5%
▪ Not discussed / no opinion	71%
<i>Euthanasia</i>	
▪ 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, benzodiazepines 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 patients¹⁵⁴. Probably physicians postpone discussing ELDs until the last week before death¹⁵⁴. 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 decide⁴³. Since most cancer patients wish to be involved in decision-making at the end-of-life¹⁵⁵, our results underscore that ELD-making for HGG patients warrants improvement. Timely organization of ACP could contribute to improve ELD-making²⁵. The aim of ACP is to reach consensus about possible ELDs between all participants, respecting both patients' and families' values¹⁵⁶. 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 treatment⁷¹.

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 importance¹⁵⁶.

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 population⁴⁸. In comparison, in the general Dutch mortality figures, 13% of non-sudden deaths was preceded by palliative sedation³⁵. The main reason for palliative sedation in terminal patients is delirium and agitation¹⁵⁷. 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 research⁹¹, 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 sedation¹⁶¹.

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.