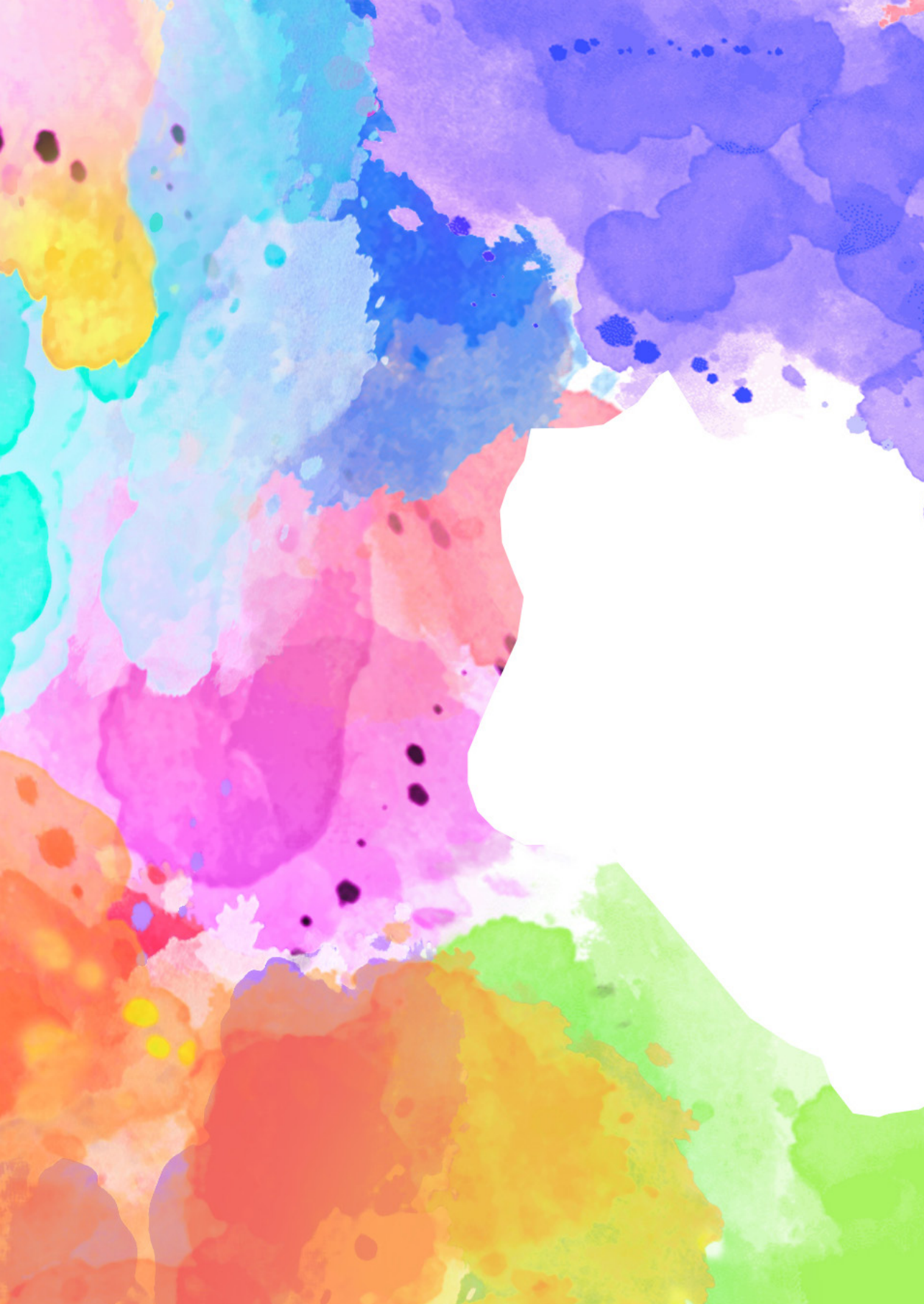
Measuring symptons and functioning in glioma patients

Peeters, M.C.M.



SUMMARY AND GENERAL DISCUSSION

CHAPTER 7

Summary and general discussion

A malignant brain tumor, either primary or secondary, is a serious condition that has a large impact on the lives of patients and their nearest. This is not limited to the patients' decreased life expectancy, but also includes the negative impact of the disease and its treatment on patients' Health-Related Quality of Life (HRQoL). **Chapter 1** of this thesis provides an overview of the epidemiology, pathophysiology and management of brain tumors, as well as the measurement of HRQoL aspects. In this chapter, the three main themes of this thesis are discussed: 1) prediagnostic symptoms and signs in glioma patients; 2) measuring HRQoL outcomes in glioma patients; and 3) implementing a disease-specific advance care planning (ACP) program for patients with glioblastoma.

First, the symptoms and signs patients with malignant primary brain tumors experience in the period before the diagnosis are discussed **(Part 1).** Knowledge on the full range of health problems patients experience in the period before diagnosis, as well as information on any prediagnostic health care usage due to these problems, was found to be scarce. A better insight into symptoms and problems in the prediagnostic period might help patients, proxies and healthcare professionals (HCPs) to recognize a glioma at an earlier stage.

Second, various aspects of the measurement of HRQoL in glioma patients are addressed, including the effect of timing of HRQoL measurements on the results and the preferences of patients, proxies and HCPs regarding their usage in routine clinical care **(Part 2)**. Insights into the optimal timing of HRQoL assessments as well as the implementation of patient-reported outcome (PRO) measures in clinical practice in glioma patients in the Netherlands was limited. More knowledge about the effect of the timing on HRQoL results could help to optimize the timing of their administration in clinical trials and in clinical practice, and subsequently enhance the value of HRQoL results. Also, information on the relevance of certain PROs, their timing and method of administration may facilitate implementation of PRO measures in clinical practice.

And third, the feasibility of implementing a disease-specific ACP program in clinical care for patients with glioblastoma and their nearest was investigated **(Part 3)**. For cancer patients in the end of life (EOL) phase, there is an increasing body of evidence that early palliative care is effective in improving HRQoL aspects, including mood. It is suggested that this might be achieved through ACP, which is a process by which patients and their physicians establish future goals of their care in the EOL phase, which offers patients the opportunity to define their goals and expectations[1]. A timely initiation of ACP seems warranted in glioblastoma patients, because they typically experience a cognitive decline which may seriously interfere with their ability to make decisions regarding treatment or care[2-4]. Early involvement in treatment decision-making therefore seems important[5], however, the optimal process of delivery of ACP in glioblastoma patients is largely unknown.

In the following sections, the results of the studies described in this thesis will be summarized and discussed.

Prediagnostic symptoms in glioma patients

Overall, and in line with previously published studies on prediagnostic symptoms and signs in brain tumor patients, both studies described in **Part 1** of this thesis (**Chapters 2 and 3**) found that several symptoms and signs (such as fatigue, mental tiredness, sleeping disorder, headache and stress) are relatively common before a patient is diagnosed with a brain tumor[6, 7]. In accordance with the conclusions of previous studies[8-10], these symptoms and signs were not more common than in other conditions, making it difficult to recognize patients with a glioma at an early stage.

The conclusions drawn in this thesis are based on two studies with different designs. First, a case-control study (**Chapter 2**) was performed, using data from anonymized general practitioner registries. In this study, the prevalence of nine clinical symptoms glioma patients may present with to the general practitioner in the five years prior to diagnosis was compared with those in patients with other central nervous system disorders or any other condition. A total of 36 glioma and 72 matched control patients were included. The control patients consisted of 36 patients with other central nervous system (CNS) diseases and 36 'other' patients (defined as those patients that did not meet the criteria for the other two groups, e.g. patients with back pain or the flu). In this case-control study, no differences in prevalence was found between the three predefined groups, except for a higher prevalence of motor symptoms in other CNS patients as compared to the glioma and 'other' patient groups in the period 60-24 months prior to diagnosis, and more mood disorders/fear in other CNS patients compared to the 'other' group in the period <6 months prior to diagnosis. Given these results, it was concluded that glioma patients could not be distinguished from both control groups with respect to the number or type of prediagnostic symptoms.

A fairly wide range of non-specific problems in the year prior to diagnosis was also seen in **Chapter 3**, describing a prospective cross-sectional study in 59 glioma patients with the aim to identify prediagnostic symptoms and signs. Using a 30-item study-specific questionnaire, it was found that the median number of perceived symptoms in the year before diagnosis was six, with the five most frequently mentioned problems being fatigue, mental tiredness, sleeping disorder, headache and stress. Twenty-six (44%) patients had visited the general practitioner (GP) related to at least one symptom. Patients who did consult their GP reported statistically significant more often muscle weakness than patients who did not consult their GP, whereas no other statistically significant differences were found.

Although the literature is in general conclusive with respect to the overall unspecific clinical presentation of glioma patients in general practice, the results from our two

studies on prediagnostic symptoms in glioma and their presentation in primary care are slightly different from previous research on this topic. It must be noted though, that previous studies are hampered by the fact that they included patients with brain tumors in general, whereas our studies comprised glioma patients only. Nevertheless, in two other clinical studies with brain tumor patients using primary care records[8, 9], and a systematic review on the symptomatic diagnosis of CNS cancer in primary care[10], it was confirmed that brain tumor patients may present with several symptoms before and/or at the time of diagnosis, for example a new-onset seizure, weakness (as a symptom), headache, confusion, memory complaints, visual disorder and the physical sign of motor loss on examination. However, patients with glioma could not be distinguished from those with other conditions, except for new-onset seizure, which was found to be associated with an elevated risk of a brain tumor, especially in those over sixty years old[8-10]. In contrast to the findings in these studies, we did *not* observe an increased prevalence of any specific symptom or sign in glioma patients as compared to patients with other conditions visiting the GP (**Chapter 2**). Moreover, within the group of patients with glioma, it appeared that symptoms in those visiting the GP were quite similar to those who did not, with the exception that patients who visited the GP experienced more often muscle weakness (**Chapter 3**). It is questionable though, if the difference in prevalence of muscle weakness is clinically sufficiently relevant to support that the GP is capable of distinguishing patients with a possible glioma from those with other conditions, with 9% of patients that did not visit the GP experiencing muscle weakness versus 42% of patients that did visit the GP. Although it could, in case of muscle weakness, be considered to perform further diagnostics, for example imaging, there is also literature suggesting otherwise. An important reason to refrain from further diagnostics lies in de overall low incidence of brain tumors and the weak association between symptoms and the presence of a tumor[8-10]. As an example, a study on direct-access computerized tomography (CT) for patients with chronic daily headache (headache for ≥15 days per month for longer than 3 months)[11] found that during the 8-year study period, a total of 4404 scans were performed. Of these, sixty scans (1.4%) yielded a probable pathophysiological cause of the headache, of which 22 concerned a brain tumor (14 meningiomas, one low-grade glioma, four pituitary tumors, and three metastases). Moreover, in case of rapidly growing aggressive brain tumors the result of imaging procedures may initially be negative. This is illustrated in various studies where patients presented with various symptoms that could possibly be related to a brain tumor, and initially showed no signs of a brain tumor, but were diagnosed with a brain tumor on repeated imaging[12, 13]. Since glioma is in almost all cases an incurable disease, earlier identification could lead to earlier treatment, but also a longer burden of disease. A recent study in incidentally discovered glioblastoma found that these tumors were often small and

patients had a good performance status, but earlier treatment did not result in a benefit in progression-free and overall survival[14].

Overall, both the literature and the results of the two studies described in this thesis indicate that the clinical presentation of glioma in general practice is usually with relatively unspecific symptoms and signs. A qualitative study reported that patients noticed subtle changes by themselves rather than a specific symptom or sign, and that relatives noticed these changes even earlier or more often than the patient itself, up to 6 months prior to diagnosis[15]. That study also provided patients' views on the possibilities to improve GP consultations to reduce diagnostic delay. The main conclusions were that vague symptoms require a thorough exploration and that patients should be encouraged to present their symptoms in the consultation, for example by bringing written lists of these symptoms and tracking multiple symptoms over time, and empowering patients to return if they think something is wrong. Several campaigns have been launched in recent years, for example in the Netherlands, to encourage patients to prepare for a visit to their doctor, by helping them to think about possibly relevant questions[16]. This may increase the quality of the consultation and perhaps also the diagnostic process. In addition, it was recommended to involve not only the patients, but their proxies as well[15]. Indeed, in our study presented in **Chapter 3,** patients were asked to fill in the study-specific questionnaire together with their proxies to minimalize the chance of missing certain signs and symptoms. A limitation of our study was that patients and proxies did not complete the survey independently, and that we were therefore not able to identify any discrepancies between their answers, and thus determine the added value of the involvement of proxies.

Prediagnostic symptoms in glioma: Implications for future research

With respect to future research, the results of both studies described in this thesis in combination with previously published literature, indicate that the early identification in general practice of patients with glioma based on their symptomatology seems extremely difficult. With respect to the management of patients presenting with a wide range of unspecific symptoms, the added value of the involvement of proxies could be a topic for future studies. In such studies, it can be determined to what extent a better and more comprehensive overview of the patients' complaints can be obtained if proxies are involved, and potential differences in experiences between patients and their proxies can be identified. Greater involvement of proxies in the assessment may not only be of value in the prediagnostic stage, but also in patients in whom the diagnosis glioma is eventually made. With a more comprehensive insight into the patient's health status before treatment, the effects of therapy and any changes in the clinical course can probably be better ascertained.

Prediagnostic symptoms in glioma: Implications for clinical practice

Regarding the implications for practice, in our prospective study (**Chapter 3**) we found that the majority of patients did not visit the GP in the year prior to diagnosis, even if they experienced symptoms. Moreover, because the majority of the prediagnostic symptoms of glioma patients are even more common in other conditions, no specific recommendation can be made that will improve the early detection of a brain tumor. Therefore, in all patients presenting with a range of unspecific symptoms, GPs are recommended to perform a thorough exploration. More education on prediagnostic symptoms could help GPs to also consider glioma as a possible diagnosis in these cases, even though the incidence is low. Consideration of this diagnosis in an earlier stage may lead to an earlier diagnosis and treatment. Moreover, it is advised to involve the patient's nearest, if possible. In particular the possible changes in personality or behavior and cognitive impairments are likely to be better recognized by proxies than patients themselves, and are common in brain tumor patients.

Education for the general population is questionable, as the incidence of primary brain tumors is low and symptoms largely overlap with many conditions that are far more common and less serious. However, as prompt and appropriate treatment for other conditions may be beneficial as well, a general encouragement to the public to visit their GP with persisting issues and appropriately prepare this visit (including an overview of the issues as well as relevant questions), is warranted.

The measurement of HRQoL in glioma patients

The studies described in **Part 2** of this thesis addressed the administration of HRQoL instruments in clinical care for glioma patients. **Chapter 4** described a randomized clinical trial in patients with glioma who completed the general cancer and brain-tumor specific EORTC Quality of Life Questionnaires (QLQ-C30 and QLQ-BN20) and the Hospital Anxiety and Depression Scale (HADS) at two time points to explore if HRQoL scores changed to a clinically relevant extent when administered between the moment of the Magnetic Resonance Imaging (MRI) scan and the day of the consultation with the physician about one week later. All 100 recruited patients completed the first measurement on the day of MRI-scan, and 49 of them completed the second questionnaire before and 51 after the consultation with the physician, respectively. Overall, there were no differences in the HRQoL scores and symptoms of anxiety or depression between the two groups at the two time points or with respect to changes over time. In the total group (n=100), the proportions of patients showing a clinically relevant change over time, either improvement or deterioration, ranged between 8-58% per scale, with only 3% of patients *not* having any clinically relevant change on any scale of the instruments in the one week period.

The finding that the HRQoL scores in this study were not influenced by the

administration of the questionnaire either before or after the consultation with the physician was not in concordance with our expectations. Previous literature showed that considerable uncertainty about the outcome of diagnostic procedures (e.g. an MRI) resulted in increased distress and worse emotional well being[17]. This finding suggests that higher anxiety levels and worse HRQoL scores are expected in patients who complete the questionnaires before the consultation with the physician. That we did not observe this could be due to the fact that most patients in our study (90%) had relatively stable disease, and their anxiety about the result of the MRI was proportionally low, irrespective of the confirmation of a favorable result by the physician, and thus not impacting their HRQoL scores.

Despite a lack of impact of the timing of the assessment relative to the MRI, clinically and statistically significant changes of HRQoL scores were seen in the one week time period, which was unexpected in a population in which the majority had (radiologically) stable disease. Possibly, the observed fluctuations are influenced by the patient's health status, as we found that patients with a better Karnofsky Performance Scale (KPS) score and patients without current antitumor treatment changed on less HRQoL scales[18]. Changes in HRQoL domains are expected when for example treatment changes. Indeed, other cancer patients reported for 9/15 scales of the EORTC QLQ-C30 an increased burden one week after chemotherapy administration compared to the day of chemotherapy administration, reflecting the impact of treatment[19]. The fact that we found clinically relevant changes in this small time period, i.e. the last week, in patients that were clinically and radiologically stable and did not undergo treatment changes, is concerning. The response format of one week is also important when analyzing clinical trial data, to determine the impact of treatment on the patients' functioning and well-being. Typically, in clinical studies so-called completion time windows are defined, reflecting the period in which a HRQoL questionnaire has to be completed with respect to the predefined moment of assessment. This is done to minimize the exclusion of questionnaires eligible for the evaluation of HRQoL at a certain time point, while retaining as much relevant information as possible. The duration of these completion time windows may vary within (i.e. different time window at different assessment points) and between studies, but typically exceeds this one week response period. The relevance of defining a completion time window has been highlighted in a study where the impact of the timing of administration of HRQoL measures relative to chemotherapy treatment of patients with small cell lung cancer or colorectal cancer was studied[20]. It was found that the definition of the time window resulted in statistical and potentially clinically relevant differences. Although not in this study, conclusions of treatment comparisons may be impacted by the definition of a time window. Careful consideration of a time window is therefore warranted, and even time windows of one week should be considered potentially problematic.

In **Chapter 5,** the perspective of patients, their proxies and healthcare professionals in the field of neuro-oncology with respect to the practicality of routinely measuring PROs in clinical practice for glioma patients was assessed. Overall, all participants were positive about the option to routinely assess PROs, including HRQoL measurements, in clinical care[21]. This observation was done in a qualitative study, where semi-structured interviews were conducted with glioma patients (n=24), their proxies (n=16) and healthcare professionals (n=35) involved in their treatment from eight Dutch neuro-oncology centers. It was found that the majority of patients, their proxies and healthcare professionals were willing to discuss the results of PRO measures during standard follow-up visits, with the questionnaires preferably being completed at home about one week before the consultation, with an equal amount preferring to complete the questionnaire on paper or online. Although healthcare professionals preferred that results would be discussed with the nurse specialist, only one third of patients and proxies agreed, with most preferring the physician as primary discussant. Functioning in daily life was considered to be an important topic to be part of the evaluation according to all three groups[21].

The overall favorable perception of patients, proxies and healthcare professionals in the field of neuro-oncology regarding the routine usage of PRO measures in clinical practice **(Chapter 5)** is in line with previous studies, reporting that patients are willing to routinely complete PRO measures and that their usage increases the frequency of discussion of relevant patient outcomes during consultations[22-25]. Although several studies have shown favorable results, these studies were performed in other countries, with different populations, and mainly the physician as discussant was investigated. To facilitate implementation of routine measurement of PRO measures in clinical practice in the Netherlands, it was therefore deemed necessary to first assess the preferences of all stakeholders involved in this specific setting.

Measurement of HRQoL in glioma patients: Implications for future research

Regarding the implications of the findings from our studies for future research on HRQoL outcomes in glioma patients, a number of recommendations can be made. To start with, the selection of instruments must be carefully considered. Regarding the content of these measures, there are measures that focus on one single concept or on multiple concepts, i.e. a multidimensional questionnaire. The selection of instruments depends on the desired topic(s) of measurement. First, it should be assessed whether there are validated questionnaires available that measure the desired topic(s), for example seizure or physical functioning. If there are no validated questionnaires, a study-specific questionnaire could be developed. For this, one could use items from existing item libraries, e.g. the EORTC Item Library or the Patient Reported Outcome Measurement Information System (PROMIS) Item Bank. If it is not

possible to select existing items, new items could be developed. It should be noted though, that these study-specific questionnaires would require additional examination of its psychometric properties, and cautious interpretation of the results is needed.

Currently, most PRO measures used in neuro-oncology are static, i.e., they consist of a fixed set of items, resulting in a separate score for all available single or multi-item scales. However, the relevance of certain scales may differ between patients, such as the impact of the disease on a patient's paid employment, which is only applicable to working patients. Moreover, the relevance of certain scales may change over time within the individual patient. For example, symptoms such as hair loss are more applicable in the actual treatment stage and not on the longer term, whereas others, such as returning to work or cognitive complaints after radiotherapy, are more relevant in the months and years after treatment[26]. To this end, the existing item libraries offer a solution: currently available questionnaires can be supplemented with single or multi-item scales from the item library. This will ensure that all relevant issues can be assessed. A downside is that the response burden for patients will increase by adding additional questions. With a computerized adaptive testing (CAT) assessment, presented items, drawn from an item library, are tailored to the answers to prior items, to estimate the patients score on a certain scale. This ensures more relevant questions for an individual patient and a reduction of the response burden, while comparability of scale scores is guaranteed. Examples of such an approach are the generic (PROMIS)[27] or the EORTC CAT[28].

The selection of PRO measures is also important for the comparability of study results. In many studies, a combination of disease-specific and generic questionnaires is chosen, enabling comparisons within and among patients with different conditions. This could give more insight in the burden of disease over time and/or in comparison with other (malignant) diseases. For example, in the study described in **Chapter 4**, a comprehensive set of instruments was used, consisting of validated disease-specific (i.e. EORTC QLQ-BN20) and cancer-specific HRQoL (i.e. EORTC QLQ-C30) questionnaires, as well as questionnaires focusing on other aspects, such as the HADS for emotional status. In **Chapter 2** a self-developed questionnaire on the presence of prediagnostic symptoms and healthcare usage was used, as no suitable existing questionnaires were available, which has hampered comparisons with other studies.

To facilitate comparisons among studies, standardization of outcome measurement is needed. In line with this demand, the Response Assessment in Neuro-Oncology Patient Reported Outcomes (RANO-PRO) working group proposed a core set of constructs that should be measured in all clinical trials for high-grade glioma patients, allowing for a better comparison of outcomes[29]. This core set does, however, not recommend specific measurement instruments, which could lead to variation in the selection of outcome measures and may hamper the interpretation and/or merging

of data from multiple studies. There are examples of core sets that are more detailed regarding the precise measurement instruments connected to the overarching constructs or domains, such as those developed by the International Consortium for Health Outcomes Measurement (ICHOM) Initiative[30-32]. In the field of cancer, currently standard sets for measuring outcomes in patients with colorectal cancer, breast cancer and advanced prostate cancer are available. Apart from the content and combination of PRO measures, the timing of follow-up is also important. In contrast with the RANO-PRO core set of constructs, the standard sets of the ICHOM initiative also provides a timeline with recommended time points for assessments. However, it should be recognized that the patient population of interest (poor prognosis versus good prognosis) and the research question also define the optimal time points for assessment (e.g. direct treatment toxicity versus longer term outcomes), which should be related to the time frames of the used instruments (e.g. last week or last month). Ideally the planning of follow-up measurements should be related to the standard follow-up schedule in clinical care, so that the results can not only provide valuable data for research but can also inform clinical decisions on the individual patient level.

Besides standardization of selection and timing of outcome measurements, standardization of data collection and the statistical analysis is also needed. For that purpose, accurate registration of *prognostic variables* such as e.g. tumor grade or age (case-mix variables), and *systematic recording of treatments* is also necessary. This would facilitate the interpretation of comparisons among populations, by enabling scientists to better adjust for case-mix variation and differences in concurrent care. In addition, there is a wide variety of analytical techniques used to evaluate HRQoL data in studies with glioma patients[33], which may possibly result in different interpretations of study results[34]. Standardization of analytical techniques with respect to certain research objectives is therefore warranted. Currently, the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) project is ongoing with the aim to provide recommendations on the analysis and interpretation of PROs in cancer clinical trials[35]. Ultimately, the goal is to use certain analytical methods for a certain research objective.

Apart from recommendations for the nature and timing of outcome measurement in the field of neuro-oncology, there may also be room for improvement of the quality of their *reporting*. In particular with the use of data that are routinely gathered in daily practice, the use of author guidelines for the reporting of observational studies, such as the reporting guidelines by The International Society of Quality of Life Research (ISOQOL)[36] and the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines[37] in neuro-oncology papers is to be advocated. This will ultimately improve the value of the reported HRQoL results for determining the net clinical benefit of a new treatment strategy as evaluated in a clinical trial or clinical decision-making.

Finally, most research in glioma patients is focused on the functioning and well-being of patients. Although this is evident, the impact of the condition on the patients' nearest must not be underestimated. Proxies of glioma patients are also affected by the disease, as may be reflected in their decreased level of HRQoL[38, 39]. As research in that area is relatively scarce, it is recommended to also study the consequences of the disease and its treatment on the functioning and well-being of proxies of glioma patients in greater detail.

Measurement of HRQoL in glioma patients: Implications for clinical practice

By routinely evaluating a patient's level of HRQoL, clinicians may be able to recognize changes in a patient earlier and respond to these changes[40, 41]. Furthermore, it may assist healthcare professionals to specifically address those topics important to the patient during the consultation and increase their awareness of the patients' overall HRQoL[24, 42]. Indeed, routine assessment of cancer patients' HRQoL was found to have a favorable impact on physician-patient communication and resulted in benefits for some patients, who reported better HRQL and emotional functioning [25].

Despite the possible benefits of routine monitoring as mentioned above, several challenges have been described, including the method of data collection (e.g., paper or electronic) and the need for training of healthcare professional to support them with the interpretation of the results[43]. Overall, the routine assessment of PROs would be easier if patients would fill in the questionnaires digitally, as scale scores can be calculated directly and presented visually, facilitating the interpretation. Nevertheless, in our study about one third of patients reported to prefer to receive the questionnaire on paper, possibly hampering implementation[21]. The main reason to prefer one method over the other concerned convenience in both the patients preferring paper and digital versions. We did not examine whether and to what extent perceived convenience was related to specific skills, in particular in those preferring pen and paper. Overall, it must be acknowledged that a proportion of patients may not have the (computer) skills or have a visual or motor impairment that hinders them to complete questionnaires. Adequate identification of those patients needing extra support or ensuring an alternative approach may prevent inequalities in the provision of care.

The studies in this thesis did not address the question as to whether and to what extent patients would like to have access to the outcomes themselves, in order to self-monitor their health status over time. That option would not only require a system where scale and summary scores are computed and presented at layman level, but also the availability of cut-off points for situations where extra or earlier clinical encounters are needed, either by warning the patient or the healthcare professional[44, 45].

Advance Care Planning (ACP)

During the course of the disease, progressive cognitive decline may seriously interfere with glioma patients' ability to make decisions regarding treatment and/or care[4]. It therefore seems important to involve glioma patients in decision-making early in the disease trajectory[5]. A way to achieve this is with ACP, a process to involve patients and their proxies at an early stage in decision-making on future (palliative) care, including EOL care[46]. **Part 3** of this thesis concerned the evaluation of the pilot implementation of an ACP program in glioblastoma patients in a Dutch neuro-oncology setting. Previously, a disease-specific ACP program was developed, of which the contents and timing were based on the outcomes of a focus group with healthcare professionals and individual, semi-structured interviews with glioblastoma patients and their proxies (of both living and deceased patients)[47]. Although participants in this qualitative study agreed on the suggested final content of the program, the optimal timing of the introduction of such a program was a matter of debate. The results indicated that it would likely be most appropriate to offer the program shortly after diagnosis, but to let patients and proxies decide which (EOL) topics they wanted to discuss[47].

The feasibility of implementing such an ACP program as well as the impact of the program with regard to several patient-related and care-related outcomes was evaluated in a next step, as described in **Chapter 6**. In a longitudinal prospective study, 20 glioblastoma patients and (if available) their proxies were recruited in a single neuro-oncology center in the Netherlands. Two scheduled ACP sessions were offered to each patient-proxy dyad, facilitated by a trained research nurse. Within this program, the facilitator, the patient and/or his/her proxy reflected on the patient's goals, values and beliefs, and discussed topics such as future choices about health care, both in terms of tumor and supportive treatment, as well as the preferred place for the delivery of care and dying. Patients were encouraged to document their wishes about EOL care in an Advance Directive (AD), but this was not mandatory. The evaluation of the ACP program was based on study-specific questionnaires and several validated measures were used to assess aspects of functioning and well-being of both patients and proxies, as well as satisfaction with the provided care and health resource utilization.

The results of the program evaluation revealed that the large majority of patients and proxies rated the different aspects of the ACP program (such as the topics, number of sessions, duration of the session, functioning of the facilitator) as acceptable, whereas the overall quality rating ranged from somewhat good to excellent by most participants. These results suggest that the content and design of the currently available ACP program is sufficient. Similar to the results from the developmental phase[47], the preference for the optimal timing of initiation of the ACP program was highly variable. Although patients and proxies appeared not open to discuss difficult topics in the early disease stages, healthcare professionals in the longitudinal follow-up study indicated

that is important to initiate these discussions as early as possible due to the possible rapid decline in cognitive functioning glioblastoma patients may experience, hampering decision-making[2-4]. Although patients in the longitudinal follow-up study had significantly lower levels of functioning and more symptoms compared to the general population[48], aspects of HRQoL overall remained relatively stable during the study period. A substantial amount of patients did report anxiety and depression, and this proportion even increased over time. Overall, patients were satisfied with the provided care over time, whereas proxies were less satisfied as compared to patients. With respect to the proxies, we found that they reported significantly lower scores in the physical and mental domains compared to the general population, and a large proportion of proxies reported anxiety and/or depression during the disease course. These results emphasize the impact of the disease on the proxies' functioning and well-being. Nevertheless, the needed level of support was relatively low throughout the disease course, and the level of feelings of caregiver mastery were relatively high.

This study contributes to an increasing body of evidence on early palliative care initiatives[49, 50]. The effectiveness of ACP, in terms of more family satisfaction and reduced stress, anxiety, and depression in surviving relatives, has previously been demonstrated by means of randomized clinical trials (RCTs) in, among others, elderly patients[51] and in patients with congestive heart failure or end-stage renal disease[52]. Until recently, research into the impact of this intervention on outcomes in patients with brain tumors was scarce. A previously published study suggested that early and structured ACP might improve symptom control and HRQoL aspects in brain tumor patients[53], although this was not investigated directly. Other studies, in glioma patients specifically, found that timely discussion of possibilities of care in the EOL phase resulted in patients dying at their preferred place and increased feelings of dying with dignity[54, 55]. In our study, we did not find a reduction in feelings of anxiety and depression in proxies, but a significant increase in feelings of anxiety and depression in patients when comparing the first and last assessment. However, there are many factors that, apart from the ACP intervention, may influence feelings of anxiety and depression. The impact of such factors may vary largely among patients and may be difficult to measure, for example societal and environmental factors. But, most importantly, the non-randomized study design in combination with the small sample size hamper the ability to draw conclusions on the exact impact of the ACP program on the outcomes of glioblastoma patients and proxies.

Advance Care Planning: Implications for future research

The relatively positive results of the longitudinal study on the implementation of a disease-specific ACP program for glioblastoma patients **(Chapter 6)** warrant the need for a larger, international controlled study. In such a possible RCT it is recommended

to involve more patients as well as centers to account for heterogeneity. By involving a larger sample size with patients from different countries, possible differences in culture and religion, which may have an impact on the effectiveness of such a program, can be taken into account[56-58]. Attention is also needed for the appropriate selection of patients and proxies who may benefit from the intervention, since some patients may decline participation in an ACP program. Indeed, in our study about one third of the eligible patients approached for participation declined, most of whom indicated that such a program was emotionally too difficult or that the topic EOL was not relevant for them yet.

To ensure the quality of the intervention, appropriate training of the facilitators, as well as regular audits of their practices are needed. With respect to the measurement of potential outcomes, it is to be discussed if HRQoL or anxiety and depression are the most suitable primary outcomes. It is conceivable that for the detection of differences in the provision of care, measures of satisfaction with various aspects of care that are particularly relevant in this stage of the disease and specifically addressed by the ACP program may be more appropriate. Thus, measures reflecting aspects of perceived quality of care such as autonomy and involvement in clinical decisions could possibly better suit the aim and nature of the intervention. Furthermore, it is hypothesized that ACP mainly benefits the relational domain[49] and therefore mastery, reflecting the belief to be able to control or influence life events and that one is competent or effective in managing those events, and might therefore also be considered a suitable primary outcome[60]. Further research into the optimal study design, timing and the primary endpoint is warranted before commencing such a study.

Advance Care Planning: Implications for clinical practice

The literature as well as the results of the studies performed to develop and evaluate the implementation of a disease-specific ACP program in glioblastoma patients[47], clearly underline the importance of appropriate care and support in the EOL phase. In fact, the care and support provided for glioblastoma patients from the moment of diagnosis must be seen as a continuum, with differences in emphasis on specific aspects throughout the disease trajectory. The conduct of the longitudinal follow-up study, that was embedded in daily practice, made it also clear that there are various issues and practicalities that need to be taken into account. Since most patients who declined to participate indicated that this was because they were emotionally overwhelmed, we let patients and proxies who did participate decide which topics they wanted to discuss to reduce the emotional burden. Nevertheless, patients were provided with a folder with all possible topics that could become relevant for them in the future (e.g. palliative sedation), possibly triggering patients to at least think about these topics. Furthermore, regarding the timing of the program, we suggest to first offer the program after

chemoradiation, and for those who decline, mention the availability of the program again at a later stage, for example after 3 and 6 adjuvant chemotherapy cycles.

It is also important to realize that the proxy plays an important role in the disease process, and may have questions and concerns other than those of the patient that need attention. The healthcare professionals providing the ACP program should be prepared for these questions and involve the proxy as much as possible in the process. Apart from providing information and concrete advice[61, 62], there are several interventions available to improve the knowledge of patients and caregivers[63], improve the caregivers' level of social support[64], or establish caregiver mastery through a psychological intervention[65]. This may not only benefit the patient, but also the well-being of proxies. In addition, from the organizational perspective, it is relevant to consider the resources, in particular time, needed to identify patients and proxies that could probably benefit from the intervention, contact and inform them and, most importantly, deliver the consultations for the program. Besides, a healthcare professional must be trained, and also needs to be available for questions and issues in-between scheduled sessions. Furthermore, the program should be in alignment with care delivered by healthcare professionals involved in palliative care in primary care such as the GP, and professionals working in home care, nursing homes or hospices.

References

1. Pace A, Dirven L, Koekkoek JAF, Golla H, Fleming J, Rudà R, et al. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. The Lancet Oncology. 2017;18(6):e330-e40.

2. Kerrigan S, Erridge S, Liaquat I, Graham C, Grant R. Mental incapacity in patients undergoing neuro-oncologic treatment: a cross-sectional study. Neurology. 2014;83(6):537-41.

3. Sizoo EM, Pasman HR, Buttolo J, Heimans JJ, Klein M, Deliens L, et al. Decision-making in the end-of-life phase of high-grade glioma patients. Eur Journal Cancer . 2012;48(2):226-32.

4. Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. Neurology. 2009;73(24):2086-92.

5. Fritz L, Dirven L, Reijneveld JC, Koekkoek JA, Stiggelbout AM, Pasman HR, et al. Advance Care Planning in Glioblastoma Patients. Cancers (Basel). 2016;8(11):102

6. Peeters MC, Dirven L, Koekkoek JA, Numans ME, Taphoorn MJ. Prediagnostic presentations of glioma in primary care: a case-control study. CNS Oncol. 2019;8(3):CNS44.

7. Peeters MCM, Dirven L, Koekkoek JAF, Gortmaker EG, Fritz L, Vos MJ, et al. Prediagnostic symptoms and signs of adult glioma: the patients' view. J Neurooncol. 2020;146(2):293-301.

8. Hamilton W, Kernick D. Clinical features of primary brain tumours: a case-control study using electronic primary care records. Br J Gen Pract. 2007;57(542):695-9.

9. Ozawa M, Brennan PM, Zienius K, Kurian KM, Hollingworth W, Weller D, et al. Symptoms in primary care with time to diagnosis of brain tumours. Fam Pract. 2018;35(5):551-8.

10. Schmidt-Hansen M, Berendse S, Hamilton W. Symptomatic diagnosis of cancer of the brain and central nervous system in primary care: a systematic review. Fam Pract. 2015;32(6):618-23.

11. Simpson GC, Forbes K, Teasdale E, Tyagi A, Santosh C. Impact of GP direct-access computerised tomography for the investigation of chronic daily headache. Br J Gen Pract. 2010;60(581):897-901.

12. Chittiboina P, Connor DE, Jr., Caldito G, Quillin JW, Wilson JD, Nanda A. Occult tumors presenting with negative imaging: analysis of the literature. J Neurosurg. 2012;116(6):1195-203.

13. Hakan T, Çelikoglu E. Glioblastoma Shortly after a Normal Conventional Brain Magnetic Resonance Imaging: A Report of Two Cases and Review of the Literature. Asian J Neurosurg. 2021;16(2):433-6.

14. Kawauchi D, Ohno M, Honda-Kitahara M, Miyakita Y, Takahashi M, Yanagisawa S, et al. The clinical characteristics and outcomes of incidentally discovered glioblastoma. J Neurooncol. 2022:156(3):551-7.

15. Walter FM, Penfold C, Joannides A, Saji S, Johnson M, Watts C, et al. Missed opportunities for diagnosing brain tumours in primary care: a qualitative study of patient experiences. Br J Gen Pract. 2019;69(681):e224-e35.

16. Patiëntenfederatie Nederland. Available from: https://begineengoedgesprek.nl/. [Accessed 7th April 2022]

17. Bauml JM, Troxel A, Epperson CN, Cohen RB, Schmitz K, Stricker C, et al. Scan-associated distress in lung cancer: Quantifying the impact of "scanxiety". Lung Cancer. 2016;100:110-3.

18. Peeters MCM, Zwinkels H, Koekkoek JAF, Vos MJ, Dirven L, Taphoorn MJB. The Impact of the Timing of Health-Related Quality of Life Assessments on the Actual Results in Glioma Patients: A Randomized Prospective Study. Cancers (Basel). 2020;12(8):2172.

19. Giesinger JM, Loth FLC, Aaronson NK, Arraras JI, Caocci G, Efficace F, et al. Thresholds for clinical importance were established to improve interpretation of the EORTC QLQ-C30 in clinical practice and research. J Clin Epidemiol. 2020;118:1-8.

20. Ediebah DE, Coens C, Maringwa JT, Quinten C, Zikos E, Ringash J, et al. Effect of completion-time windows in the analysis of health-related quality of life outcomes in cancer patients. Ann Oncol. 2013;24(1):231-7.

21. Peeters M, Ottenheijm G, Bienfait P, Eekers D, Gijtenbeek A, Hanse M, et al. Glioma patient-reported outcomes: patients and clinicians. BMJ Support Palliat Care. 2021;bmjspcare-2020-002699.

22. Kotronoulas G, Kearney N, Maguire R, Harrow A, Di Domenico D, Croy S, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol. 2014;32(14):1480-501.

23. Brown RF, Butow PN, Dunn SM, Tattersall MH. Promoting patient participation and shortening cancer consultations: a randomised trial. Br J Cancer. 2001;85(9):1273-9.

24. Detmar SB, Muller MJ, Schornagel JH, Wever LD, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. JAMA. 2002;288(23):3027-34. (Erratum in: JAMA. 2003;289(8):987)

25. Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clinical Oncol. 2004;22(4):714-24.

26. IJzerman-Korevaar M, Snijders TJ, de Graeff A, Teunissen S, de Vos FYF. Prevalence of symptoms in glioma patients throughout the disease trajectory: a systematic review. J Neurooncol. 2018;140(3):485-96.

27. Alonso J, Bartlett SJ, Rose M, Aaronson NK, Chaplin JE, Efficace F, et al. The case for an international patient-reported outcomes measurement information system (PROMIS®) initiative. Health Qual life Outcomes. 2013;11:210.

28. Petersen MA, Aaronson NK, Arraras JI, Chie WC, Conroy T, Costantini A, et al. The EORTC CAT Core-The computer adaptive version of the EORTC QLQ-C30 questionnaire. Eur JCancer. 2018;100:8-16.

29. Armstrong TS, Dirven L, Arons D, Bates A, Chang SM, Coens C, et al. Glioma patient-reported outcome assessment in clinical care and research: a Response Assessment in Neuro-Oncology collaborative report. The Lancet Oncology. 2020;21(2):e97-e103.

30. Zerillo JA, Schouwenburg MG, van Bommel ACM, Stowell C, Lippa J, Bauer D, et al. An International Collaborative Standardizing a Comprehensive Patient-Centered Outcomes Measurement Set for Colorectal Cancer. JAMA Oncol. 2017;3(5):686-94.

31. Ong WL, Schouwenburg MG, van Bommel ACM, Stowell C, Allison KH, Benn KE, et al. A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer: The International Consortium for Health Outcomes Measurement (ICHOM) Initiative. JAMA Oncol. 2017;3(5):677-85.

32. Morgans AK, van Bommel AC, Stowell C, Abrahm JL, Basch E, Bekelman JE, et al. Development of a Standardized Set of Patient-centered Outcomes for Advanced Prostate Cancer: An International Effort for a Unified Approach. Eur Urol. 2015;68(5):891-8.

33. Coomans MB, Peeters MCM, Koekkoek JAF, Schoones JW, Reijneveld J, Taphoorn MJB, et al. Research Objectives, Statistical Analyses and Interpretation of Health-Related Quality of Life Data in Glioma Research: A Systematic Review. Cancers (Basel). 2020;12(12).

34. Coomans MB, Taphoorn MJB, Aaronson NK, Baumert BG, van den Bent M, Bottomley A, et al. Measuring change in health-related quality of life: the impact of different analytical methods on the interpretation of treatment effects in glioma patients. Neurooncol Pract. 2020;7(6):668-75.

35. Coens C, Pe M, Dueck AC, Sloan J, Basch E, Calvert M, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. Lancet Oncol. 2020;21(2):e83-e96.

36. Brundage M, Blazeby J, Revicki D, Bass B, de Vet H, Duffy H, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Qual Life Res. 2013;22(6):1161-75.

37. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.

38. Minaya Flores P, Berbis J, Chinot O, Auquier P. Assessing the quality of life among caregivers of patients with gliomas. Neurooncol Pract. 2014;1(4):191-7.

39. Faithfull S, Cook K, Lucas C. Palliative care of patients with a primary malignant brain tumour: case review of service use and support provided. Palliat Med. 2005;19(7):545-50.

40. Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA. 2017;318(2):197-8.

41. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clinical Oncol. 2016;34(6):557-65. Erratum in: J Clin Oncol. 2016;34(18):2198. Erratum in: J Clin Oncol. 2019;37(6):528.

42. Velikova G, Keding A, Harley C, Cocks K, Booth L, Smith AB, et al. Patients report improvements in continuity of care when quality of life assessments are used routinely in oncology practice: secondary outcomes of a randomised controlled trial. Eur J Cancer. 2010;46(13):2381-8.

43. Sztankay M, Wintner LM, Roggendorf S, Nordhausen T, Dirven L, Taphoorn MJB, et al. Developing an e-learning course on the use of PRO measures in oncological practice: health care professionals' preferences for learning content and methods. Support Care Cancer. 2022;30(3):2555-67.

44. Hughes EF, Wu AW, Carducci MA, Snyder CF. What can I do? Recommendations for responding to issues identified by patient-reported outcomes assessments used in clinical practice. J Support Oncol. 2012;10(4):143-8.

45. Blackford AL, Wu AW, Snyder C. Interpreting and Acting on PRO Results in Clinical Practice: Lessons Learned From the PatientViewpoint System and Beyond. Medi Care. 2019;57 Suppl 5 Suppl 1(Suppl 5 1):S46-s51.

46. Andreassen P, Neergaard MA, Brogaard T, Skorstengaard MH, Jensen AB. The diverse impact of advance care planning: a long-term follow-up study on patients' and relatives' experiences. BMJ Support Palliat Care. 2017;7(3):335-40.

47. Fritz L, Zwinkels H, Koekkoek JAF, Reijneveld JC, Vos MJ, Dirven L, et al. Advance care planning in glioblastoma patients: development of a disease-specific ACP program. Support Care. 2020;28(3):1315-24.

48. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur J Cancer. 2019;107:153-63.

49. Korfage IJ, Carreras G, Arnfeldt Christensen CM, Billekens P, Bramley L, Briggs L, et al. Advance care planning in patients with advanced cancer: A 6-country, cluster-randomised clinical trial. PLoS Med. 2020;17(11):e1003422.

50. Jain A, Corriveau S, Quinn K, Gardhouse A, Vegas DB, You JJ. Video decision aids to assist with advance care planning: a systematic review and meta-analysis. BMJ Open. 2015;5(6):e007491.

51. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. BMJ. 2010;340:c1345.

52. Finlay E, Shreve S, Casarett D. Nationwide veterans affairs quality measure for cancer: the family assessment of treatment at end of life. J Clinl Oncol. 2008;26(23):3838-44.

53. Walbert T. Integration of palliative care into the neuro-oncology practice: patterns in the United States. Neurooncol Pract. 2014;1(1):3-7.

54. Flechl B, Ackerl M, Sax C, Oberndorfer S, Calabek B, Sizoo E, et al. The caregivers' perspective on the end-of-life phase of glioblastoma patients. J Neuro-oncol. 2013;112(3):403-11.

55. Sizoo EM, Taphoorn MJ, Uitdehaag B, Heimans JJ, Deliens L, Reijneveld JC, et al. The end-of-life phase of high-grade glioma patients: dying with dignity? Oncologist. 2013;18(2):198-203.

56. Perkins HS, Geppert CMA, Gonzales A, Cortez JD, Hazuda HP. Cross-cultural similarities and differences in attitudes about advance care planning. J Gen Intern Med. 2002;17(1):48-57.

57. Pereira-Salgado A, Mader P, Boyd LM. Advance care planning, culture and religion: an environmental scan of Australian-based online resources. Austral Health Rev. 2018;42(2):152-63.

58. Jimenez G, Tan WS, Virk AK, Low CK, Car J, Ho AHY. Overview of Systematic Reviews of Advance Care Planning: Summary of Evidence and Global Lessons. J Pain Symptom Manage. 2018;56(3):436-59.e25.

59. Barnes K, Jones L, Tookman A, King M. Acceptability of an advance care planning interview schedule: a focus group study. Palliat Med. 2007;21(1):23-8.

60. Christensen KA, Stephens MA, Townsend AL. Mastery in women's multiple roles and well-being: adult daughters providing care to impaired parents. Health Psychol. 1998;17(2):163-71.

61. Schubart JR, Kinzie MB, Farace E. Caring for the brain tumor patient: family caregiver burden and unmet needs. Neuro Oncol. 2008;10(1):61-72.

62. Boele FW, Grant R, Sherwood P. Challenges and support for family caregivers of glioma patients. British Journal of Neuroscience Nursing. 2017;13(1):8-16.

63. Langbecker D, Janda M. Systematic review of interventions to improve the provision of information for adults with primary brain tumors and their caregivers. Front Oncol. 2015;5:1.

64. Hricik A, Donovan H, Bradley SE, Given BA, Bender CM, Newberry A, et al. Changes in caregiver perceptions over time in response to providing care for a loved one with a primary malignant brain tumor. Oncol Nurs Forum. 2011;38(2):149-55.

65. Boele FW, Hoeben W, Hilverda K, Lenting J, Calis AL, Sizoo EM, et al. Enhancing quality of life and mastery of informal caregivers of high-grade glioma patients: a randomized controlled trial. J Neurooncol. 2013;111(3):303-11.