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

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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 data¹⁰⁸. 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 study⁹¹. 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 designs⁹¹. First, it is far less intensive and complex¹⁷⁷. 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 patients⁹¹.

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 setting¹³²⁻¹³⁵, 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 process¹²⁸⁻¹³⁰. 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 research¹³⁸.

Although patients are generally considered to be the best source to rate their quality of life¹⁷⁸, 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 research¹⁷⁹.

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 impairment¹⁰⁷. Furthermore, proxies tend to report more HRQOL problems than do patients themselves^{105, 147}. Differences in responses do not necessarily 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 depression¹⁸². Bereaved relatives may alter their assessments during bereavement¹⁸¹ and ratings on the presence and severity of pain and depressive symptoms appear to decrease over time¹⁸³. Probably, mood and mourning stage of the bereaved relative will affect the responses¹⁸¹. 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 study¹⁴⁹ 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.

End-of-life phase and palliative care

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 care¹⁸⁶ 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 elderly¹⁸⁶, 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, 2003¹⁸⁶

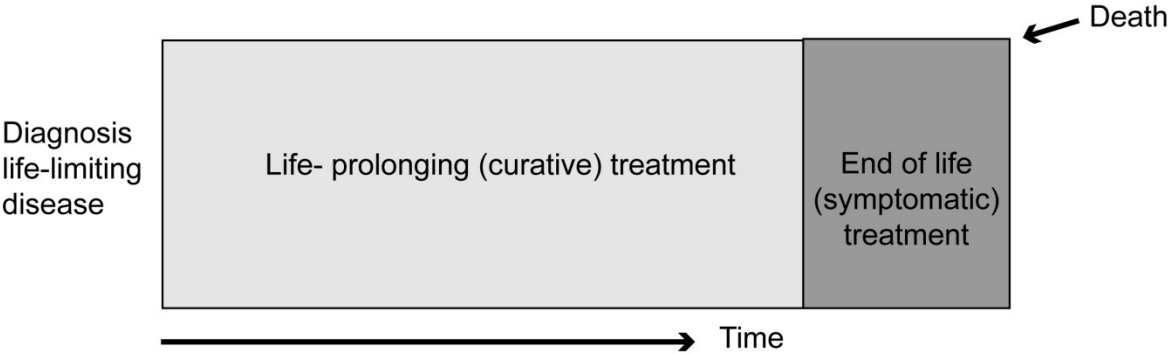
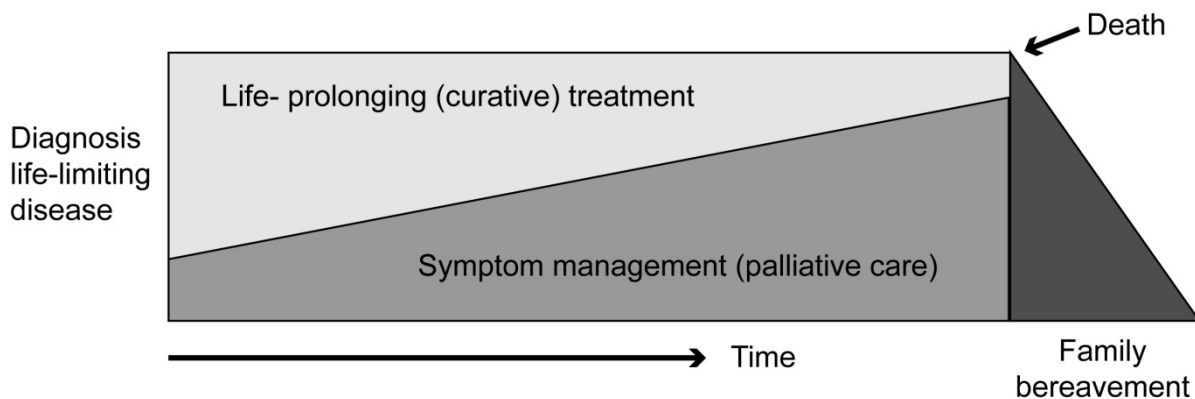


Figure 2 Trajectory model of care: palliative care is started from diagnosis along with life-prolonging treatment, and becomes increasingly important over time. This model of care may be more appropriate for HGG patients. Adapted from Lynn et al. 2003)¹⁸⁶



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 patients⁴⁹. 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 steroids¹²². Steroid myopathy induced by long-term use is another potential source of immobility¹⁹². 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 HRQoL¹⁹³. 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 HRQoL¹⁹⁶.

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 months⁵⁷. Moreover, patients participating in the home-rehabilitation programme were less often hospitalized in the last month of life than patients receiving usual care⁴⁴. (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 patients¹⁹⁹. 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 control²⁰⁰. 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 prognosis²⁰¹. 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 relatives²⁰²⁻²⁰⁷. 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 seizures²⁰⁹. 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 disorder²¹⁴. 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 treatment⁴⁷ and 29 % in the last week of life²¹⁶. 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 tapered²¹⁶. 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 routes⁶⁷. 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 predictors²¹⁶.

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 EOL¹⁵⁵ 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 life¹⁵⁴. 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 diagnosis⁴³. In ACP, one aims to reach consensus about how to act in possible EOL scenario's respecting both patients' and families' values¹⁵⁶. 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 scenarios⁷¹. 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 patients²¹⁷.

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 sedation²⁴. 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 cultures¹⁵⁰. Pace reported on EOL practices in an Italian population⁴⁸: 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.

Dying with dignity

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 dignity¹⁶⁹.

In line with previous studies¹⁶⁵, 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 findings²¹⁹. 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 increase²²⁰. As described above, home rehabilitation has proven to be effective in reducing the number of hospital admissions at the EOL⁴⁴.

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 patient²²¹.

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 life⁴⁴. 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 reluctance 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 treatment⁷¹. 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 patients²¹⁷. 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 EOL¹⁹⁰.

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.