Measuring symptons and functioning in glioma patients

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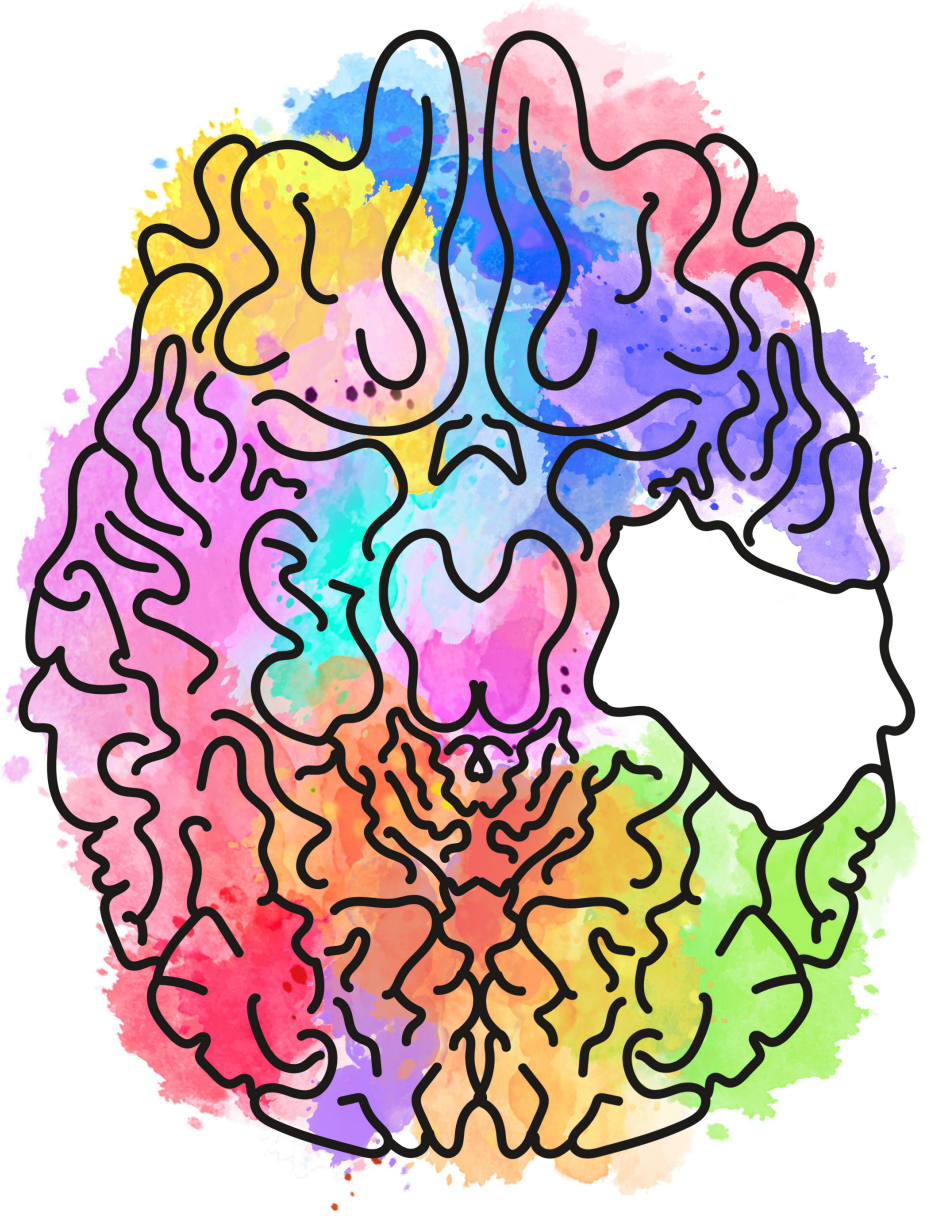

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"We must row in whatever boat we find ourselves in."
Christie Watson

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INTRODUCTION

CHAPTER 1

General introduction and outline

Introduction

Having a malignant brain tumor is a serious condition, with a significant impact on the patient's health-related quality of life (HRQoL) and life expectancy. This thesis focuses on patients with glioma, the most common form of primary malignant brain tumors. In short, this thesis addresses the symptoms glioma patients experience before the diagnosis and during the disease course. In addition, aspects related to the measurement of HRQoL are described, including the impact of the timing of the assessments on the actual obtained HRQoL scores and the preferences of patients, their partners and healthcare professionals with respect to the assessment of HRQoL in daily clinical practice. Moreover, with respect to glioma patients in the End of Life (EOL) phase, an Advance Care Planning intervention is evaluated.

Epidemiology, pathophysiology and management of brain tumors

Brain tumors can be classified into primary brain tumors, of which gliomas - originating from the glial cells of the brain - are the major subtype, and secondary brain tumors or brain metastases, originating from a malignancy outside the central nervous system that has metastasized to the brain. This thesis focuses on gliomas.

Gliomas

Although gliomas account for less than 2% of all cancers, they contribute significantly to overall cancer morbidity and mortality. Gliomas are the most common malignant primary tumors of the brain, with a yearly incidence in Europe of 5.6 and 7.8 per 100.000 women and men, respectively[1]. The median age at diagnosis ranges from 41 years in low-grade glioma[2] to 64 years in glioblastoma patients[3].

Gliomas originate from the supporting glial cells in the central nervous system (CNS) and were traditionally classified into four grades, according to their histology, with the highest grade usually having the worst prognosis[4]. This World Health Organization (WHO) 2007 histological grading system was based on findings of proliferative activity, nuclear atypia, vascular proliferation and necrosis[5].

According to the WHO 2016 classification, gliomas are graded by both their phenotype and genotype[6]. Roughly, gliomas are divided into low- and high-grade gliomas, based on the presence of both histological and molecular-genetic characteristics. Survival in patients with WHO grade II tumors is usually more than 5 years and in patients with grade III tumors 2–3 years[4]. In WHO grade IV tumors, the majority of which are glioblastomas, the survival ranges from 9-31 months, largely depending on the isocitrate dehydrogenase (IDH) mutational status[6]. The presence of an IDH mutation is a major favorable prognostic factor for survival, with the prognosis of IDH1-mutant astrocytomas being better than that of IDH1-wildtype glioblastoma[7].

Furthermore, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is predictive for response to alkylating agents, such as temozolomide[8, 9]. Moreover, 1p/19q codeletion is the molecular genetic signature of oligodendrogliomas and is a prognostic marker for better survival and a predictive biomarker for a good response to chemotherapy[10, 11]. Other favorable prognostic factors in glioma patients are lower age, better functional status, smaller tumor size and larger extent of resection[12].

Treatment in glioma

Treatment in primary brain tumors comprises both antitumor treatment and supportive treatment, for which a multidisciplinary approach is crucial[13]. In all glioma subtypes, surgery, or at least a biopsy of the tumor is the first step to obtain a histopathological diagnosis and subsequently, which treatment will suit best. The major goal of surgery is to do a maximally safe resection, since this could reduce the symptom burden of patients and prevent permanent neurological deficits, while it also results in a better prognosis[14, 15]. In most cases, surgery is followed by adjuvant radiotherapy and/or chemotherapy. In glioblastoma patients, 6 weeks combined radio-chemotherapy, usually 60 Gy in 2 Gy daily fractions, with concomitant and adjuvant temozolomide chemotherapy is given. In patients with a poor prognosis and/or in elderly patients, hypofractionated radiotherapy (higher dose per fraction and a lower total dose over a 3-week treatment period) should be considered[16]. For lower-grade gliomas, the regular photon beam radiotherapy is gradually being replaced by proton beam radiotherapy, as it is suggested that this type of treatment has a less negative impact on surrounding healthy brain tissue and may therefore prevent or reduce neurocognitive deficits, which are common after brain irradiation[17]. Chemotherapy for glioma patients, either given in combination with radiotherapy, or alone, usually consists of temozolomide, the combination of procarbazine, lomustine, and vincristine (PCV) chemotherapy or lomustine alone, and can be administered both in newly diagnosed gliomas and in case of tumor recurrence. Moreover, new treatment opportunities are currently being explored and include targeted treatment and immunotherapy. In patients with glioma, monoclonal antibodies such as depatuxizumab mafodotin (ABT-414) and bevacizumab have been investigated, but have not shown benefits in terms of overall survival[18].

Common symptoms such as seizures, headache, focal neurological and cognitive dysfunction and mood disturbance, caused by the tumor and/or surrounding tumor-associated edema, can be reduced with supportive treatment, next to antitumor treatment[19, 20]. The most common medications are dexamethasone to relieve headache or focal neurological deficits due to cerebral edema, antiepileptic drugs to reduce the risk of seizures in glioma patients with epilepsy, and antidepressants for mood disturbances.

A comprehensive framework for the health status of patients with brain tumors

Patients with glioma not only have an incurable form of cancer, but also a progressive brain disease. They often experience severe symptoms, such as epilepsy and cognitive impairment, not only caused by the disease, but also by the treatment they receive. Since glioma patients typically have a poor prognosis, it is crucial that their level of functioning and well-being is maintained during that period, as they should be able to spend the limited time they have in good quality. Therefore, the patients' health status is becoming more and more important as a treatment goal. According to the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF), a patient's health status can be described according to three health domains, which are intrinsic to a person's psychological and physiological entity, and two health-related domains, which are closely related to a person's health, but not part of it, i.e. contextual factors (See Figure 1)[21]. The domains are described from the perspective of the body, the individual and society. The three health domains comprise the components Body functions & Structures, Activities, and Participation. Impairments are problems in body functions or structures in terms of a significant deviation or loss. An example of a common impairment in glioma patients is the occurrence of seizures. Activity limitations are problems patients experience in performing tasks or actions, for example not being able to drive a car due to seizures. Participation restrictions are problems experienced by the patient with the involvement in life situations, such as not being able to work because of problems with memory or the planning of complex tasks. The ICF also describes Contextual factors, i.e. Environmental and Personal factors, that may have an impact on a patient's functioning. These include aspects such as the social and physical environment a patient lives in, or age, gender, educational level, coping styles or cultural beliefs of an individual.

Clinical outcomes and clinical outcome assessments in glioma patients

The most fundamental determinants of health status are on the level of body functions & body structures and include biological and (patho)physiological factors, for example genetic and molecular factors. The assessment of these factors focuses on the function of cells, organs and organ systems. When the focus shifts from specific cells and organs to the organism as a whole, the measurement will become more patient-centered. Indeed, symptoms, functional status, psychosocial, role and other domains of functioning, general health perceptions and overall quality of life are clinical outcomes that place patients in the center of health assessment[22].

Measurement of patient-centered outcomes

To assess clinical outcomes, the Food and Drug Administration (FDA) has approved several assessments for use in clinical trials, which are denominated as Clinical

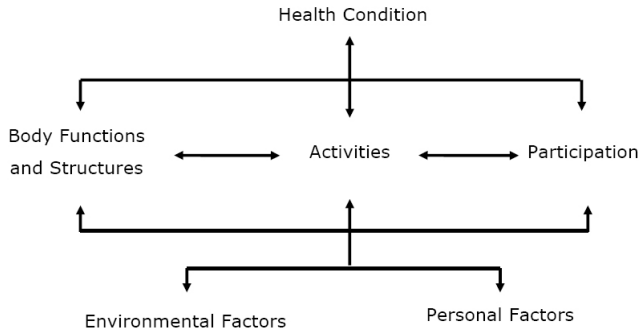

Figure 1. Representation of the model of disability according to the World Health Organization

Outcome Assessments (COAs). These include all assessments that could be influenced by the patient's motivation, choice or judgement and should directly or indirectly measure the benefits of a treatment. COA's comprise observer-reported outcome (ObsRO) measures, clinician-reported outcome (ClinRO) measures, performance outcome (PerfO) measures and patient-reported outcome (PRO) measures. In clinical studies, it is important to select a suitable COA that measures the subject of interest, by determining the context of use (COU). The COU of a specific COA is a statement that describes the appropriate use of the COA and how qualified the COA is.

In this thesis, the focus will be on patient-reported outcomes (PROs), in particular symptoms and other aspects of HRQoL, and the tools to measure these outcomes (PROMs). Typically, PROs provide information as perceived and reported by the patient, and the tools may range from a symptom list only to a questionnaire measuring the multidimensional concept HRQoL. The PROMs could be used in clinical trials to determine the impact of treatment on the patient's functioning and wellbeing, or in clinical care, to start a conversation between a healthcare professional and the patient on the impact of the disease and the treatment, and to focus the conversation on those topics that are important to patients. Also monitoring of symptoms and functioning by routine administration of PROMs is valuable in clinical care, as previous studies in advanced cancer patients have shown that this may result in prolonged survival and improved aspects of HRQoL, by more accurate or timely treatment[23, 24].

There are several instruments available to measure symptoms and other aspects of HRQoL in glioma patients. HRQoL instruments can be either generic, applicable to all persons including healthy subjects, or disease-specific. There are several cancer-specific or brain tumor-specific HRQoL instruments. For example, the European Organisation for Research and Treatment of Cancer (EORTC) has developed a core HRQoL instrument which is deemed relevant for all cancer patients, the EORTC

QLQ-C30[25], as well as modules for specific tumor types. For brain tumor patients, the EORTC QLQ-Brain Neoplasm (BN-20) questionnaire is available to supplement the core QLQ-C30[26]. Other brain-tumor specific HRQoL instruments that are frequently used in clinical practice or trials with glioma patients include the Functional Assessment of Cancer Therapy-General (FACT-BR)[27] or the MD Anderson Symptom Inventory (MDASI) questionnaire[28].

Symptoms in glioma patients

One of the main topics in this thesis are the symptoms glioma patients experience. As mentioned, in glioma patients symptoms can either be caused by the tumor itself or by the antitumor treatment. The tumor may cause symptoms because it invades and destructs the brain tissue directly, or because it displaces/compresses healthy brain tissue. Additionally, brain tumors may disrupt the blood-brain barrier, resulting in vasogenic edema, causing an increased mass effect and further compression of the surrounding tissue. Tumor growth may affect the occurrence and severity of symptoms as well. Low-grade gliomas tend to grow slower than high-grade gliomas, but are more epileptogenic. On the other hand, patients with rapidly growing high-grade gliomas often present with progressive symptoms such as headache, caused by elevated intracranial pressure, and neurological deficits[29, 30]. Furthermore, tumor location partly determines symptomatology, for example a tumor in the frontal lobe is typically associated with changes in personality and behavior[31], whereas a location in the temporal lobe is more likely associated with seizures, visual deficits and dysphasia. Other, more general mental changes, such as increased irritability, apathy, or a memory disorder, are usually not related to a certain tumor location, but may indicate infiltration of the tumor in deep structures affecting the corpus callosum, reticular formation and thalamocortical fibers. These latter symptoms are relatively common with an occurrence in 16-34% of glioma patients[32]. Finally, symptoms directly caused by antitumor treatment are for example nausea, vomiting and myelotoxicity as a side effect from chemotherapy, and fatigue and hair loss as a side effect of radiotherapy.

Symptoms during the disease course

Although some symptoms may be present during the entire disease course, some are related to a specific disease stage. The initial presentation of a glioma can be acute or subacute, for example with focal neurological deficits comprising motor paresis, sensory disorder, visual disturbances, and/or speech disturbance or seizures. Some symptoms may occur more gradually, for instance behavioral disorders or cognitive problems, which are typically progressive over time[33]. Therefore, the time between the onset of symptoms and diagnosis varies widely between patients, ranging from minutes to even a few years[34]. A relatively long time period between the onset of symptoms

and the diagnosis can be attributed to several factors. First, many patients report non-specific symptoms, i.e. not indicating a specific disease or involving a specific body system, such as fatigue[34]. It could be difficult for patients, relatives and healthcare professionals to attribute such common symptoms to the diagnosis of a brain tumor, as other causes not related to a brain tumor are a priori much more probable. Patient-related factors may also contribute to a delayed diagnosis, for example a change in personality, avoidance or adaptation[34].

Early recognition of symptoms may lead to a prompt diagnosis, possibly resulting in less morbidity. Although there is literature on prediagnostic symptoms, i.e. the symptoms that patients experience in the period before the diagnosis of glioma, most of these studies are retrospective studies of medical records, performed in hospitals, and typically focused on symptoms at the time of diagnosis[30, 35-47]. Furthermore, some studies presented data on prediagnostic symptoms for a mixed population of primary brain tumors, hampering interpretation of prediagnostic symptoms in the glioma population specifically[48-50]. Moreover, most studies addressed categories of symptoms only (e.g. isolated cranial nerve symptom[30], motor symptomatology or mental change[36]), and not the specific symptoms included in the various categories. Thus, little is known on the full range of health problems patients experienced in the period before diagnosis. A further limitation is that these studies did not include an assessment of the health care usage before the tumor diagnosis, which could provide more insight in the pathway to diagnosing glioma patients.

Symptoms that are present during the course of the disease, particularly during treatment and follow-up phases, are either caused by the treatment, or due the residual tumor, or due to progressive tumor growth, with the most prevalent symptoms being seizures, nausea and vomiting, cognitive deficits, fatigue, visual deficits and anorexia[51]. In the end-of-life (EOL) phase, when antitumor treatment is no longer meaningful, the most frequently reported symptoms are decreased consciousness, dysphagia or a combination of both. Other possible symptoms in this stage are seizures, headache and agitation. It is important to mention that relief of these symptoms is increasingly challenging at this stage, because of the impaired consciousness of patients as well as swallowing difficulties, hampering the administration of medication[52].

HRQoL instruments in clinical trials: optimal timing

As previously addressed, there are various PROMs available to evaluate HRQoL in glioma patients. Apart from their methodological properties, it is also relevant to pay attention to the way they are administered. An important aspect when measuring HRQoL of glioma patients concerns the timing. This aspect is relevant, particularly in clinical trials, as results should reflect the impact of the treatments under investigation and should not be an effect of timing[53]. For example, if HRQoL is measured during the

immediate toxicity of the treatment, or later during the disease when the toxicity effect has faded, erroneous conclusions on the impact of treatment would be drawn. It is currently unknown what the optimal timing of HRQoL assessments is in glioma trials, and whether assessments at different time points, although within a prespecified time window, would result in different outcomes. There are recommendations about the appropriate timing of the administration of PROMs, for example by specifying a standardized moment of questionnaire delivery (e.g., before/whilst/after seeing a clinician). In addition, a time window needs to be specified that allows questionnaires to be included in the analysis, since a deviation from scheduled assessments is likely in practice. In clinical studies with glioma patients, these time windows range from 1 week to 6 months[54, 55]. These large time windows may be problematic, as a study by Ediebah et al. found that conclusions about treatment effects were altered by the width of a time window; a wider completion time window for HRQoL assessments during treatment produced statistically and clinically significant differences compared to a narrow time window[55].

Glioma patients are usually asked to fill in questionnaires during follow-up right before their scheduled appointment with the physician to discuss the results of the Magnetic Resonance Imaging (MRI) scan and further treatment. However, HRQoL scores might possibly be negatively influenced by anxiety or feelings of fear for possible progressive disease. Correspondingly, feelings of relief or depression might influence HRQoL scores if questionnaires are administered after the consultation. Alternatively, the administration could be planned on the day of the MRI, which is typically a few days to a week before the consultation with the physician. It is currently unknown if HRQoL scores change to a clinically relevant extent between the moment of the MRI scan and the day of the consultation with the physician, and whether feelings of anxiety or depression influence these HRQoL scores.

PROMs in clinical practice: Routine monitoring

Routine use of PROMs in clinical practice in oncology has shown to result in better communication between the patients and their physicians[57-59], and an increased frequency of discussions of HRQoL issue[58] and other topics that are important to patients[60]. In advanced stage cancer patients, routine monitoring even resulted in prolonged overall survival, because routine PROMs assessment might help in early detection of adverse effects of treatment or tumor progression, for which treatment or referral to another healthcare professional could be initiated if necessary[24]. Although the implementation of routine assessment of PROMs can possibly improve the quality of care as well as patient outcomes, this is not common practice in glioma care in The Netherlands. One of the goals of the Dutch Neuro-oncology Society (Landelijke Werkgroep Neuro-Oncologie, LWNO) is to implement routine assessments of PROMs

in neuro-oncological care, with the goal to improve psychosocial care. As a first step towards a better uptake by both healthcare professionals and patients, insight in the preferred topics, frequency and method of assessments is needed, as well as the willingness of patients, their relatives and healthcare professionals to discuss the results. In addition, practical barriers for implementation must be identified, which may facilitate implementation of routine PROMs assessment in the future.

Advance care planning

Previous research has found that aspects of HRQoL that are most relevant for patients with glioma may change over time. Important phases in this respect are the final stages. Like in any phase of the disease, the care provided may have a significant impact on the HRQoL as perceived by patient. Especially in the last phases of illness, when the options for life prolongation are limited and quality of life becomes more important[61,62], patients may wish to have a shared or active role in treatment decisions. Patients with glioma not only have cancer, but also a progressive brain disease, which may, in later stages, seriously interfere with their ability to make their own decisions regarding treatment. The incurable nature of the disease, in conjunction with the cognitive decline glioblastoma patients experience over time, warrants early discussion of the patients' wishes in the EOL phase in this patient population.

A frequently used process to document patient's wishes regarding treatment and EOL care is advance care planning (ACP), with preferences being documented in Advance Directives (ADs)[63, 64]. Although patients and their proxies should be involved in decision making sufficiently early, this is not always the case in clinical practice, because both physicians and patients have the tendency to avoid this subject. However, with a timely initiation of ACP, both patients and proxies are empowered to make more well-informed decisions according to their own values during the course of disease, especially in the EOL phase. Furthermore, several studies have shown that patients who participated in ACP discussions appreciated having such discussions and wondered why no one had raised these issues earlier[65, 66]. Other research, however, showed that more than 40% of patients did not want to participate in a focus group on advance care planning with one of the main reasons being that they did not want to discuss EOL issues[67].

In patients with other types of cancer in the EOL phase, there is evidence that early palliative care improves HRQoL and mood of both patients and proxies[68, 69]. This effect could also be achieved by an ACP program. An analysis of several systematic reviews showed that a structured, patient-centered program of APC, with multiple sessions and direct interaction between patients and healthcare professionals could improve the completion rate of ADs[70]. A randomized clinical trial (RCT) showed that facilitated ACP improves quality of EOL care in elderly patients, improves patient and family

satisfaction, and reduces stress, anxiety, and depression in surviving relatives[65]. Another RCT in patients with congestive heart failure or end-stage renal disease showed that with facilitated ACP most patients received the care they desired[66]. A recent study by Fritz et al [71]. developed an ACP program tailored to the needs of glioblastoma patients specifically. By means of a literature search, a focus group with healthcare professionals, as well as semi-structured interviews with patients and their proxies, and with proxies of deceased patients, relevant topics were identified. The results were synthesized, resulting in an ACP program tailored to the needs of glioblastoma patients. As a sequal to this study, one study in this thesis aims to assess whether the implementation of an ACP program would be feasible in daily clinical practice for glioblastoma patients, and will also evaluate if the ACP program is feasible.

Aim and outline of this thesis

The general aims of this thesis are to improve knowledge on the prediagnostic symptoms of glioma patients and to optimize the measurement of HRQoL of primary brain tumor patients in clinical care and research. Furthermore, in this thesis an ACP program tailored to the needs of glioblastoma patients is evaluated.

Part 1 of this thesis focuses on prediagnostic symptoms experienced by glioma patients and related health care usage, in order to determine if there is a specific pattern that is characteristic for glioma patients. ***Chapter 2*** concerns a retrospective case-control study evaluating prediagnostic symptoms and is based on data extracted from medical records at both the general practitioner and the hospital. ***Chapter 3*** describes a prospective study in which patients completed a questionnaire together with a proxy about their symptoms in the year before diagnosis.

Part 2 of this thesis addresses aspects of the measurement of PROs, such as HRQoL, in glioma patients. The knowledge obtained in these studies can be used to improve the assessment of PROs in glioma patients in both clinical trials and practice. The optimal timing of the administration of two HRQoL instruments, the EORTC-QLQ C30 and QLQ-BN20, and its association with feelings of anxiety and depression is examined in ***Chapter 4.*** In addition, an inventory of the perspectives of glioma patients, their proxies and healthcare professionals regarding the practicalities of measuring PROs in clinical care in Dutch hospitals is made in ***Chapter 5***.

Part 3 (*Chapter 6)* is dedicated to a study evaluating the feasibility of implementing an Advance Care Planning program especially tailored for glioblastoma patients in daily clinical practice, and its impact on several patient-centered outcomes.

Chapter 7 provides a summary of the research described in this thesis. It also includes a general discussion on its contribution to the current literature and implications for future research.

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PART ONE

CHAPTER 2

Prediagnostic presentations of glioma in primary care: a case–control study

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Abstract

Background

This study aimed to assess the prevalence of symptoms glioma patients may present with to the general practitioner, and whether these can be distinguished from patients with other central nervous system disorders or any other condition.

Methods

Glioma patients were matched to controls using anonymized general practitioner registries. Prevalences were evaluated in the five years prior to diagnosis.

Result

Central nervous system patients reported significantly more motor symptoms in the period 60-24 months, (p=0.039). Moreover, <6 months before diagnosis central nervous system patients differed significantly in mood disorders/fear compared to 'other controls' (p=0.012) but not glioma patients (p=0.816).

Conclusion

Glioma patients could not be distinguished from both control groups with respect to the number or type of prediagnostic symptoms.

Introduction

Gliomas are the most common malignant primary brain tumours in adults[1, 2]. Of these, glioblastoma is the most frequently occurring subtype. The annual age-adjusted incidence of primary malignant tumours ranged from 4.53 to 8.18 per 100,000 population[3]. Nearly all glioma patients have an incurable disease with a dismal prognosis. These patients not only have cancer, but also a progressive brain disease, and may therefore experience symptoms such as increased intracranial pressure (drowsiness and headache), progressive motor dysfunction, seizures, and changes in cognition, behaviour and personality[4-8].

Patients are often diagnosed with glioma after presenting with a focal neurological deficit, a first seizure or more diffuse symptoms such as drowsiness and headache[9, 10]. Currently, little is known about the onset of symptoms and signs of glioma in the year(s) before diagnosis. One study, in which semi-structured interviews with 28 glioma patients and their partners were conducted, showed that most patients first consult their general practitioner (GP) about their symptoms, and that the time between onset of symptoms and diagnosis of glioma varies widely between patients[9, 10]. The latter could be due to a gradual onset of symptoms, a lack of recognition of these symptoms by the patient, or because the GP made another differential diagnosis. A better insight into these early symptoms, especially symptoms and signs that could distinguish glioma patients from other patients with central nervous system diseases or any other condition, may help earlier identification of patients with glioma. This may subsequently lead to earlier initiation of anti-tumour treatment in these patients, which could be beneficial. For example, early introduction of chemoradiation at the time of diagnosis in patients with low-grade glioma improves progression-free and overall survival[11].

This study aimed to identify the prevalence of symptoms and signs in the five years prior to glioma diagnosis from extracted medical records of the GP, and to determine whether these can be distinguished from patients with other central nervous system (CNS) diseases and patients visiting the GP for any other condition. In addition, we aimed to assess if glioma patients visit the GP more frequently in the years before diagnosis compared to control patients.

Methods

Identification of potential signs and symptoms

Possible early clinical symptoms were identified by means of a literature study and semi-structured interviews with health care professionals involved in the care of glioma patients.

For the literature study, an article reporting on the presenting symptoms in glioma patients[12] was used to create a list of potential prediagnostic symptoms for glioma patients. Next, we developed a search strategy in Pubmed (conducted up to the 15th of October 2015) in which the terms related to 'glioma', 'prediagnostic' and one of the 'symptoms' as identified in the article by Posti et al [12]. were used. Articles were eligible if a population of adult glioma patients was described, including a description of the specific symptoms at diagnosis or before initial treatment, as well as the percentage of patients experiencing those symptoms. Reviews, case reports and case series (<20 patients) were excluded, as well as articles describing treatment of recurrent glioma, articles including children, or articles focusing on multiple brain tumour patients without a separate description of symptoms of glioma patients.

Semi-structured interviews with five experts (three neuro-oncologists, one neuropsychologist and one nurse specialized in neuro-oncology) in the field of glioma were conducted in person by one researcher (MCMP). Experts were asked to rate the frequency of occurrence of all symptoms glioma patients could present with (as identified in the literature review) on a 4-point Likert scale, ranging from 'never' to 'frequent', and to indicate if prediagnostic symptoms and signs were missing.

Next, we selected signs and symptoms that were reported in >25% of the glioma patients in the eligible articles identified with the literature search, and those symptoms with a mean score ≥3 (representing often to frequent) as identified in the semi-structured interviews for further analyses. Comparable symptoms were categorized into one category and all categories of symptoms were subsequently recoded into International Classification of Primary Care (ICPC) codes. These ICPC codes are widely used by GPs to code complaints, symptoms, and diseases since the mid 90s of the last century[13].

Study population

Three groups of patients were included: glioma patients, patients with other CNS diseases, and 'other' patients. These 'other' patients were defined as those patients that did not meet the criteria for the other two groups (e.g. patients with back pain or the flu). Patients in the 'CNS disease' and 'other' groups were the controls for glioma patients and were matched in a 1:1:1 ratio to glioma patients on age (range 5 years older or younger), sex and date of diagnosis (month and year).

Glioma patients were selected from two sources. First, patients with a histologically confirmed glioma who visited the neuro-oncology outpatient clinic in the Leiden University Medical Center in Leiden, or the Haaglanden Medical Center in The Hague, the Netherlands, between September 2005 and September 2015 were selected. Second, additional patients were selected from an anonymized GP database, the Registration Network of General Practices associated with Leiden University (RNUH—LEO). This

database comprises data of 44.350 patients from 19 GP's in four practices in Leiden (The Netherlands) and the surrounding area, and contains information on the medical history, prescriptions, diagnostic record, and morbidity of patients, and coded symptoms and signs via ICPC codes. Glioma patients were selected from this database if their medical record contained an ICPC code coding for central nerve system neoplasm, they were adults (≥18 years), diagnosed from 2002 onwards, and if the GP had described the diagnosis 'glioma' in the free text of the medical record. All relevant data in the database was extracted for patients identified via this database. For glioma patients identified via the outpatient clinics, their medical record was requested at their GP.

All control patients were selected from the RNUH-LEO database. ICPC codes representing central nervous system diseases were used to select CNS patients (see supplementary Table 1 for the used ICPC codes). All remaining codes were eligible for the 'other' control patients. The study was approved by the local medical ethical review board and glioma patients selected from the outpatient clinic provided written informed consent for participation in this study, including insight in their medical record at their GP. Patients selected from the RNUH-LEO database were prone to an "informed opt out" procedure, since their data was anonymized.

Data extraction

All visits to the GP of both glioma patients and controls were reviewed during 5 years prior to the index date (i.e. date of diagnosis of the glioma patient). The number of visits were evaluated, as well as the signs and symptoms during each visit. Actual visits to the GP were counted as a visit (including a visit for a procedure, such as an influenza vaccination), while telephone consultations were only counted if they addressed a new symptom or sign. In case the GP described the ICPC codes within the medical records, these codes were used. If the ICPC codes were not provided, we recoded the symptoms and signs using the ICPC code system.

Statistical analysis

Baseline demographic and clinical characteristics of glioma patients and their controls, as well as the number and type of symptoms, were described using descriptive statistics. Period prevalence (i.e. the number of current cases (new and pre-existing) over a specified period of time) was calculated for the number of visits and selected symptoms, and compared between groups with the Chi-square test. Since the number of visits and symptoms was expected to rise in the months prior to diagnosis in glioma and CNS control patients, not only the period prevalence for the complete five years was calculated, but also for the time intervals (a) 5 years to 2 years, (b) 2 years to 6 months and (c) 6 months up to diagnosis. Lastly, we have explored if patients experienced multiple symptoms during the five-year observation period.

All statistical analyses were performed using SPSS version 23 (SPSS, Chicago, IL, USA). All tests were two-sided and $p<0.05$ was considered to be significant.

Results

Literature review and semi-structured interviews

Eleven symptoms identified in 14 articles with the literature review were found to have an incidence of more than 25%; seizures, headache, motor impairment, confusion, language problem, memory problem, personality change, change in consciousness, nausea, visual problem and sensory problem[14-26]. The five participating health care providers agreed that 8/11 (i.e. seizures, motor impairment, confusion, language problem, memory problem, personality change, change in consciousness and visual problem) (pre)diagnostic symptoms occurred frequently (i.e. mean score ≥3). Missing symptoms included burnout, mood swings, fatigue and problems with concentration, processing of information, planning and initiation (see Supplementary Table 2). Ten symptoms were merged because they showed similarity, resulting in nine symptom categories that were recoded into ICPC codes (see Supplementary Table 3): seizures, headache, motor impairments, cognitive/mental impairments, visual disorders, mood disorders/fear, sensory complaints, metabolic/endocrine symptoms and general symptoms (e.g. tiredness, overall deterioration).

Patient population

Patient characteristics are presented in Table 1. Thirty-six glioma patients were matched with 36 CNS control patients and 36 'other' control patients. The median age of patients ranged between 60-61 years, and the majority in all groups was men (58%), suggesting that the matching procedure was successful. Patients in the CNS control group were mostly diagnosed with stroke (28%), other head trauma (11%), concussion (14%) or depression (22%). Patients in the 'other' control group had musculoskeletal (17%) or skin (14%) problems, an infection (14%), or other problems (56%).

Prevalence and type of symptoms

A total of 10/36 (28%) glioma, 9/36 (25%) CNS and 18/36 (50%) 'other' control patients visited the GP with one symptom from the nine categories, while 8/36 (22%) glioma patients, 15/36 (42%) CNS patients and 13/36 (36%) 'other' patients visited the GP with ≥2 symptoms (see Figure 1). Thirty-one per cent of glioma patients (11/36), 28% (10/36) of CNS patients and 39% (14/36) of 'other' control patients did not report any of the nine symptoms, but did present with other symptoms, for example painful miction, eczema or a fractured tibia.

Table 1. Characteristics of patients with glioma and CNS and 'other' control patients

	Glioma (n=36)	CNS controls (n=36)	'Other' controls (n= 36)
Age, years; median (range)	61 (26-79)	61 (26-79)	60 (26-79)
Men; no. (%)	21 (58%)	21 (58%)	21 (58%)
Diagnosis			
Glioma	36 (100%)		
Stroke		10 (28%)	
Other head trauma		4 (11%)	
Concussion		5 (14%)	
Depression		8 (22%)	
Epilepsy		3 (8%)	
Other		3 (8%)	
Musculoskeletal system			6 (17%)
Skin			5 (14%)
Infection			5 (14%)
Other			20 (56%)

Number of visits to the general practitioner

The number of visits with any symptom or sign to the GP did not differ significantly between groups over the five year period (median of 17 versus 24 and 23 visits in glioma, CNS controls and 'other controls, respectively; p=0.381). Similarly, no significant differences were found in the number of visits in the smaller time intervals (see Table 2).

Table 2. Total and median (range) number of visits to the general practitioner for any sign or symptom per time period, separately for the three groups

	All patients (n=108)	Glioma patients (n=36)	CNS controls (n=36)	Other controls (n=36)	p-value
Whole period (5 years), median (range)	2491 20 (0-102)	711 17 (0-60)	989 24 (0-102)	791 23 (0-65)	0.381
5-2 years (36 months), median (range)	1425 11 (0-62)	399 9 (0-32)	582 14 (0-62)	444 12 (0-38)	0.187
2 years to 6 months (18 months), median (range)	728 5 (0-30)	217 4 (0-23)	273 5 (0-30)	238 5 (0-23)	0.939
6 months to diagnosis (6 months), median (range)	338 2 (0-15)	95 2 (0-15)	134 2 (0-15)	109 3 (0-14)	0.522

In general, glioma patients did not differ from the other groups with respect to the prevalence of the nine symptoms (see Table 3). Mood disorders/fear was the most prevalent symptom in all three patient groups in all three time periods. In addition, general symptoms and sensory complaints were frequently reported. There was a significant difference between CNS patients and 'other' controls (8 versus 0, respectively, *p*=0.014) in the 6 months prior to diagnosis regarding the prevalence of mood disorders/fear but not compared to glioma patients (5 versus 8, p=0.816). Moreover, in the 60-24

months prior to diagnosis, four CNS patients presented with motor symptoms where the glioma patients and patients with other symptoms did not (both p=0.039).

We have also explored if patients experienced multiple symptoms during the five-year observation period, and which these were (Table 4). Mood and general symptoms were observed in seven glioma and six CNS patients, while this combination was found in three 'other' controls. Mood and sensory symptoms occurred in six glioma patients, in nine patients in the CNS disease group, and only one time in the 'other' control group. Moreover, visual and sensory problems were observed in three glioma, five CNS and one 'other' patient, whereas visual problems and mood symptoms were observed in four glioma patients, six CNS patients and not in the 'other' patients. There were only a few patients in each group in whom ≥3 symptoms were observed during the study period (data not shown).

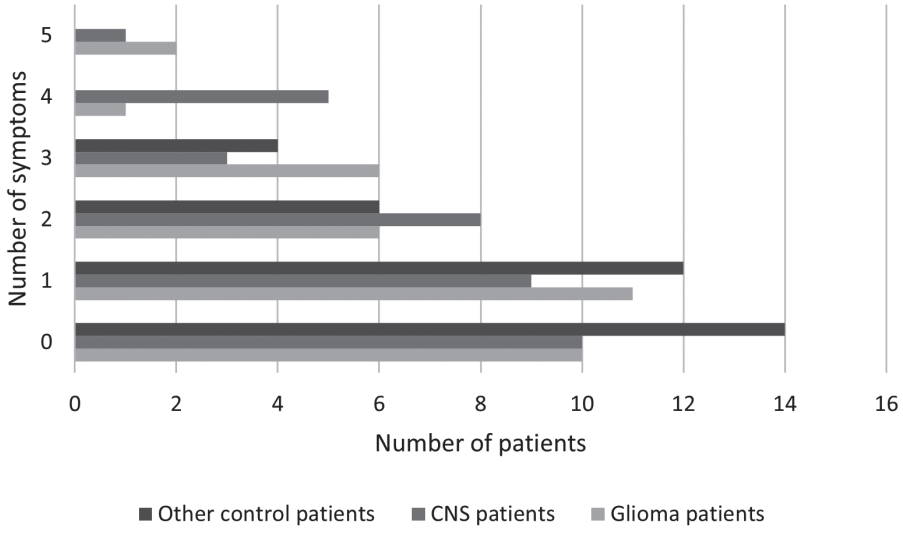

Figure 1. Number of prediagnostic symptoms patients present with to the general practitioner per patient group.

Discussion

This case-control study did not show a difference in the frequency of GP visits nor in the prevalence of presenting symptoms and signs in the five years before diagnosis between glioma patients, patients with other CNS disease or patients with any other condition. It may therefore be difficult for a GP to distinguish glioma patients from

Table 3. Period prevalence of symptoms in the nine categories, separately for glioma, CNS and 'other' control patients, and separately for the three time periods and the complete five-year period

	Total 5 year period				5-2 years (36 months)			
	Glioma (n=36)	CNS (n=36)	Control (n=36)	P-value	Glioma (n=36)	CNS (n=36)	Control (n=36)	P-value
Seizure	1	1	0	0.361	0	0	0	1.000
Headache	4	4	2	0.646	3	3	1	0.536
Motor impairments	3	6	1	0.126	0	4	0	0.016
Cognitive/ mental impaiments	1	3	3	0.546	0	2	3	0.236
Progressive loss of vision	5	6	4	0.601	2	5	1	0.180
Mood disorders/fear	15	18	9	0.088	7	14	8	0.087
General symptoms	11	9	8	0.716	7	5	2	0.198
Sensory complaints	11	10	7	0.537	5	7	4	0.623
Metabolic/endocrine	1	0	2	0.361	0	0	0	1.000

	2 years to 6 months (18 months)				6 months to diagnosis (6 months)			
	Glioma (n=36)	CNS (n=36)	Control (n=36)	P-value	Glioma (n=36)	CNS (n=36)	Control (n=36)	P-value
Seizure	1	1	0	0.604	0	1	0	0.368
Headache	0	0	1	0.368	2	1	0	0.358
Motor impairments	3	2	1	0.602	1	1	0	0.604
Cognitive/ mental impaiments	0	0	1	0.368	1	1	0	0.604
Progressive loss of vision	2	1	0	0.368	1	2	3	0.615
Mood disorders/fear	8	10	5	0.349	5	8	0	0.014
General symptoms	2	5	4	0.497	3	1	3	0.532
Sensory complaints	6	2	2	0.192	2	2	2	0.998
Metabolic/endocrine	1	0	1	0.604	0	0	1	0.368

both patients with other CNS diseases and those with other conditions based on their prediagnostic symptoms, hampering timely referral to a neuro-oncologist.

An explanation for the absence of differences between glioma patients and the other groups, besides the fact that they may simply not be there, may be that detecting glioma-specific symptoms and signs is difficult when only routine care data are the source. First, patients may not visit the GP with their complaints. This could be the case in control patients as well, however, one study described that specifically glioma patients with headache were found to often delay their help-seeking because they found another cause for this symptom in the everyday life context[10]. Similarly, experts in this study mentioned that glioma patients often report that they associated mental and cognitive symptoms with being tired or a high workload, suggesting that this would also be a reason not to visit the GP with their complaints. Indeed, underreporting of symptoms by glioma patients may be due to lack of insight in their illness as a

Table 4. Number of patients presenting with multiple symptoms in glioma, CNS and 'other' control patients in the whole five year period

	Seizure & headache	Seizure & motor	Seizure & cognitive problems	Seizure & visual problems	Seizure & mood disorder	Seizure & general symptoms	Seizure & sensory problems	Seizure & metabolic problems	Headache & motor problems	Headache & cognitive problems	Headache & visual problems	Headache & mood disorder	Headache & general symptoms	Headache & sensory problems	Headache & metabolic problems	Motor problems & cognitive problems
Glioma	0	0	0	0	0	0	0	0	0	0	0	2	2	2	1	0
CNS patients	0	0	0	1	1	0	1	0	1	0	1	2	2	1	0	0
Other control patients	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0

consequence of the condition itself. Second, GP's usually prioritize only one major complaint in their registration and may thus not always be consistently registering all complaints and diagnoses with which the patient presents in one visit, potentially resulting in missing data. Moreover, the format of using ICPC codes during registration may have resulted in imprecise data. One ICPC code can contain more than one symptom; for example, the code P20 contains memory, concentration, and orientation disorders. Furthermore, some GP's did not register the ICPC codes, for which cases we had to derive the code from text parts for these symptoms. Due to misinterpretation, this may have resulted in inaccurate data. The way of registering symptoms may have therefore refrained us from obtaining information on the occurrence of more unlikely symptoms, or certain combinations of symptoms. Third, our study design may have not been optimal. Unfortunately, tumour-related information such as tumour grade was not available in this anonymised dataset. It therefore remains unknown whether the prediagnostic symptoms differed between subgroups of glioma patients, even though differences might be expected due to differences in tumour biology and growth rate. Indeed, due to the slow growth rate, it may be possible that we included patients with delayed diagnosis of childhood low-grade glioma[26]. Another limitation of the study design is that we were not able to verify if CNS or other controls did not have a brain tumour. Furthermore, the number of glioma patients identified with this approach may have been too small to obtain an appropriate representation of the prediagnostic

	Motor problems & visual problems	Motor problems & mood disorder	Motor problems & general symptoms	Motor problems & sensory problems	Motor problems & metabolic problems	Cognitive problems & visual problems	Cognitive problems & mood disorder	Cognitive problems & general problems	Cognitive problems & sensory problems	Cognitive problems & metabolic problems	Visual problems & mood disorder	Visual problems & general symptoms	Visual problems & sensory problems	Visual problems& metabolic problems	Mood disorder & general symptoms	Mood disorder & sensory problems	Mood disorder & metabolic problems	General symptoms & sensory problems	General symptoms & metabolic problems	Sensory problems & metabolic problems
	1	3	3	2	0	0	0	0	0	0	4	2	3	0	7	6	1	6	1	1
	2	4	2	3	0	1	2	1	1	0	6	2	5	0	6	9	0	3	0	0
	0	1	0	1	0	0	2	0	0	0	0	0	1	0	3	1	1	3	1	0

symptoms and signs in glioma patients. With the low incidence of this disease, a large regional or national registry may yield better results, but is still under construction in the Netherlands. In the United Kingdom (UK), The Health Improvement Network (THIN) comprises records of over 11 million individuals in more than 500 primary care practices across the UK, covering around 6% of the population[27]. This database was used in a study on the prediagnostic presentations in Parkinson patients, which resulted in the inclusion of 8166 patients and 46755 matched controls, allowing a more extensive statistical analysis, for example a big data analysis, and generalisability of the results[28]. Moreover, sampling control patients that are diagnosed in the same year as the patients could cause inclusion bias, since patients that do not frequently visit their GP, or those who switched GP in the five years prior to diagnosis, could not be included in this study. Lastly, the literature search was conducted up to the 15th of October 2015 and therefore more recent studies were not included. However, it is doubtful whether the presenting symptoms of glioma have changed in the past years.

Mood disorders or fear of disease was the most reported problem in this study, during all time periods. The finding that the prevalence of mental health problems ranges from 4.3%-26.4% in the general population supports this[29]. Nevertheless, patients with CNS disease had the highest prevalence which could be due to our inclusion criteria, as patients in the CNS group were included if they had, for example, depression as a diagnosis. Thus, although glioma patients often visit the GP with mood

disorders, or fear of disease (in general), it may be difficult for a GP to consider glioma as diagnosis, as this symptom does not distinguish these patients from other patients. Therefore, when mood disorders occur, all CNS disorders should be considered by the GP, including glioma.

In conclusion, our exploration did not reveal solid indications that would enable us to distinguish glioma patients from CNS and 'other' control patients based on the number of visits to the GP, nor based on the specific prediagnostic symptoms in the five years prior to diagnosis. Possibly, a study design in which a questionnaire is used to inventory if glioma patients experienced certain symptoms and signs in the year prior to diagnosis could be considered an alternative to elucidate symptoms and signs experienced by the patients for which the GP is not consulted.

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Supplementary Table 1.

ICPC codes used for the selection of CNS control patients	
K89	Passing cerebral ischemia/TIA
K90	Cerebrovascular accident (CVA)
N71	Meningitis/encephalitis
N72	Tetanus
N73	Other infectious disease(s) nervous system
N79	Concussion
N80	Other injury head
N81	Other injury nervous system
N85	Birth defect nervous system
N86	Multiple sclerosis
N87	Parkinsonism, Parkinson's disease
N88	Epilepsy (all forms)
N89	Migraine
N90	Cluster headache
N91	Facial nerve paresis/Bell's palsy
N92	Trigeminus neuralgia
N99	Other disease nervous system
P70	Senile dementia/Alzheimer
P71	Other organic psychosis
P72	Schizophrenia
P73	Affective psychosis
P76	Depression

Supplementary Table 2.

Symptoms and signs found in literature study and semi-structured interviews, sorted by category			
Literature search	**Prevalence in literature**	**Semi-structured interviews**	**Score HCP**
Seizure	3.1%-82.8%%	Epilepsy	4
Memory problem	15%-36.7%	Short term memory	4
Visual problem	2%-39%	Progressive loss of vision	4
Motor impairment	3%-44%	Neurological deficit extremities	3.8
		Neurological deficit of the trunk	3.25
		Neurological deficit in one half of the body	3.25
		Difficulties fine motor skills	3
		Weakness extremities	3
Change in consciousness	3%-39%	Periods of reduced consciousness	3.4
		Alertness	3.33
Confusion	13.4%-57%	Orientation	3.25
		Processing of information	3.8
		Initiating	3.5
		Planning	4
		Concentration	3.8
		Mood swings	3
Personality change	1%-34%	Personality change	3.2
Language problems	4%-36.4%	Aphasia	3
Headache	19.7%-86%		
Nausea	0%-45%		
Sensory problems	1%-23%		
		Burn out	4
		Tiredness	4
		Stress	4

Supplementary Table 3.

ICPC codes used in the nine categories of prediagnostic symptoms	
Seizure	
N07	Convulsions (including febrile seizure)
N88	Epilepsy (all forms)
A06	Fainting/syncope
Headache	
N01	Headache [ex. N02,N89,R09]
N02	Tension headache
N03	Facial pain
N89	Migraine
N90	Cluster headache
N92	Trigeminus neuralgia
Motor impairments	
A28	Disability/handicap
D17	Incontinence for stool
D21	Swallowing problems
L19	Symptoms multiple/non-specified muscles
L28	Disability/handicap musculoskeletal system
N04	Restless legs
N18	Paralysis/weakness [ex. A04]
N19	Speak-/phonation disorder
N28	Disability/handicap nervous system
N91	Paralysis facial nerve /Bell's palsy
P10	Stammering/stuttering/tics
U04	Incontinence for urine [ex. P12]
Cognitive/mental impairments	
P20	Memory-/concentration-/orientation disorder
P71	Other organic psychosis
P73	Affective psychosis
P80	Personality-/character
P85	Mental retardation/intellectual disability
P98	Other/non-specified psychosis
Progressive loss of vision	
F01	Pain eye
F04	Mouches volantes/flashing/flickering
F05	Other visual symptoms/complaints [ex. F94]
F13	Altered sensation in eye
F14	Altered eye movements
F16	Symptoms/complaints eye lids
F17	Symptoms/complaints glasses
F18	Symptoms/complaints contact lens(es)
F28	Disability/handicap eye/adnexa of the eye
F29	Other symptoms/complaints eye/adnexa of the eye
F94	Blindness (every degree/form)
F95	Strabismus/squint
F99	Other disease(s) eye/adnexa of the eye

Supplementary Table 3. Continued

ICPC codes used in the nine categories of prediagnostic symptoms	
Mood disorders /fear	
P01	Anxious/nervous/tensed feeling
P03	Down/depressed feeling
P04	Irritable/angry feeling/behaviour
P05	Feeling/behaving old
P06	Sleeplessness/other sleeping disorder
P07	Libido loss/reduction
P08	Sexual satisfaction loss/reduction
P27	Fear for psychic disease
P28	Disability/handicap psychic disease
P29	Other psychic symptoms/complaints
P74	Anxiety disorder/anxiety
P75	Hysteria/hypochondria
P76	Depression
P77	Suicide attempt
P78	Neurasthenia/surmenage
P79	Other neurosis
P99	Other psychic disorder
Z27	Fear of having a social problem
A13	Concern about side effect medicine
A25	Fear of death
A26	Fear of cancer
A27	Fear of other disease
F27	Fear of disease eye
N26	Fear of cancer nervous system
N27	Fear of other disease nervous system
General symptoms	
A04	Fatigue/weakness
A05	Overall deterioration
A29	Other general symptoms/complaints
A85	Drug side-effect
N29	Other symptoms/complaints nervous system
N99	Other disease(s) nervous system
Sensory complaints	
H02	Hearing complaints [ex. H84,H85,H86]
H03	Tinnitus
H82	Vertigo syndrome/labyrinthitis [ex. N17]
N05	Tingling fingers/feet/toes
N06	Other sensibility disorder/involuntary movements
N16	Other alterations smell/taste
N17	Vertigo/dizziness [ex. H82]
N93	Carpal tunnel syndrome
N94	Other peripheral neuritis/neuropathy
Metabolic/endocrine	
T01	Excessive thirst
T02	Excessive appetite
T03	Decreased appetite
T05	Nutritional problem adult [ex. T06]

CHAPTER 3

Prediagnostic symptoms and signs of adult glioma: the patients' view

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Abstract

Background

Little is known about the symptoms glioma patients experience in the year before diagnosis, either or not resulting in health care usage. This study aimed to determine the incidence of symptoms glioma patients experienced in the year prior to diagnosis, and subsequent visits to a general practitioner (GP).

Methods

Glioma patients were asked to complete a 30-item study-specific questionnaire focusing on symptoms they experienced in the 12 months before diagnosis. For each indicated symptom, patients were asked whether they consulted the GP for this issue.

Results

Fifty-nine patients completed the questionnaires, 54 (93%) with input of a proxy. The median time since diagnosis was 4 months (range 1-12). The median number of symptoms experienced in the year before diagnosis was similar between gliomas with favourable and poor prognosis, i.e. 6 (range 0-24), as were the five most frequently mentioned problems: fatigue (n=34, 58%), mental tiredness (n=30, 51%), sleeping disorder (n=24, 41%), headache (n=23, 39%) and stress (n=20, 34%). Twenty-six (44%) patients visited the GP with at least one issue. Patients who did consult their GP reported significantly more often muscle weakness (11 vs 3, p=0.003) than patients who did not, which remained significant after correction for multiple testing, which was not the case for paralysis in hand/leg (10 vs 4), focussing (11 vs 6) or a change in awareness (9 vs 4).

Conclusions

Glioma patients experience a range of non-specific problems in the year prior to diagnosis, but only patients who consult the GP report more often neurological problems.

Introduction

Gliomas are the most common malignant primary tumours of the brain, with reported incidences of 5.6 and 7.8 per 100,000 persons for women and men, respectively[1]. Patients may present with a variety of symptoms, often linked to the tumour location and grade[2, 3]. Several symptoms, such as seizures, motor impairments and loss of consciousness, have an acute presentation, while other symptoms have a more gradual course, including headache, personality change or cognitive problems[4].

Earlier recognition of symptoms may lead to an earlier diagnosis, possibly resulting in less morbidity. However, recognizing symptoms and complaints as a presentation of a brain tumour may be difficult for both patients, their relatives and health care professionals, as symptoms may be non-specific (i.e. not indicating a specific disease or involving a specific body system, such as fatigue)[5]. Other factors that may contribute to a delayed diagnosis are patient characteristics, for example a change in personality and avoidance or adaptation and lack of recognition by a health care professional and/or the relatives[5].

In the last decades, studies reporting on the presenting symptoms of glioma mainly concerned retrospective medical record studies[2, 3, 6-17], some of which did not describe glioma patients separately from other brain tumour patients[18-20]. Moreover, most studies described categories of symptoms only (e.g. isolated cranial nerve symptom[3], motor symptomatology or mental change[6]), and not the specific symptoms included in the various categories. The most commonly reported symptoms or symptom groups in these studies were seizures[2, 3, 6-16, 21], headache[2, 3, 6, 9, 11, 13, 17, 21-23], nausea[3, 6, 11, 21, 23], motor impairments[3, 6, 9, 11, 17, 21], sensory problems[3, 6, 21], visual problems[3, 6, 9, 11, 17, 21, 23], confusion[3, 9, 11, 17], memory problems[9, 11, 17, 21, 23], a change in consciousness[6, 17, 21, 23], problems with language or speaking[3, 6, 9, 11, 17, 21] and a change in personality[6, 9, 21].

Patients' symptoms at the time of diagnosis or during treatment were most frequently described. Yet, little is known on the full range of health problems patients experienced in the period before diagnosis, as well as any health care usage due to these problems. One method to identify symptoms in the period before diagnosis is to extract information from the medical records of health care professionals, e.g. a general practitioner (GP)[24, 25]. A systematic review on prediagnostic symptoms in primary care showed that only new-onset epilepsy was able to predict which patients would be diagnosed with a brain or central nervous system tumour (i.e. positive predictive value of 1.2%)[26]. However, it is likely that patients did not visit a health care professional for all their symptoms, if any.

The objective of this study was to determine the incidence of symptoms Dutch glioma patients experience in the year prior to diagnosis, as well as the number of visits to a GP related to these issues. Moreover, we aimed to determine for which

symptoms glioma patients visited the GP, and whether subgroups of patients reported different prediagnostic symptoms.

Methods

Study design and patients

This was a cross-sectional study including consecutive patients with a histologically confirmed grade II-IV glioma (according to the WHO 2016 classification criteria), up to one year after diagnosis, who visited the neuro-oncology outpatient clinic of the Haaglanden Medical Center in The Hague, The Netherlands, between July 2016 and April 2019. In addition, their proxies (e.g. relatives or friends) were invited to help the patient completing the questionnaire. The time frame of a maximum of 12 months after diagnosis was chosen to minimize recall bias concerning the prediagnostic, self-reported symptoms.

The study was approved by the medical ethical review board, and all patients and proxies provided written informed consent prior to participation.

Assessments

Sociodemographic and clinical characteristics of the patients were retracted from the medical records, or through a short questionnaire (e.g. level of education). Also, information was collected on whether the patient completed the 30-item questionnaire on prediagnostic symptoms and healthcare use together with their proxy, as well as the nature of the relationship with their proxy. This 30-item study-specific questionnaire included questions on prediagnostic symptoms, consulted health care professionals in the year prior to diagnosis, and the presence of comorbidity and other chronic complaints in the year prior to diagnosis (see Supplementary File 1). The symptoms mentioned in the study-specific questionnaire were based on the literature[3, 27, 28] and semi-structured interviews with five experts (three neuro-oncologists, one neuropsychologist and one nurse specialized in neuro-oncology) about the presenting symptoms in patients with glioma. During these interviews, each of the symptoms on the list derived from the literature were systematically discussed. The experts were asked to estimate the frequency of each symptom using a four-point Likert scale, ranging from (1) 'never', (2) 'unusual', (3) 'less common' to (4) 'common'. Only symptoms with a mean score >3 were included, resulting in the inclusion of 30 symptoms. For each symptom, patients were asked to indicate if they had experienced that symptom in the 12 months before the diagnosis (Yes/No). If the answer was yes, they were also asked to report if they consulted their GP for this problem (Yes/No), as in the Netherlands, the GP is the gatekeeper to hospital- and specialist care. The questions

on comorbidity were based on an existing questionnaire used by the Dutch Central Bureau of Statistics (CBS) on 19 different comorbidities[29]. We also asked patients which other healthcare professionals were consulted in the year prior to diagnosis. Patients were encouraged to complete the questionnaires together with their proxy, in order to minimise recall bias.

Statistical analysis

Descriptive statistics were used to the report the sociodemographic and clinical characteristics of the participants and their proxies, the number of visits to the GP and for which symptoms, the other consulted healthcare professionals in the year prior to diagnosis, and the level of comorbidity. Furthermore, the occurrence of neurological symptoms (question 1, 2, 3, 20, 21 and 22) and non-specific symptoms (question 4, 5, 24, 28, 29 and 30) was described separately for patient who did and did not visit the GP. Differences in the frequency of symptoms between patients who did and who did not visit their GP for any symptom, and between patients with poor (i.e. IDH wildtype and both IDH-mutant and wildtype glioblastoma) and favourable prognosis (grade II and III IDH mutant) glioma were compared by means of Chi-Square tests.

All data were analysed using the SPSS statistical package (version 23.0, SPSS, Chicago, Illinois). The level of statistical significance was set at 0.05 for all analyses, and the Benjamini-Hochberg procedure was used to correct for multiple testing in each comparison.

Results

Patient characteristics

Of the 126 patients who were considered eligible and were invited for participation, 59 (47%) returned the questionnaires. Forty-five (76%) questionnaires were returned without missing data, and when items were missing, this number was low (on average 97.5% of the incomplete questionnaires was filled in). Moreover, 54 (93%) patients completed the questionnaire with the help of a proxy, which was the spouse in most cases (89%). Non-responders (n=67) did not differ significantly from responders (n=59) regarding any of the measured variables, including age (57 vs 60 years, p=0.345), sex (64% versus 68% male, p=0.710), tumour type (22% versus 10% poor prognosis, p=0.093) and tumour grade (73% versus 81% grade IV, p=0.144).

Table 1 shows the characteristics of the 59 participating patients. The majority was male (40/59, 68%) with a median age of 60 years (range 43-85) and a median time since diagnosis of 4 months (range 1-12). The most frequent diagnosis was glioblastoma (48/59, 81%) - for only 24/48 patients the Isocytrate Dehydrogenase (IDH) status was

available and all were IDH wildtype - followed by IDH mutant astrocytoma (5/59, 8%), IDH mutant, 1p19q codeleted oligodendroglioma (4/59 7%) and astrocytoma IDH wild type (2/59, 3%). All 59 patients had undergone resection or biopsy, 55 (93%) received radiotherapy and the majority of patients (47/59, 80%) received chemotherapy. Most patients (40/59, 68%) reported any comorbidity, particularly problems with the musculoskeletal system (20/59, 34%), neurological problems (16/59, 27%) and heart and vascular disease (15/59, 25%).

Table 1. Characteristics of 59 patients with a glioma participating in a survey on prediagnostic symptoms and signs

Age, years; Median (range); n=59	60 (43-85)
Sex; No (%) male; n=59	40 (68%)
Time since diagnosis (months) (range); n=59	4 (range 1-12)
Tumour type; n=59	
Diffuse astrocytoma, IDH mutant	2 (3%)
Oligodendroglioma, IDH mutant, 1p19q codeletion	4 (7%)
Anaplastic astrocytoma, IDH wildtype	2 (3%)
Anaplastic astrocytoma, IDH mutant	3 (5%)
Glioblastoma	48 (81%)
Tumour grade; n=59	
II	6 (10%)
III	5 (9%)
IV	48 (81%)
Tumour location; n=59	
Left hemisphere	31 (53%)
Right hemisphere	29 (49%)
Frontal	23 (39%)
Occipital	5 (9%)
Temporal	23 (39%)
Parietal	15 (35%)
Cerebellum	2 (3%)
Midline	3 (5%)
MGMT-status	
Methylated	15 (25%)
Unknown/not determined	8 (14%)
1p19q-status	
Co-deletion	5 (9%)
Unknown/not determined	21 (36%)
IDH-status	
Mutated	9 (15%)
Unknown/not determined	23 (39%)
Treatment; n=59	
Biopsy; No (%)	8 (14%)
Partial resection; No (%)	43 (73%)
Macroscopic resection; No (%)	8 (14%)
Chemotherapy; No (%)	47 (80%)
Radiotherapy; No (%)	5 (93%)

Table 1. Continued

Level of education* n=56	
Primary school	6 (10%)
Lower secondary school	11 (20%)
Upper secondary school	16 (29%)
Short cycle tertiary	14 (25%)
Bachelor or equivalent	0 (0%)
Master or equivalent	7 (13%)
Doctoral or equivalent	2 (4%)
Comorbidity n=59	
Any	40 (68%)
Diabetes	2 (3%)
Pulmonary	6 (10%)
Dermatological	5 (9%)
Bowel disorder	5 (9%)
Incontinence for urine	2 (3%)
Heart and vascular disease	15 (25%)
Neurology	16 (27%)
Musculoskeletal system	20 (34%)
Proxy relationship with patient n=56	
Spouse	49 (89%)
Child	6 (11%)
Intensity relationship with patients n=54	
Living together	46 (78%)
Daily	7 (12%)
Weekly	1 (2%)

*Categories: Primary school (Entry age: 5-7 years old. Duration: ± 4-7 years. Programs typically designed to provide students with fundamental skills in reading, writing and mathematics and to establish a solid foundation for learning.) Lower secondary school (Entry age: 10-13 years old. Duration: ≥2 years. First stage of secondary education building on primary education, typically with a more subject oriented curriculum.) Upper secondary school (Entry age: ≥13 years old. Duration: ≥2 years. Second/final stage of secondary education preparing for tertiary education and/or providing skills relevant to employment.) Post-secondary, non-tertiary (Duration: 0.5-3 years. Programs providing learning experiences that build on secondary education and prepare for labour market entry and/or tertiary education.) Short cycle tertiary (Duration: 2-3 years.
Practical/technical/occupationally specific programs leading to professional qualifications) Bachelor or equivalent. Master or equivalent. Doctoral or equivalent

Frequency of symptoms

Table 2 shows the frequency of symptoms patients' experienced in the year prior to diagnosis. The five most frequently reported symptoms were fatigue (34/59, 58%), mental tiredness (30/59, 51%), sleeping disorder (24/59, 41%), headache (23/59, 39%) and stress (20/59, 34%). Patients reported a median of six symptoms in total (range 0-24, see figure 1). Double vision, stress and burnout were significantly more often reported in patients with a favourable prognosis compared to patients with a poor prognosis, but these differences were no longer significant after correction for multiple testing (table 2).

Table 2. Frequency of signs and symptoms and related visits to GP in 59 patients with glioma; All figures are numbers (%).

In the 12 months prior to diagnosis, did you experience problems with:	12 months before diagnosis	GP visit related to symptoms	Grade II and III IDH mutant glioma (low-grade glioma); n=9	IDH wildtype and glioblastoma (high grade glioma); n=50	p-value	Not visited the GP; n=33	Visited the GP; n=26	p-value
1. The extent to which you were aware of the things around you (awareness)	13 (22%)	6 (46%)	2 (22%)	11 (22%)	0.988	4 (12%)	9 (35%)	0.040
2. Seizure(s)	12 (20%)	2 (8%)	3 (33%)	9 (18%)	0.297	8 (24%)	4 (15%)	0.405
3. Changes of personality or character	15 (25%)	3 (20%)	4 (44%)	11 (22%)	0.158	5 (15%)	10 (39%)	0.043
4. Mental tiredness (motivation to do activities or to the ability to endure less)	30 (51%)	5 (17%)	6 (67%)	24 (48%)	0.307	14 (42%)	16 (62%)	0.148
5. Sleeping (falling asleep, waking up during the night or waking up early in the morning)	24 (41%)	2 (8%)	4 (44%)	20 (40%)	0.804	14 (42%)	10 (39%)	0.760
6. Attention (ability to hold attention)	18 (31%)	2 (11%)	4 (44%)	14 (28%)	0.328	8 (24%)	10 (39%)	0.243
7. Short-term memory	16 (27%)	5 (31%)	2 (22%)	14 (28%)	0.722	6 (18%)	10 (39%)	0.085
8. Long-term memory	5 (9%)	1 (20%)	0	5 (10%)	0.326	3 (9%)	2 (8%)	0.849
9. Mood (fear, depression)	14 (24%)	4 (29%)	3 (33%)	11 (22%)	0.466	5 (15%)	9 (35%)	0.084
10. Recognizing a stimulus (sound, picture,	8 (14%)	2 (25%)	3 (33%)	5 (10%)	0.062	5 (15%)	3 (12%)	0.690
11. Thinking (speed of thinking or logical thinking)	20 (34%)	3 (15%)	5 (56%)	15 (30%)	0.139	10 (30%)	10 (39%)	0.515
12. Complicated mental tasks (planning, calculating, time management)	17 (29%)	2 (12%)	5 (56%)	12 (24%)	0.056	7 (21%)	10 (39%)	0.150
13. Understanding language (written text or a conversation)	12 (20%)	3 (25%)	1 (11%)	11 (22%)	0.459	5 (15%)	7 (27%)	0.269
14. Expressing language (speaking or writing language)	19 (32%)	3 (16%)	3 (33%)	16 (32%)	0.938	10 (30%)	9 (35%)	0.727
15. Fine motor skills (closing buttons on a shirt)	8 (14%)	1 (13%)	1 (11%)	7 (14%)	0.817	4 (12%)	4 (15%)	0.719
16. Reduced field of view (the area you see when you keep your head still is reduced)	16 (27%)	4 (25%)	2 (22%)	14 (28%)	0.722	7 (21%)	9 (35%)	0.254
17. Double vision	3 (5%)	1 (33%)	2 (22%)	1 (2%)	0.012	1 (3%)	2 (8%)	0.422
18. Awareness of the position of the limbs	8 (14%)	2 (25%)	1 (11%)	7 (14%)	0.817	2 (6%)	6 (23%)	0.060

In the 12 months prior to diagnosis, did you experience problems with:	12 months before diagnosis	GP visit related to symptoms	Grade II and III IDH mutant glioma (low-grade glioma); n=9	IDH wildtype and glioblastoma (high grade glioma); n=50	p-value	Not visited the GP; n=33	Visited the GP; n=26	p-value
19. Sensibility disorder (tingling sensation or diminished or numb feeling somewhere on your body)	12 (20%)	5 (42%)	4 (44%)	8 (16%)	0.053	4 (12%)	8 (31%)	0.080
20. Focussing on one particular task	17 (29%)	2 (12%)	3 (33%)	14 (28%)	0.747	6 (18%)	11 (42%)	0.044
21. Paralysis of for example hand or leg	14 (24%)	5 (36%)	1 (11%)	13 (26%)	0.338	4 (12%)	10 (39%)	0.019
22. Weakness in muscles	14 (24%)	5 (36%)	2 (22%)	12 (24%)	0.909	3 (9%)	11 (42%)	0.003
23. Altered speech	17 (29%)	6 (35%)	3 (33%)	14 (28%)	0.747	8 (24%)	9 (35%)	0.386
24. Tingling sensation	11 (19%)	2 (18%)	3 (33%)	8 (16%)	0.223	5 (15%)	6 (23%)	0.442
25. Headache	23 (39%)	6 (26%)	2 (22%)	21 (42%)	0.267	13 (39%)	10 (39%)	0.942
26. Nausea	11 (19%)	3 (27%)	2 (22%)	9 (18%)	0.767	6 (18%)	5 (19%)	0.919
27. Vomiting	7 (12%)	2 (29%)	2 (22%)	5 (10%)	0.301	4 (12%)	3 (12%)	0.946
28. Stress	20 (34%)	5 (25%)	6 (67%)	14 (28%)	0.025	10 (30%)	10 (39%)	0.515
29. Fatigue	34 (58%)	5 (15%)	7 (78%)	27 (54%)	0.188	20 (61%)	14 (54%)	0.605
30. Burn-out	7 (12%)	2 (29%)	3 (33%)	4 (8%)	0.032	3 (9%)	4 (15%)	0.462
In total (median, range)	6 (0-24)		8 (0-21)	5 (0-24)	0.267	5 (0-24)	7.5 (1-21)	0.058

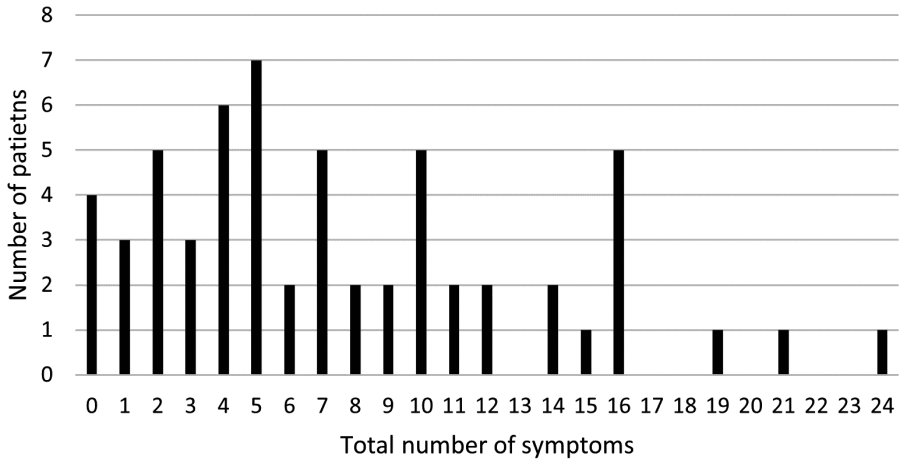

Figure 1. Distribution of the total number of symptoms reported per patient

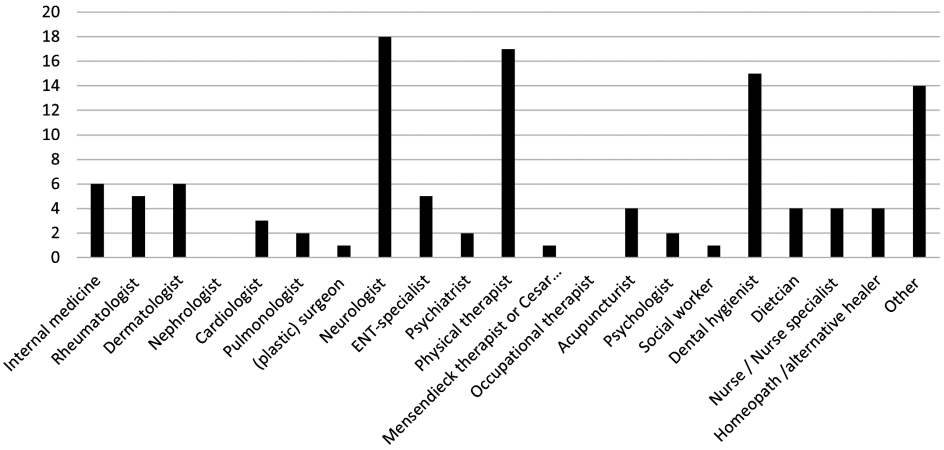

Figure 2. Number of patients visiting health-care professionals

Visits to the general practitioner

Twenty-six (44%) patients visited the GP with at least one symptom. Weakness in muscles was significantly more often reported by patients who visited the GP than patients who did not (11 versus 3, p=0.003). Paralysis of for example hand or leg (10 versus 4), awareness of things around (9 versus 4), changes of personality or character (10 versus 5) and focussing on one particular task (11 versus 6) were reported more often by patients visiting the GP, but did not remain significant after correcting for multiple testing (Table 2). Moreover, patients visiting the GP reported more symptoms

in total (median 7.5, range 1-21) than patients that did not visit the GP (median 5, range 0-24), although this was not significant (p=0.058). Of the patients who did and did not visit the GP for their symptoms, 22 versus 20 reported neurological symptoms only, 20 versus 24 non-specific symptoms only, and 18 versus 17 patients reported both neurological and non-specific symptoms, respectively.

Health care usage

Patients reported that they visited several other health care providers in the year prior to diagnosis, mostly the dentist (78%, 45/58), followed by the neurologist (31%, 18/59), physical therapist (29%, 17/59) and the dental hygienist (26%, 15/58) (figure 2).

Discussion

In this study, we found that more than half of the patients reported fatigue in the year before diagnosis, and that mental tiredness, sleeping disorder, headache and stress were also frequently reported symptoms. These symptoms did not depend on tumour type, i.e. grade II and III IDH-mutant glioma versus IDH wildtype glioma and glioblastoma. An important finding is that patients do not visit the GP for all their complaints, but if they did, this was mostly because of weakness in muscles.

Patients in this study most frequently reported more general or non-specific symptoms, such as fatigue, headache and stress, which are not usually characteristic symptoms for a glioma and could also be a self-contained symptom, whether or not related to another disease. Another study, using data from medical records of GPs, showed that it is difficult to distinguish glioma patients from 'other' patients visiting the GP with respect to their prediagnostic symptoms[30]. Typically, persons do not visit the GP for these common complaints if not sufficiently severe or not having a negative impact on functioning in daily life, which was also observed in our study. In the general population, patient-reported difficulty with initiating sleep or maintaining sleep was found in 16-21% of patients[31]. We found that 41% reported a sleeping disorder, indicating that this is a serious problem in this patient population, even before diagnosis. Similarly, headache and stress (reported in 39% and 34% of patients in our study, respectively) are also frequently reported in the general population, with 46% of the general population reporting headache in the past year[32] and 13% of patients in a Swedish population reporting stress[33]. Nineteen percent of patients visited the GP with stress in the employed population in Norway versus 25% in our population[34], and only 5.4% of patients with headache in the general Dutch population versus 26% in our population[35].

In contrast, patients with disease-specific symptoms, such as problems with awareness, a sensibility disorder, weakness or paralysis and altered speech, which can all be classified as neurological problems, who also reported non-specific symptoms in most cases, did visit the general practitioner more often. It is plausible that these neurological symptoms could not be attributed to more common or less severe disorders, and therefore required follow-up or work up at a hospital as it is important to rule out severe diseases.

This study has several strengths. Most studies assessing prediagnostic symptoms, or symptoms patients present with at diagnosis, use data from medical records at the GP. With that design it is likely that not all symptoms which patients experience are detected. After all, patients do not always visit a health care professionals, e.g. GP with their symptoms or mention all their symptoms when they visit the emergency department or outpatient clinic. Furthermore, with the participation of the proxies, is it likely that a more comprehensive overview of all complaints experienced was provided. Some limitations of our study, and of studies using questionnaires in general, should also be acknowledged. First, selection bias should be taken into account, since not all patients could be included due to their physical or mental condition. This might hamper generalisability of our study results to the whole glioma patient population. In this study, however, there were no significant differences between important clinical characteristics between patients who participated and those who did not. Moreover, due to the inclusion of patients that were diagnosed in 2015, the IDH status was only available for half of glioblastoma patients. Besides, growth rate is also an important factor in the onset and nature of prediagnostic symptoms, although we did not find differences between patients with different molecular profiles. We also lack knowledge on the exacttime of onset of the symptoms (only a wide period, i.e. 12-3 and 3-0 months prior to diagnosis), and whether specific symptoms were the trigger for the GPs to refer the patients to the neurologist that subsequently led to the diagnosis of the brain tumour. Furthermore, recall bias is also an important issue, as patients have to remember symptoms they experienced in the year before diagnosis and treatment, while having a disease in which cognition can be affected as well. Indeed, more than 60% of brain tumour patients have impaired neurocognitive functioning in any domain prior to anti-tumour treatment[36], which progresses over time[37].

To minimise the effect of recall bias, patients were included up to one year after diagnosis, and were asked to fill in the questionnaire with a proxy, who may remember similar or even other symptoms. Recall bias varies between diseases, with remembering the diagnosis of cancer having false positive rates of 5% and false negatives of around 17%[38]. Similarly, recall bias may occur with respect to location and severity of symptoms, e.g. the agreement between two measurements on the location of pain was found to be low to moderate, while the agreement on the severity of pain was low[39]. Although

recall bias may have impacted our results, this approach was considered more solid than exploring symptoms described in the medical records of certain health care professionals, such as GPs or the hospitals, as we expected that not all patients would visit health care professionals with their complaints, or that not all complaints would be reported in the medical records. Ideally, a large prospective cohort of healthy participants should be screened for their symptoms over time, and in time those diagnosed with a glioma could be evaluated for their prediagnostic symptoms. However, this would require a large number of participants, a long follow-up time and considerable resources. Lastly, we asked proxies to help the patient complete the questionnaire together and therefore we do not know whether there were differences between the reported symptoms by the patient or the proxy. Instead, our approach provided a 'consensus insight' into the patients symptom burden, reflecting both the patient and proxy views. For example, a change in personality will probably only be noticed by a proxy and not the patient. In a study by Walter et al, it has been reported 'something was not quite right' or 'changed' about the patient, and these changes were often noticed earlier by others than the patient[40].

In conclusion, recognizing a glioma based on prediagnostic symptoms is challenging as most patients report non-specific symptoms[5]. However, healthcare professionals seeing patients with new neurological symptoms should also ask if they experience non-specific symptoms, and consider the diagnosis of a glioma with the corresponding workup.

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Supplementary File 1. Study-specific questionnaire

Early symptoms in glioma patients

Patient code: | | | | | | | | | |

Date: | | | - | | | - | | | | |

Why this questionnaire?

With this questionnaire we want to gain more insight in the symptoms patients with a brain tumour experience before their diagnosis. Brain tumours can cause several symptoms, for example loss of strength, sensory disorders, language problems, seizures or headaches. Furthermore, many patients with a brain tumour experience disorders in memory or concentration.

Currently it is unclear which symptoms patients experience before the diagnosis of a brain tumour. With this research, we want to explore if there are specific symptoms that will help with the timely recognition of new patients with a brain tumour.

Instructions for completing the questionnaire

We ask you to complete the questionnaire <u>together with your partner or proxy.</u> In this way, we will obtain a more comprehensive overview of your symptoms.

When completing the questions, only your opinion and experience count. There are no wrong or right answers. It is important that you consider the mentioned time frame (i.e. last year) during completion of the questions.

The questionnaire consists of two parts. The first part is about the symptoms you experienced that are related to your brain tumour <u>in the 12 months prior to your diagnosis.</u> The second part is about the doctors and other health care professionals you visited <u>in the 12 months prior to your diagnosis</u> and other disorders and complaints you experienced during this period.

Before you fill out the questionnaire

- Take your time, you can complete the questionnaire in stages if needed.
- Please do not skip any of the questions and answer the questions as complete as possible.
- Tick only one answer, unless otherwise indicated.
- If you make a mistake, please colour this box completely black.
- Do not think too long about one answer.

The date of your diagnosis was: _____ / _____ / 20

Consider this date during the following questions.

First, note the date of today: _____ / _____ / 20

This part is about the symptoms you experienced and are related to your brain tumour. We are interested in the symptoms you experienced in the 12 months prior to your diagnosis.

	In the 12 months prior to your diagnosis, did you experience problems with:	No	Yes	Did you consult your GP for this problem?
1	The extent to which you were aware of the things happening around you (e.g. awareness)	☐	☐	☐
2	Epileptic seizures	☐	☐	☐
3	Change of personality or character	☐	☐	☐
4	Mental tiredness (e.g. motivation to do things or being able to endure less)	☐	☐	☐
5	Sleeping (e.g. falling asleep, waking up frequently, or waking up too early in the morning)	☐	☐	☐
6	Attention (e.g. maintaining attention)	☐	☐	☐
7	Short term memory	☐	☐	☐
8	Long term memory	☐	☐	☐
9	Mood (e.g. fear, depression)	☐	☐	☐
10	Recognizing a stimulus (i.e. sound, image, touch, smell or taste)	☐	☐	☐
11	Thinking (e.g. the speed of thinking or thinking clearly)	☐	☐	☐
12	Complicated mental tasks (e.g. planning, calculating, time management)	☐	☐	☐
13	Understanding language (e.g. written text or a conversation)	☐	☐	☐
14	Expressing language (e.g. speaking or writing language)	☐	☐	☐
15	Fine motor skills (e.g. closing the buttons of a shirt)	☐	☐	☐
16	Reduced visual field (e.g. the area you see when your head is not turning is reduced)	☐	☐	☐
17	Double vision	☐	☐	☐
18	Awareness of the position of your limbs	☐	☐	☐
19	Sensory disorders (e.g. tingling sensation or diminished or numb feeling somewhere on your body)	☐	☐	☐
20	Focussing on a particular task	☐	☐	☐
21	Paralysis in hand or leg	☐	☐	☐
22	Weakness in muscles	☐	☐	☐
23	Altered speech	☐	☐	☐
24	Tingling sensation	☐	☐	☐
25	Headache	☐	☐	☐
26	Nausea	☐	☐	☐
27	Vomiting	☐	☐	☐
28	Stress	☐	☐	☐
29	Physical tiredness	☐	☐	☐
30	Burn-out	☐	☐	☐

Comorbidity

The next part of the questionnaire is about a number of chronic diseases and disorders that are common. Please indicate for each condition if you experienced symptoms in the 12 months prior to your diagnosis of a brain tumour. If yes, please also answer the follow-up questions in the section below the disease or disorder.

		Yes	No
1	Do you have diabetes?	☐	☐
	a If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
	b Are you currently using insulin?	☐	☐
	c Have you started using insulin within 6 months after the diagnosis of diabetes?	☐	☐
2	Have you ever suffered from a stroke, cerebral haemorrhage or cerebral infarction?	☐	☐
	a If yes, have you had this in the last 12 months?	☐	☐
	b If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
	c Do you still experience health problems due to this condition?	☐	☐
3	Have you ever had a heart attack (myocardial infarction?)	☐	☐
	a If yes, have you had this in the last 12 months?	☐	☐
	b If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
	Have you had any other severe heart condition in the 12 past months (e.g. heart failure or angina)?	☐	☐
	a If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
4	Have you ever had any form of cancer (malignant condition)?	☐	☐
	a If yes, have you had this in the last 12 months?	☐	☐
	b If yes, have you visited the general practitioner or specialist for this condition in the 12 months prior to your diagnosis?	☐	☐
	c With which type(s) of cancer have you been diagnosed?	☐ Leukaemia ☐ Lung cancer ☐ Bowel cancer ☐ Breast cancer ☐ Prostate cancer ☐ Skin cancer ☐ Other	

Please indicate (yes/no) if you experienced the following conditions in the 12 months prior to your diagnosis.

				If yes, have you visited the general practitioner for this condition in the 12 months prior to your diagnosis?	
		Yes	**No**	**Yes**	**No**
1	Migraine or (regular) severe headache	☐	☐	☐	☐
2	High blood pressure	☐	☐	☐	☐
3	Narrowing of the blood vessels in the stomach or legs (also called intermittent claudication, but not varicose veins)	☐	☐	☐	☐
4	Asthma, COPD, chronic bronchitis or lung emphysema	☐	☐	☐	☐
5	Psoriasis or chronic eczema	☐	☐	☐	☐
6	Dizziness with falling	☐	☐	☐	☐
7	Severe or persistent bowel disorders, longer than 3 months	☐	☐	☐	☐
8	Involuntary urine loss (incontinence)	☐	☐	☐	☐
9	Osteoarthritis of the hips or knees	☐	☐	☐	☐
10	Chronic joint inflammation (rheumatoid arthritis)	☐	☐	☐	☐
11	Severe or persistent disorder of the back (including spinal disc herniation)	☐	☐	☐	☐
12	Severe or persistent disorder of the neck or shoulder	☐	☐	☐	☐
13	Severe or persistent disorder of the elbow, wrist or hand	☐	☐	☐	☐

Which of the following healthcare professionals have you visited or consulted in the 12 months prior to your diagnosis of a brain tumour?

	No	Yes
General practitioner	☐	☐
Internal medicine physician	☐	☐
Rheumatologist	☐	☐
Dermatologist (physician for the skin)	☐	☐
Nephrologist (physician for the kidney)	☐	☐
Cardiologist (physician for the heart)	☐	☐
Pulmonologist (physician for the lung)	☐	☐
(Plastic) surgeon	☐	☐
Neurologist	☐	☐
ENT specialist	☐	☐
Psychiatrist	☐	☐
Dentist	☐	☐
Physical therapist	☐	☐
Mensendieck therapist or Cesar therapy	☐	☐
Occupational therapist	☐	☐
Acupuncturist	☐	☐
Psychologist	☐	☐
Social worker	☐	☐
Dental hygienist	☐	☐
Beautician	☐	☐
Dietician	☐	☐
District nurse / Home health nurse	☐	☐
Homeopath /alternative healer _____	☐	☐
Other: _____	☐	☐
Other: _____	☐	☐

Educational level

☐	Primary school	☐	Lower secondary school
☐	Upper secondary school	☐	Post-secondary, non-tertiary
☐	Short cycle tertiary	☐	Bachelor or equivalent
☐	Master or equivalent	☐	Doctoral or equivalent

Current or last profession: _____

For proxies only:

Relation to the patient

- ☐ Partner
- ☐ Parent
- ☐ Other:
- ☐ Sibling
- ☐ Child

Intensity of contact with the patient

- ☐ Living together
- ☐ Weekly
- ☐ Daily
- ☐ Monthly

Duration relationship in years: ☐☐

PART TWO

CHAPTER 4

The impact of the timing of health-related quality of life assessments on the actual results in glioma patients: a randomized prospective study

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Abstract

Background

The aim of this study was to explore the impact of the timing of health-related quality of life (HRQoL) measurements in clinical care on the obtained HRQoL scores in glioma patients, and the association with feelings of anxiety or depression.

Methods

Patients completed the European Organisation for Research and Treatment of Cancer (EORTC)'s Quality of Life Questionnaires (QLQ-C30 and QLQ-BN20), and the Hospital Anxiety and Depression Scale (HADS) twice. All patients completed the first measurement on the day of the Magnetic Resonance Imaging (MRI) scan (t=0), but the second measurement (t=1) depended on randomization; Group 1 (n=49) completed the questionnaires before and Group 2 (n=51) after the consultation with the physician.

Results

Median HRQoL scale scores on t0/t1 and change scores were comparable between the two groups. Between 8-58% of patients changed to a clinically relevant extent (i.e., ≥10 points) on the evaluated HRQoL scales in about one-week time, in both directions, with only 3% of patients remaining stable in all scales. Patients with a stable role functioning had a lower HADS anxiety change score. The HADS depression score was not associated with a change in HRQoL.

Conclusions

Measuring HRQoL before or after the consultation did not impact HRQoL scores on a group level. However, most patients reported a clinically relevant difference in at least one HRQoL scale between the two time points. These findings highlight the importance of a standardized HRQoL assessments, or patient-reported outcomes in general, during treatment and follow-up in clinical trials.

Introduction

Gliomas are the most common malignant primary brain tumors in adults, and although rare – a yearly incidence of 6 cases per 100.000 persons[1] - these tumors have a disproportionate share in morbidity. Glioma patients suffer from both cancer, with a dismal outcome, and a progressive neurological disease. Patients experience symptoms such as headaches, seizures, focal and/or neurocognitive deficits, and changes in personality and behavior[2], which may subsequently negatively influence their Health-Related Quality of Life (HRQoL)[3-6]. HRQoL is a multidimensional concept covering physical, psychological and social domains, as well as symptoms induced by the disease and its treatment[7]. Both the tumor and its treatment may affect the functioning and well-being of patients[8]. This resulted in patient-reported outcomes such as HRQoL becoming more important in recent decades, besides traditional outcomes such as survival and tumor response on imaging, as they are valuable in evaluating the clinical benefit of a (antitumor) treatment strategy[9]. Indeed, for glioma patients the quality of survival is considered at least as important as the quantity of survival[10]. Furthermore, measuring a patient's functioning and well-being is an essential part of an integrated approach to disease management. Several instruments are available to assess a patient's HRQoL, including the Functional Assessment of Cancer Therapy – Brain (FACT-Br)[11], the MD Anderson Symptom Inventory for Brain Tumor (MDASI-BT)[12] and the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), which can be complemented with a brain tumor module, the EORTC QLQ-BN20[13].

Appropriate timing of Patient-Reported Outcome Measures (PROMs) is important, particularly in clinical trials, as results should reflect the impact of the treatments under investigation and should not be an effect of timing[14]. For example, if HRQoL is measured during the immediate toxicity of the treatment in one arm and two weeks later in the other arm, when the toxicity effect has faded, erroneous conclusions on the impact of treatment would be drawn. Recommendations about the appropriate timing of PROMs have been formulated, including specifying a standardized moment of questionnaire delivery (e.g. before/whilst/after seeing a clinician). As deviation from these scheduled assessments is likely in practice, a time window needs to be specified that allows questionnaires to be included in the analysis when completed within this window[15, 16]. Currently, in trials with glioma patients the predetermined time window differs from 1 week to 6 months[17, 18]. However, Ediebah et al. found that the definition of a time window has an impact on the obtained HRQoL results of a study, and could alter conclusions about treatment effects[19]. Particularly the width of the time window seems important; a wider completion time window for HRQoL assessments during treatment produced statistically and clinically significant differences compared to a narrow time window[20].

Typically, HRQoL questionnaires are administered to glioma patients during follow-up right before their scheduled appointment with the physician to discuss the results of the Magnetic Resonance Imaging (MRI) scan and further treatment. However, at that moment the patient might be suffering from anxiety or may experience feelings of fear for possible progressive disease, which may negatively influence HRQoL scores. Likewise, if administered after the consultation with the physician, feelings of depression or relieve might influence the HRQoL scores, depending on the outcome of the consultation. An alternative moment would be to administer the questionnaires at the day of the MRI, which is typically a few days to a week before the consultation with the physician. It is currently unknown what the optimal timing of HRQoL assessments is, and whether assessments at different time points, although within a prespecified time window, would result in different outcomes. The aim of this study was to explore if HRQoL scores changed to a clinically relevant extent when administered between the moment of the MRI scan and the day of the consultation with the physician, and whether feelings of anxiety or depression had an influence on these HRQoL scores.

Materials and Methods

Study design and patients

This was a randomized prospective study for which adult patients (≥18 years of age) with a histologically confirmed grade II-IV glioma (WHO 2016 classification criteria) or radiologically suspected glioma were recruited. Patients were eligible if they did not show progression on previous imaging and were scheduled for a follow-up MRI and corresponding visit to the outpatient clinic. Eligible patients were recruited in Haaglanden Medical Center in The Hague, The Netherlands, between July 2016 and July 2018. The study was conducted in accordance with the Declaration of Helsinki. A declaration of no-objection was granted by the medical ethical review board of the institution (METC Zuidwest Holland, ethic code '2016-062') and all patients provided written informed consent prior to participation.

Tools

HRQoL was assessed with the EORTC QLQ-C30[21] and QLQ-BN20[22]. The EORTC QLQ-C30 is a generic questionnaire developed to measure HRQoL in cancer patients, and comprises five functional scales, one global health status/QOL scale and six single-item scales. The QLQ-C30 was supplemented with the brain-specific questionnaire, the EORTC QLQ-BN20, which includes 20 items assessing four functional scales and seven single-item scales. Both questionnaires are available in Dutch. For functional scales

and the global health status/QOL scale, a higher score represents better functioning. For the symptom scales, a higher score means more problems/symptomatology. All single-item and multi-item scales were scored on a 4-point Likert scale, except for the items "overall health" and "overall quality of life" which were scored on a 7-point Likert scale, and subsequently linearly transformed to 0-100 scales. Mean differences of at least 10 points were considered clinically significant[23].

The Hospital Anxiety and Depression Scale (HADS) is a test of psychological wellbeing and consists of two subscales, one for anxiety and one for depression, each consisting of seven questions. Each question was rated by the patient on a four-point scale, representing the degree of distress suffered by the patient (0=none, 3=unbearable). Items for each subscale were summated (range from 0 to 21) and a score of ≥11 on either subscale represented a definite case of anxiety and/or depression.

The sociodemographic and clinical characteristics were collected using medical records and via a study-specific questionnaire.

Randomization and timing of assessments

Patients were randomized into one of two groups (1:1 ratio). Both groups completed the HADS and HRQoL questionnaires at baseline, but the timing of the second measurement differed. Group 1 completed the questionnaires for the second time before the consultation with the physician, and Group 2) directly after the consultation with the physician to discuss the MRI results (see Figure 2 for an overview). As it was impossible to blind patients and nurses to group allocation, the latter were encouraged not to discuss the possible impact of the timing of the HRQoL assessments on the actual HRQoL scores with the patients. Questionnaires were handed out on paper by the nurse-specialist (HZ).

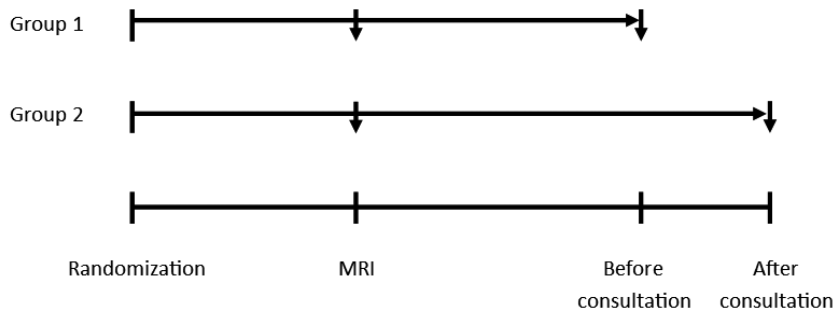

Figure 1. Overview of HRQoL measurements after randomization in glioma patients in group 1 (assessment at the day of the MRI scan and before the consultation with the physician) and group 2 (assessment at the day of MRI and after the consultation with the physician).

Statistical analysis

Descriptive statistics were used to report HRQoL scores as well as the sociodemographic and clinical variables. Means and standard deviations or medians and ranges were calculated for continuous variables, depending on the distribution of the variable. Frequencies and percentages were calculated for nominal variables. Dependent on the type of variable and its distribution, a Student *t*-test, the Mann-Whitney U test, or Chi Square test, were used to compare characteristics between groups. In addition, the percentage of patients whose HRQoL scores had decreased/increased ≥10 points between assessment times were computed, as well as the percentage of patients whose scores remained stable (<10 points change).

We analyzed whether the timing of the second measurement had an impact on HRQoL change scores (comparing change scores between Groups 1 and 2), while adjusting for potential confounding factors (age, sex, KPS, disease status, current anti-tumor treatment (yes/no)), and baseline HADS and HRQoL scores, by means of Analysis of Covariance (ANCOVA). To examine the determinants of clinically relevant changes in scale scores, logistic regression analyses were used. First, univariable models were constructed assessing which patient- and treatment-related characteristics were predictive of experiencing a clinically relevant change in at least three scales. Associations with a *p*-value ≤0.1 were subsequently included in a stepwise backward conditional multivariable logistic regression model. Sensitivity analyses were performed using ≥4 or ≥5 scales, showing a clinically relevant change as cut-off (instead of ≥3 scales as used in the primary analysis). All data were analyzed using the SPSS statistical package (version 25, SPSS, Chicago, Illinois). The level of statistical significance was set at 0.05 for all analyses. Due to the explorative character of this study, we did not correct for multiple testing.

Results

Patient population

Table 1 shows the sociodemographic and clinical characteristics of the 100 participating patients (*n*=49 in group 1 and *n*=51 in group 2). There were no significant differences between the two groups. The majority was male (58/100, 58%) with a mean age of 56 years (Standard Deviation (SD) 12). The median time since diagnosis of 26 months (interquartile range 9-82 months). Forty-three percent patients had a glioblastoma, 87% had stable disease and 45% a median Karnofsky Performance Score (KPS) of 90. The mean time between the first and second HRQoL assessment was 7 days (SD=5), and a few HRQoL and HADS scales were not completed in three patients, representing <1% of all data.

Table 1. Baseline sociodemographic and clinical characteristics of glioma patients participating in a randomized trial on the impact of timing of HRQoL measurements.

	All (n=100)	Group 1 (Before consultation) n=49	Group 2 (After consultation) n=51	p-value
Age, years; mean (sd)	56 (12)	56 (12)	55 (13)	0.855
Sex; n (%) male	58 (58%)	26 (53%)	32 (63%)	0.418
Time since diagnosis (months) (median, range)	26 (6-298)	34 (6-298)	23 (7-256)	0.274
Time between HRQoL assessments (days) (mean, sd)	7 (5)	6 (4)	7 (6)	0.152
Tumor type; n (%)				
Non-glioblastoma	57 (57%)	30 (61%)	29 (57%)	0.447
Glioblastoma	43 (43%)	19 (39%)	22 (43%)	
KPS; median (range)	90 (60-100)	80 (60-100)	90 (60-100)	0.076
Radiological response on MRI; n (%)				
Minor response	3 (3%)	1 (2%)	2 (4%)	0.494
Stable disease	87 (87%)	42 (86%)	45 (88%)	
Progressive disease	9 (9%)	6 (12%)	3 (6%)	
Pseudoprogression	1 (1%)		1 (2%)	
Hemisphere; n (%)				0.340
Left hemisphere	47 (47%)	23 (47%)	24 (47%)	
Right hemisphere	51 (51%)	24 (49%)	27 (53%)	
Both hemispheres	2 (2%)	2 (4%)		
Prior antitumor treatment (multiple options possible); n (%) (maximum n=99)				
Biopsy	14 (14%)	6 (13%)	8 (16%)	0.788
Resection	85 (86%)	42 (88%)	43 (84%)	
Chemotherapy	74 (75%)	38 (78%)	36 (71%)	
Radiotherapy	91 (92%)	44 (90%)	47 (92%)	
Current anti-tumor treatment; n (%)				0.871
No active treatment	48 (48%)	23 (47%)	25 (49%)	
Chemotherapy	46 (46%)	23 (47%)	23 (45%)	
Other	6 (6%)	3 (6%)	3 (6%)	
Marital status; n (%)				0.310
Without partner	19 (19%)	7 (14%)	12 (12%)	
With partner	81 (81%)	42 (86%)	39 (76%)	
Dexamethasone; n (%)				0.521
Yes	10 (10%)	6 (12%)	4 (8%)	
No	90 (90%)	43 (88%	47 (92%)	
Antiepileptic drug; n (%)				0.227
Yes	56 (56%)	24 (49%)	32 (63%)	
No	44 (44%)	25 (51%)	19 (37%)	
Level of education; n (%)				0.830
Lower	31 (31%)	16 (33%)	15 (29%)	
Higher	69 (69%)	33 (67%)	36 (71%)	

SD: standard deviation
KPS: Karnofsky Performance Status
Level of education: Lower educational status includes primary school, lower secondary school, upper secondary school and post-secondary, non-tertiary school; higher level of education includes short cycle tertiary, bachelor or equivalent, master or equivalent and doctoral or equivalent

HRQoL scores

Median HRQoL scores on the first measurement moment (t0; at the day of the MRI) and the second measurement moment (t1) were comparable between the two groups (Supplementary Table 1), except for pain on t0, where Group 1 scored significantly lower (median 0 (range: 0-83) vs. median 0 (range: 0-100), p=0.049). On group level, in both groups, we found that mean changes in HRQoL from t0 to t1 were stable (<10-point change from baseline) for all HRQoL scales. However, at the individual patient level, we found that a large proportion of patients did report a clinically meaningful improvement or deterioration in certain scales, although the percentages varied across scales (Table 2). There were no significant differences between the two groups with respect to the percentages of patients improving or deteriorating to a clinically relevant extent. Therefore, in the next analyses, all patients participating in the study (n=100) were combined. Percentages of patients that changed to a clinically relevant extent ranged between 8-58% for the evaluated scales, with only three patients (3%) remaining stable on all scales. Twelve patients (out of 97) did not deteriorate (i.e. they only reported stable or improved scores) and six patients did not improve (i.e. they reported stable or deteriorated scores). The mean number of the 26 evaluated HRQoL scales/ that changed to a clinically relevant extent per patient was 7 (SD=4) (see Figure 2).

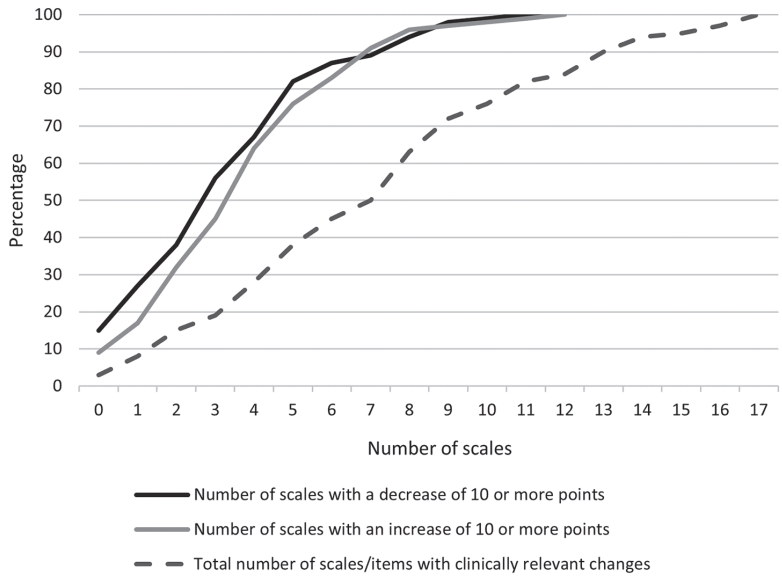

Figure 2. The cumulative percentage of patients with a clinically relevant change in a HRQoL scale, reflecting how the percentage of patients with a change in a specific number of scales add together. Results are shown for the total number of HRQoL scales (dashed line), but also separately for the scales showing a clinically relevant deterioration or improvement.

In the univariable logistic regression analyses, only KPS score and currently receiving antitumor treatment (no/yes) were predictive (p<0.1) of patients who reported a clinically meaningful change in at least three scales (see Table 3). In the multivariable analyses, both a lower KPS (OR 0.92, 95% CI 0.85-0.99) and current antitumor treatment (OR 4.64, 95% CI 1.18-18.17) were found to be independently predictive of reporting clinically relevant changes (either improvement or deterioration) in three or more HRQoL scales. Results were similar when a cut-off with four or five scales was used (data not shown).

Impact of anxiety and depression

There were no significant differences between the anxiety and depression scores between the two groups on both measurement moments (Table S1), as well as the change scores from t0 to t1 (Table 2). We evaluated whether a change in the level of anxiety or depression was associated with a change in HRQoL scores using univariable regression. We found that patients that were stable in role functioning had a lower anxiety change score from t0 to t1 (OR 0.781, 95% CI: 0.619-0.984, *p*=0.036) compared to patients who had a clinically meaningful change, however, not on the other scales. However, this association was no longer significant in the multivariable regression analysis when corrected for confounding factors (OR 0.828, 95% CI: 0.624-1.098, *p*=0.190). The depression change score was not associated with a change on any of the HRQoL scales, in either group.

Furthermore, table 3 shows that both the mean anxiety and depression change scores were not different between patients classified as experiencing clinically meaningful changes (i.e. in ≥3 scales) versus those who were not (i.e. <3 scales).

Discussion

This study aimed to explore if HRQoL scores changed to a clinically relevant extent between two time points: during the routine MRI scan and the subsequent consultation with the physician. In particular, it was investigated whether the timing of the second assessment was also important, as feelings of anxiety and depression may impact on how patients report their HRQoL. We found that, on the group level, there were no significant differences in any of the HRQoL scores between patients completing the EORTC QLQ-C30 and QLQ-BN20 either before or after the consultation with their treating physician, nor in changes in any of the HRQoL scale scores over time. However, on the individual level, we found that there were considerable differences between and within patients. In only 3% of the patients we did not observe clinically relevant changes on any of the EORTC scale scores, whereas in the large majority the number

Table 2. Mean changes in HRQoL scale scores and HADS scores between t0 and t1, between group 1 and group 2, and the number (and percentage) of patients with a clinically relevant change score (i.e. ten or more points).

Scale	Mean change scores (95% CI of the difference) of the total group (n=100)	Unpaired t-test mean change scores	Mean (sd) change (t0 to t1) in HRQoL Group 1	Mean (sd) change (t0 to t1) in HRQoL Group 2	p-value for change (t0 to t1) between group 1 and 2	Number of patients in the total group (n=100) with a change score of <10 or >10 points, n (%)
QLQc30: Global health status	2.0 (-3.4 – 7.5)	0.464	-2.3 (14.8)	-4.4 (12.7)	0.840	14 (27.5%)
QLQc30: Physical functioning	-0.4 (-3.9 – 3.0)	0.798	-1.4 (9.7)	-0.9 (7.5)	0.968	8 (15.7%)
QLQc30: Role functioning	-1.2 (-9.8 – 7.4)	0.783	-5.4 (21.6)	-4.2 (21.6)	0.414	22 (43.1%)
QLQc30: Emotional functioning	-2.0 (-8.0 – 4.0)	0.504	-1.5 (15.9)	0.5 (14.2)	0.563	11 (21.6%)
QLQc30: Cognitive functioning	0.6 (-7.7 – 8.8)	0.893	-2.3 (19.2)	-2.9 (22.0)	0.667	29 (56.9%)
QLQc30: Social functioning	-1.6 (-9.2 – 6.1)	0.684	-6.8 (20.9)	-5.2 (17.5)	0.903	22 (43.1%)
QLQc30: Fatigue	3.1 (-2.6 – 8.8)	0.281	7.5 (15.1)	4.4 (13.7)	0.348	28 (54.9%)
QLQc30: Nausea and vomiting	-0.3 (-3.8 – 3.3)	0.884	1.7 (7.8)	2.0 (9.8)	0.938	7 (13.7%)
QLQc30: Pain	-1.4 (-8.1 – 5.4)	0.693	-1.0 (18.1)	0.3 (15.8)	0.531	19 (37.7%)
QLQc30: Dyspnea	0.8 (-6.1 – 7.6)	0.827	2.7 (17.8)	2.0 (16.9)	0.880	10 (19.6%)
QLQc30: Insomnia	0.7 (-6.7 – 8.1)	0.845	2.0 (19.7)	1.3 (17.6)	0.681	14 (27.5%)
QLQc30: Appetite loss	1.5 (-5.8 – 8.8)	0.681	5.4 (19.7)	3.9 (17.2)	0.782	11 (21.6%)
QLQc30: Constipation	5.4 (-2.3 – 13.1)	0.165	4.8 (22.6)	-0.65 (15.6)	0.292	11 (21.6%)
QLQc30: Diarrhea	-1.4 (-7.4 – 4.7)	0.655	-1.4 (15.1)	0 (15.1)	0.386	7 (14%)
QLQc30: Financial difficulties	4.1 (-3.7 – 11.8)	0.301	3.4 (17.0)	-0.65 (21.6)	0.363	10 (19.6%)
QLQBN20: Future uncertainty	1.1 (-3.7 – 5.8)	0.655	3.9 (10.9)	2.8 (12.9)	0.387	18 (36%)
QLQBN20: Visual deficits	3.5 (-0.4 – 7.4)	0.076	2.4 (8.3)	-1.1 (10.8)	0.142	19 (39%)
QLQBN20: Motor dysfunction	0 (-5.4 – 5.3)	0.992	-1.4 (14.6)	-1.3 (12.0)	0.754	25 (50%)
QLQBN20: Communication deficit	1.6 (-4.7 – 8.0)	0.615	2.9 (12.8)	1.3 (18.5)	0.411	20 (40%)
QLQBN20: Headache	0.7 (-7.6 – 9.1)	0.862	3.4 (23.8)	2.7 (17.6)	0.834	11 (22%)
QLQBN20: Seizures	-5.4 (-11.6 – .9)	0.090	-2.0 (12.6)	3.3 (18.1)	0.153	4 (8%)
QLQBN20: Drowsiness	-1.3 (-10 – 7.4)	0.768	2.0 (24.9)	3.3 (18.1)	0.864	15 (30%)
QLQBN20: Hair loss	0.7 (-6.6 – 7.9)	0.859	-0.7 (17.3)	-1.3 (19.0)	0.600	7 (14%)
QLQBN20: Itchy skin	0 (-6.6 – 6.6)	0.997	0.7 (18.6)	0.7 (14.2)	0.802	6 (12%)
QLQBN20: Weakness of legs	3.3 (-3.1 – 9.8)	0.304	0.7 (18.6)	-2.7 (13.2)	0.241	8 (16%)
QLQBN20: Bladder control	1.5 (-4.2 – 7.1)	0.608	3.4 (15.7)	2.0 (12.4)	0.935	7 (14%)
HADS: Anxiety score	0.1 (-.7 – .9)	0.893	0.2 (2.2)	0.1 (1.5)	0.792	
HADS: Depression score	0.8 (0 – 1.6)	0.060	1.0 (2.4)	0.3 (1.7)	0.105	

Table 3. Univariable and multivariable logistic regression of associations between clinical characteristics and patients with a change of ten or more points on three or more HRQoL scales.

	Univariable regression		Multivariable regression	
Variable	**p-value**	**Exp(B), 95%CI**	**p-value**	**Exp(B), 95%CI**
Current antitumor treatment			0.028	4.636 (1.183-18.170)
No	0.013	*Ref*		
Yes		5.444 (1.431-20.716		
Age (years)	0.360	1.020 (0.977-1.065)		
Sex				
Male	0.463	Ref		
Female		1.542 (0.485-4.898)		
Educational level				
Low	0.694	*Ref*		
High		0.781 (0.228-2.678)		
Partner				
No	0.547	*Ref*		
Yes		0.615 (0.127-2.990)		
KPS	0.016	0.913 (0.848-0.983)	0.035	0.920 (0.851-0.994)
Disease status				
Stable	0.998	*Ref*		
Progressive		3846368672 (0-		
AED use				
No	0.432	*Ref*		
Yes		1.556 (0.517-4.682)		
Corticosteroid use				
No	0.644	*Ref*		
Yes		1.658 (0.194-14.136)		
HADS anxiety change score	0.930	0.987 (0.731-1.331)		
HADS depression change score	0.641	0.940 (0.727-1.217)		

Level of education: Lower educational status includes primary school, lower secondary school, upper secondary school and post-secondary, non-tertiary school; higher level of education includes short cycle tertiary, bachelor or equivalent, master or equivalent and doctoral or equivalent
KPS: Karnofsky Performance Status
AED: anti-epileptic drugs
HADS anxiety: Hospital Anxiety and Depression Scale anxiety score
HADS depression: Hospital Anxiety and Depression Scale depression score

of scales with clinically meaningful changes ranged from 0 to 17 (mean of 7). Within patients, some of these clinically meaningful changes concerned improvements and others a deterioration, indicating that not all dimensions of HRQoL are affected equally. Possibly, these changes are affected by the patient's health status, as patients with a better KPS and patients without current antitumor treatment changed on less HRQoL scales, suggesting that health status is of influence. One other study investigating the changes in HRQoL on the individual patient level in glioma patients also found that the majority (84%) of patients showed both deterioration and improvement between two times points[24]. The time between assessments in this study was at least one month and included the initiation of antitumor treatment, which may explain the observed change in HRQoL on the individual patient level. In our study, on the other hand, the two time points were only one week apart and it is not expected that patients change to a clinically relevant extent within that week if they have a stable health status. Indeed, patients in our study did not initiate treatment in that one-week period, nor did they report a clinical deterioration. In addition, a one- or two-week time period is often chosen in studies that develop a new questionnaire to determine the reliability of that questionnaire (with a test-retest), as patients are not expected to change within that period.

The finding on the group level is in line with the literature in glioma patients, showing that there were no clinically meaningful changes in mean HRQoL scores between different moments of questionnaire administration in situations where the health status of patients was considered not to change significantly, as was the case in our study, where treatment was not altered during this period[22].

This study emphasizes that the time windows of Patient Reported Outcome (PRO) assessment in clinical trials should be carefully considered, but the exact timing in the disease trajectory may be of importance as well. Although we did not find a relation with anxiety and depression, the period around the MRI and the subsequent consultation may be burdensome for patients. A relatively more stable period, without MRI scans, and changes in treatment or consultations could be considered for the administration of PROMs, although this may be practically challenging. Using a web-based PRO data collection could facilitate timely evaluation of PROs during the conduct of a clinical trial.

The changes in HRQoL scores in this study were not influenced by the level of anxiety or depression patients experienced. This is different from a study on patients with a primary diagnosis of recurrent or metastatic non-small cell lung cancer, showing that 'scanxiety' is a true phenomenon, resulting in a statistically significant association between greater scan-associated distress and impaired emotional well-being[25]. Furthermore, in our sample, only 10 patients (10%) had either progression or (pseudo) progression as outcome of their MRI-scan, equally distributed over the two groups.

This small number of patients with (pseudo)progression could be an explanation for the fact that there were no differences in HADS scores on both time points as well as in the change scores between patients with and without (pseudo)progression. Moreover, we found no differences in any HRQoL scale scores at t0 and t1 or the change scores between patients with and without (pseudo)progression. However, all patients with (pseudo)progression reported clinically meaningful changes in three or more scales, therefore the influence of progression remains unclear.

This study has several strengths. First, this was a randomized prospective study, which allowed investigation of the impact of the timing of the second administration of HRQoL questionnaires on the reported HRQoL scores. Due to the collection of data at regularly scheduled medical visits, as recommended[26], and because of the short time period between the two assessments, there was almost no missing data. Although we do not have information on the patient characteristics of those not participating (i.e. selection bias), our sample of glioma patients was heterogenous and therefore seems representative of the general glioma population, ensuring generalizability of our results. The choice of a clinically relevant difference, i.e. ≥10 points on a scale, may have also have impacted our results. Although this value is universally accepted as a clinically meaningful change and used in cancer clinical trials, recent research has shown that this value may be different for different cancers and may not be applicable to changes on the individual patient level[27-29]. More appropriately defined clinically relevant differences may therefore be useful in both clinical trials and practice, when evaluating the impact of treatment over time.

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Supplementary Table 1. Mean scores of HRQoL scales in glioma patients measured before (group1) or after (group 2) the consultation with the physician.

		T0				
Nr.	Scale	N=	Total Median (range)	Group 1 Median (range)	Group 2 Median (range)	p-value for difference in HRQoL scores between group 1 and group 2 on t0
1	QLQc30: Global health status	100	75.0 (16.7-100)	66.7 (16.7-100)	75 (41.7-100)	0.256
2	QLQc30: Physical functioning	100	86.7 (0-100)	86.67 (0-100)	93.3 (13.3-100)	0.305
3	QLQc30: Role functioning	100	66.7 (0-100)	66.67 (0-100)	66.7 (0-100)	0.558
4	QLQc30: Emotional functioning	100	83.3 (8.3-100)	75 (8.3-100)	83.3 (8.3-100)	0.082
5	QLQc30: Cognitive functioning	100	83.3 (0-100)	66.7 (16.7-100)	83.3 (0-100)	0.192
6	QLQc30: Social functioning	100	83.3 (0-100)	83.3 (0-100)	83.3 (16.7-100)	0.412
7	QLQc30: Fatigue	100	33.3 (0-100)	44.4 (0-100)	33.3 (0-100)	0.133
8	QLQc30: Nausea and vomiting	100	0 (0-100)	0 (0-66.7)	0 (0-100)	0.472
9	QLQc30: Pain	100	0 (0-100)	0 (0-83.3)	0 (0-100)	0.049
10	QLQc30: Dyspnea	100	0 (0-100)	0 (0-66.7)	0 (0-100)	0.976
11	QLQc30: Insomnia	100	0 (0-100)	0 (0-100)	0 (0-66.7)	0.658
12	QLQc30: Appetite loss	100	0 (0-100)	0 (0-100)	0 (0-100)	0.193
13	QLQc30: Constipation	100	0 (0-100)	0 (0-100)	0 (0-100)	0.186
14	QLQc30: Diarrhea	99	0 (0-66.67)	0 (0-66.7)	0 (0-66.7)	0.170
15	QLQc30: Financial difficulties	100	0 (0-100)	0 (0-100)	0 (0-100)	0.179
16	QLQBN20: Future uncertainty	99	20.8 (0-100)	25 (0-100)	16.7 (0-58.3)	0.126
17	QLQBN20: Visual deficits	99	5.6 (0-66.7)	11.1 (0-66.7)	0 (0-66.7)	0.134
18	QLQBN20: Motor dysfunction	99	11.1 (0-55.6)	11.1 (0-55.6)	0 (0-55.6)	0.085
19	QLQBN20: Communication deficit	99	11.1 (0-100)	11.1 (0-88.9)	11.1 (0-100)	0.937
20	QLQBN20: Headache	99	0 (0-100)	0 (0-100)	0 (0-66.7)	0.482
21	QLQBN20: Seizures	99	0 (0-100)	0 (0-66.7)	0 (0-100)	0.509
22	QLQBN20: Drowsiness	99	0 (0-66.7)	0 (0-66.7)	0 (0-66.7)	0.436
23	QLQBN20: Hair loss	99	0 (0-100)	0 (0-100)	0 (0-100)	0.992
24	QLQBN20: Itchy skin	99	0 (0-100)	0 (0-100)	0 (0-100)	0.550
25	QLQBN20: Weakness of legs	99	0 (0-100)	0 (0-100)	0 (0-33.3)	0.804
26	QLQBN20: Bladder control	99	0 (0-100)	0 (0-66.7)	0 (0-100)	0.445
27	HADS: Anxiety score	99	3 (0-16)	3.5 (0-16)	3 (0-9)	0.193
28	HADS: Depression score	99	3 (0-15)	4 (0-15)	2 (0-11)	0.080

*Each analysis is corrected for the following variables: score at t0, KPS, MRI outcome, gender, age, anti-tumor treatment and anxiety and depression scores

	T1				
	Total Median (range)	Group 1 Median (range)	Group 2 Median (range)	p-value for difference in HRQoL scores between group 1 and group 2 on t1	ANCOVA group 1 vs group 2 on t1*
	83.3 (8.3-100)	75 (8.3-100)	75 (41.7-100)	0.059	0.270
	86.7 (0-100)	86.7 (0-100)	93.3 (13.3-100)	0.206	0.770
	75 (0-100)	66.7 (0-100)	83.3 (0-100)	0.403	0.358
	83.3 (0-100)	75 (0-100)	83.3 (0-100)	0.236	0.322
	83.3 (0-100)	66.67 (0-100)	83.3 (0-100)	0.191	0.829
	100 (0-100)	100 (0-100)	100 (16.7-100	0.552	0.633
	33.3 (0-88.9)	33.3 (0-88.9)	22.2 (0-77.8)	0.403	0.397
	0 (0-100)	0 (0-50)	0 (0-100)	0.404	0.999
	0 (0-83.3)	0 (0-83.3)	0 (0-83.3)	0.092	0.746
	0 (0-66.7)	0 (0-66.7)	0 (0-66.7)	0.883	0.544
	0 (0-100)	0 (0-100)	0 (0-66.7)	0.615	0.887
	0 (0-100)	0 (0-100)	0 (0-66.7)	0.147	0.656
	0 (0-66.67)	0 (0-66.7)	0 (0-66.7)	0.889	0.154
	0 (0-100)	0 (0-66.7)	0 (0-100)	0.995	0.645
	0 (0-100)	0 (0-100)	0 (0-100)	0.992	0.624
	16.7 (0-91.7)	16.7 (0-91.7)	16.7 (0-66.7)	0.091	0.823
	0 (0-66.7)	0 (0-66.7)	0 (0-66.7)	0.696	0.090
	0 (0-88.9)	11.1 (0-88.9)	0 (0-77.8)	0.111	0.799
	11.1 (77.8)	11.1 (0-77.8)	11.1 (0-77.8)	0.780	0.518
	0 (0-66.7)	0 (0-66.7)	0 (0-66.7)	0.197	0.915
	0 (0-66.7)	0 (0-66.7)	0 (0-33.3)	0.264	0.183
	0 (0-100)	0 (0-100)	0 (0-66.7)	0.483	0.728
	0 (0-100)	0 (0-100)	0 (0-100)	0.783	0.596
	0 (0-100)	0 (0-66.7)	0 (0-100)	0.926	0.610
	0 (0-100)	0 (0-100)	0 (0-66.7)	0.441	0.123
	0 (0-100)	0 (0-66.7)	0 (0-100)	0.618	0.999
	4 (0-17)	4 (0-17)	3 (0-9)	0.117	0.920
	2 (0-19)	2 (0-19)	1 (0-10)	0.571	0.104

CHAPTER 5

Measuring patient-reported outcomes in glioma patients in clinical practice: the perspective of patients and clinicians

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Abstract

Introduction

Routine assessment of patient-reported outcomes (PROs) in oncology has shown to improve the quality of the delivered care and to prolong survival. However, for successful implementation of routine assessment of PROs, more knowledge on their usability in clinical practice is needed.

Objective

This study aimed to cross sectionally assess the perspective of patients and clinicians on the practicality of routinely measuring PROs in clinical practice for glioma patients.

Methods

Semi-structured interviews were conducted evaluating the role of health care professionals (HCP) in discussing results of PRO measures (PROMs), and the preferred topics, methods and frequency of PRO assessment. Glioma patients, their proxies and HCPs involved in the treatment of glioma patients from 8 centers in the Netherlands were included.

Results

Twenty-four patients, 16 proxies and 35 HCPs were interviewed. The majority of patients, proxies and HCPs (92%, 81% and 80%) were willing to discuss PRO results during consultations. Although HCPs prefer that results are discussed with the nurse specialist, only one third of patients/proxies agreed. Functioning of daily life was considered important in all three groups. Most participants indicated that discussion of PROM results should take place during standard follow-up visits, and completed at home about one week in advance. On group level, there was no preference for administration of questionnaires on paper or digitally. Lastly, all centers had staff available to send questionnaires on paper.

Conclusion

This study shows that routine assessment of PROs is desired by patients, proxies and HCP's in neuro-oncological care in Dutch hospitals.

Introduction

Gliomas are the most common malignant primary brain tumors in adults, with an incidence of six cases per 100.000 persons per year[1, 2].The prognosis of glioma patients depends on the histological type, grade and molecular markers of the tumor, with median survival rates ranging from 15 months in high-grade gliomas up to 16 years in low-grade gliomas[3-5]. Due to the incurable nature of gliomas, treatment is not only directed at prolonging survival, but also at maintaining or improving the patients' functioning and well-being. Patient-reported outcome measures (PROMs) are increasingly being used to monitor these outcomes. A patient-reported outcome (PRO) is directly reported by patients and based on the patient's perception of the impact of a disease and its treatment on their health[6].

In clinical trials, PROMs can be used in conjunction with information on survival to determine the net clinical benefit of a new treatment strategy. In clinical practice, PROMs can be used to monitor patients' functioning during the disease trajectory[7]. Routine use of PROMs in clinical practice in oncology has shown to result in better communication between the patients and their physicians[8-10], and an increased frequency of discussions of health-related quality-of-life (HRQoL) issues[9] and other topics that are important to patients[11]. Furthermore, the incorporation of PROMs in routine clinical care in patients with a metastatic malignancy resulted in improved HRQoL and also led to significantly prolonged survival[12, 13]. An explanation was that routine PRO assessment might help in early detection of adverse treatment effects or tumor progression[12], and that treatment or referral to another health care professional (HCP) could be initiated if necessary.

Although implementation of routine assessment of PROs can possibly improve the quality of patient care and outcomes[8-13], it is not yet widely used in healthcare in glioma patients. Several challenges have been described, including the choice of PROM, the method of data collection (e.g. paper or electronic), and the frequency and timing of assessments[14]. Other possible barriers are the need to train physicians to interpret the results of PROMs and the need for human resources to administer the questionnaires[15] or discuss the results.

Routine assessment of PROMs in standard neuro-oncological care in Dutch hospitals, with the goal to improve psychosocial care, is one of the quality aspects of glioma care deemed important by the Dutch Neuro-Oncology Society (Landelijke Werkgroep Neuro-Oncologie, LWNO). Currently, this quality aspect is not yet met in most hospitals and the LWNO has initiated a study to assess how this can be achieved. A first step was to gain more insight in the preferred type of PRO(M)s, frequency and method of assessments, and the willingness to discuss the results of PROMs. In addition, practical barriers for implementation needed to be identified. Here we present

the perspectives of patients, their proxies and HCPs on the practicality of measuring PROs in clinical practice of glioma patients in Dutch hospitals.

Methods

Study design

In this cross-sectional study, we evaluated the view of patients, proxies and HCPs (including both physicians and nurses) using semi-structured interviews on the practicability of measuring PROs in clinical practice of glioma patients in four academic and four non-academic (teaching) hospitals in the Netherlands. Written consent was obtained from patients and proxies.

In addition, an inventory was sent to the local principal investigator (PI) of each hospital to assess aspects of their infrastructure which were deemed important to measure PROs in a clinical practice setting.

Study population and sample size

Per center, three adult patients with a histologically confirmed glioma visiting the neuro-oncology outpatient clinic, their proxies (if available and willing to participate), and HCPs on a regular basis involved in the treatment of glioma patients were recruited. Patients were selected by their treating physician based on purposive sampling (i.e. heterogeneous sample with respect to tumor type). Patients had to have sufficient understanding of the Dutch language to undergo the interview, as determined by the treating physician. Proxies were eligible if they were a spouse, family member or close friend of the patient, providing emotional and physical support. Lastly, we aimed to include a neuro-oncologist, neurosurgeon, radiation oncologist, medical oncologist, nurse specialist per center.

Data collection

Sociodemographic and disease-related characteristics of patients were obtained from the medical records or via the study-specific questionnaire. In addition, information about the HCPs and proxies was retrieved by means of an interview.

The interviews, based on directed content analysis, were pilot tested and conducted by two trained researchers without any relationship to the patient (GSGJO, medicine student and MCMP, PhD student). Interviews took place by means of a telephone call or at the patients' home, depending on their preference, and were digitally audio recorded with permission of the participant.

The following topics were discussed with patients and proxies (open questions): (1) willingness to discuss PROM results and reasons for not wanting to complete

PROMs; (2) preference for a specific HCP (physician/nurse) to discuss PROM results with and reasons for this specific choice; (3) preference for prespecified topics (that could be measured with PROMs) and the three most important topics; (4) preferred frequency of completion of PROMs; and (5) preference to complete PROMs on paper or digitally with reason. HCPs also had to answer questions 1-4, but in addition answered a question (6) on their ability to interpret PROM results and on the necessity to train HCPs to interpret the results obtained with different PROMs. Furthermore, data on the infrastructure (e.g. human resources, available systems, etc.) in each participating center was assessed by means of a questionnaire sent to the local PI.

Analysis

This study was designed to combine both qualitative and quantitative analysis. The interviews were independently and thematically analyzed per topic by two researchers (GSGJO and LD), according to the framework approach[16]. This approach consists of seven stages; (1) transcription of the data, (2) familiarization with the interview, (3) coding of the data, (4) development of a working analytical framework, (5) application of the analytical framework, (6) charting data into the framework matrix, and (7) interpretation of the data. Disagreements were resolved in consensus. If data saturation was not achieved after the intended number of patients, more patients would be approached. Due to the limited sample size and the qualitative nature of the data resulting from the interviews, findings were not reported as numbers or percentages, but merely as general descriptions.

Descriptive statistics have been used to report patient- and tumor-related characteristics, characteristics of proxies and HCPs and to quantify data, only where relevant, from the interviews. All quantitative analyses were performed with SPSS 23.0 for Windows.

Results

Participant and interview characteristics

Table 1 shows the characteristics of the participants; 24 patients, 16 partners and 35 HCPs. Interviews lasted a median of 12 minutes (range 4-323). One patient interview was not considered, as the recorder stopped recording after 35 seconds.

Question 1. Willingness to discuss PRO results

Overall, most participants were willing to discuss the results of PROMs during a consultation (Supplementary figure 1). The reason patients/proxies, and a minority of HCPs, did not want to discuss results was that they felt it had no added value. Some

HCPs, mostly physicians, indicated that they had insufficient time or considered this a task for the nurse specialist.

The most frequently mentioned reasons to discuss PROM results by all participants were to generate new or other information, focus on topics that are important for patients, and monitoring and solving problems (Supplementary Table 1 for all reasons). A minority of patients wanted to compare their level of performance with other brain tumor patients. About a quarter of HCPs also mentioned that PROMs are a tool to better structure the consultation.

Table 1. Sociodemographic and clinical characteristics of patients, proxies and health care professionals participating in a study on the practicality of routinely measuring patient-reported outcomes in clinical practice for glioma patients

	Patients n=24	**Proxies n=16**	**Health care professionals n=35**
Sex, n (%)			
Women	13 (54%)	7 (44%)	15 (43%)
Men	11 (46%)	9 (56%)	20 (75%)
Age (years), median (range)	53 (37-71)	50 (37-66)	47 (36-65)
Level of education, n (%)			
Low	10 (42%)	9 (56%)	
High	14 (58%)	7 (44%)	
Marital status, n (%)			
Single	1 (4%)	-	-
With partner	23 (96%)		
Time since diagnosis (months) median (range)	29 (1-227)	-	-
WHO[†] 2016 grade			
Diffuse astrocytoma, IDH[‡] mutant	3 (13%)		
Diffuse astrocytoma, NOS	1 (4%)		
Anaplastic astrocytoma, IDH mutant	2 (8%)		
Glioblastoma, IDH wildtype	8 (33%)		
Glioblastoma, IDH mutant	1 (4%)		
Glioblastoma, NOS	2 (8%)		
Oligodendroglioma, IDH mutant and 1p19q codeleted	3 (13%)		
Oligodendroglioma, NOS			
Missing	2 (8%)		
	2 (8%)		
Tumor location, n (%)			
Left hemisphere	12 (50%)	-	-
Right hemisphere	12 (50%)		
Tumor position, multiple options possible n (%)[a]			
Frontal	11 (46%)	-	-
Occipital	4 (17%)		
Temporal	10 (42%)		
Parietal	8 (33%)		

Table 1. Continued

	Patients n=24	Proxies n=16	Health care professionals n=35
Previous anti-tumor treatment, n (%)[a]			
Resection	19 (79%)	-	-
Re-resection	3 (13%)		
Chemotherapy	15 (63%)		
Radiotherapy	20 (83%)		
Current anti-tumor treatment, n (%)[a]			
Chemotherapy	10 (42%)	-	-
Radiotherapy	4 (17%)		
Karnofsky performance Status (KPS) score median (range)	80 (70-100)	-	-
Specialism, n (%)			
Neuro-oncologist	-	-	10 (29%)
Neurosurgeon			4 (11%)
Radiation oncologist			8 (23%)
Medical oncologist			4 (11%)
Nurse specialist			9 (26%)
Experience with care of gliomas (years), median (interquartile range)	-	-	10 (6-18)
Number of gliomas treated on an annual basis, median (interquartile range)	-	-	50 (35-100)
Duration interview in minutes (median (range))	14 (6-32)	9 (4-19)	12 (7-20)

†WHO: World Health Organization. ‡ IDH: isocitrate dehydrogenase. [a] Multiple options possible.

Question 2. Preference for HCPs to discuss results of PROMs with patients

Half of patients and one third of proxies indicated that they preferred to discuss the results with the physician, the main reason being that the physician has more medical knowledge. Others preferred discussion of the results with the nurse specialist, mainly because they are more accessible and more frequently in contact with patients. The remaining patients and proxies indicated that both the nurse specialist and physician should discuss the results, or had no preference (Figure 1).

All HCPs indicated that a nurse specialist should be involved in the discussion of the results. More specifically, half of the HCPs reported that the results should be discussed by the nurse specialist only (8/9 nurse specialist preferred this versus 10/26 physicians), while almost half of the HCPs indicated that the nurse specialist should discuss these results extensively, and subsequently inform the physician. The preference for the nurse specialist was substantiated by the consideration that the nurse specialist has more time and tranquility, is more approachable and has more experience with psychosocial topics (Supplementary Table 2 for all reasons).

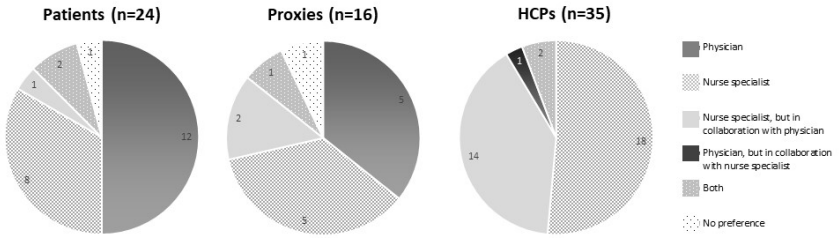

Figure 1. Preference of patients and proxies for a specific healthcare professional (HCP) to discuss the patient-reported outcome results with, as well as the preference of HCPs.

Question 3. Preference for topics of PROMs

Participants were presented a list of possible topics to be measured. In patients, cognitive complaints (75%), followed by functioning of daily life (67%) and HRQoL (50%) were most frequently reported as being important. Proxies reported HRQoL most frequently (63%), followed by cognitive complaints (56%) and functioning in daily life (50%). Both patients and proxies mentioned the topic mood less often (17% and 19%, respectively).

In contrast, HCPs reported functioning of daily life (77%) most frequently, followed by mood (including anxiety and depression; 60%) and symptoms and signs (57%). Furthermore, about a quarter of HCPs indicated that it would also be important to include questionnaires to evaluate the patients' experiences with care. Table 2 presents an overview of all preferences.

Question 4. Preferred frequency of completing PROMs

In line with the frequency of standard follow-up visits, the majority of low-grade glioma patients and HCPs indicated that a PROM should be completed twice a year (71% and 51%, respectively) and four times a year for high-grade glioma patients (35% in patients versus 43% in HCPs). Other preferences are displayed in Supplementary Figure 2.

Question 5. Preferences to complete PROMs

Overall, patients and proxies had a similar preference for the completion of PROMs on paper or digitally (Supplementary Figure 3). Reasons to prefer one mode over the other was that participants found that specific mode of administration more pleasant or convenient.

Moreover, all patients and proxies preferred to complete questionnaires at home, and liked to receive the questionnaires one week, or a few days, in advance.

Table 2. Preference for topics of patient-reported outcome measures

Topics	Glioma patients			Proxies (n=16)	Health care professionals (n=35)
	Total (n=24)	Low-grade glioma (n=7)	High-grade glioma (n=17)		
Health-related quality of Life (n)	12	4	8	10	19
Symptoms and signs (n)	10	2	8	7	20
Mood (n)	4	1	3	3	21
Cognitive complaints (n)	18	7	11	9	17
Functioning in daily life (n)	16	6	10	8	27

n = number

Question 6. Ability to interpret PRO results

Slightly more than half of HCPs had previously worked with PROMs, mostly in clinical practice or in the context of a clinical trial. About half of HCPs answered that they were able to interpret the results of PROMs, the main reason being that the results speak for itself, while about one third indicated that they need some explanation. Only 20% of HCPs (all physicians) said they could not interpret the results because of a lack of knowledge. Notably, only about half of HCPs who had ever worked with PROMs in clinical trials or even practice indicated they were able to interpret the results. The majority of HCPs indicated that training would be necessary to interpret the results uniformly.

Infrastructure

All eight participating centers indicated that it is possible to send questionnaires to patients on paper, for which staff is available, i.e. the nurse specialist (63%) or the secretary (38%). In almost all centers (88%) this person could also monitor when a completed questionnaire is returned and when a new questionnaire should be sent. In 75% of hospitals the completed questionnaires could be loaded into the hospital system as a document only.

Only 3/8 (38%) of the centers, one academic and two non-academic, had the possibility to send questionnaires digitally and 2/3 centers had an online system available to send the questionnaires by the nurse specialist, although it was not possible to calculate scores automatically or present results graphically.

Discussion

This study on the practicality of routinely measuring PROs in the care of glioma patients in Dutch hospitals focused on the perspective of patients, their proxies and clinicians. We found that patients and their proxies, as well as HCPs are positive regarding the discussion of PROM results during a consultation. Potential advantages were the generation of new or other information that is potentially useful in treatment decision-making, better focus on issues that are important to the patient, and better ability to monitor and solve patient-perceived problems. Possible barriers included the interpretation of the results, lack of suitable online tools, lack of time and the preference of patients and their proxies to discuss PROM results with their treating physician, whereas HCPs indicated that the results should preferably be addressed during consultations with nurses.

In other diseases, similar results with respect to implementation of PROMs in clinical practice have been found. Indeed, barriers for HCPs were lack of training and practice on the interpretation of PROM results, and lack of time[17]. Furthermore, patients' compliance with the completion of PROMs is an important barrier. For example, in a study on the administration of the Short Form Health Survey 36 (SF-36) questionnaire in the general population, patients with a lower educational status and those over 75 years old had more missing data and were inconsistent in their answers[18], limiting the value of routine PROM assessment. In glioma patients, the median age at diagnosis ranges from 43-63 years[19], with more than half of them being highly educated, so their ability to complete PROMs is likely to be relatively favorable. Nevertheless, in daily clinical care impaired health literacy and neurocognitive problems could possibly play a role in non-completion of PROMs. In those cases, proxies may be considered the source of information on the patients' functioning and well-being.

An important issue with the implementation of PROMs in routine care is not only to administer them, but also to act according to the obtained results and taking the necessary follow-up steps, e.g. an intervention or referral[17, 20]. A review on screening for cancer-related distress showed that psychosocial care was received in only 20-30% of patients that indicated problems, and that patients were most likely to receive psychosocial care if screening was directly linked with an intervention or referral[17]. The Dutch study on the organization of glioma care, initiated by the LWNO and which led to the initiation of the current study, found that more than half of the neurologists in the Netherlands do not screen for physical and neurocognitive impairments, HRQoL and/or psychosocial care[21]. Importantly, they found that psychosocial care in neuro-oncological hospitals is still is not widely available.

Regarding the topics that were considered most important to measure with PROMs, we found that functioning of daily life was considered important by all participants. Particularly instrumental activities of daily living (IADL) (e.g. activities such as

housekeeping or working) may be important for glioma patients, as these activities are sensitive to changes in neurocognitive functioning, which is characteristic of brain tumor patients[22]. An instrument to measure IADL in brain tumor patients is currently under development[23]. Moreover, neurocognitive complaints, symptoms and signs, and mood were also considered important. A multidimensional questionnaire addressing all relevant aspects seems preferable. Implementation of selected PROMs in glioma routine care would be the next step. We found that most patients and a third of proxies preferred to discuss PROM results with the physician, the main reason being that the physician has more medical knowledge. However, most HCPs found the nurse specialist more suitable, since they often have the role of case manager, more time for their consultation, and more experience with psychosocial topics. Therefore, we recommend that the nurse specialist discusses the results with the patients, and then provides the treating physician with a short summary of this discussion, focusing on issues that require action from the physician. Regarding the timing of PROMs, patients and proxies in our study indicated that they were willing to complete PROMs at standard follow-up (MRI) visits, two times a year for low-grade and four times for high-grade gliomas. This is both practical and valuable, as possible changes in functioning and well-being can be detected within this time period, which can also be linked to radiological and neurological outcomes.

Another barrier in the implementation of PROMs in routine practice are the anticipated difficulties interpreting PROM results. Indeed, the scoring systems of PROMs that are regularly used in glioma care may be perceived as complicated. Scores of scales/domains can in most cases not be directly interpreted from completed questionnaires, but need to be calculated first. Furthermore, in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 for example, a higher score may reflect better functioning but also more symptomatology, complicating interpretation[24-27]. To facilitate the knowledge of HCPs on assessment, interpretation and discussion of PROM results, we would recommend a repeated training by the (inter)national organizations (in person or via an e-learning, which is currently developed at the EORTC) for HCPs. Moreover, the introduction of an electronic data capture system would be very useful to facilitate PRO assessment in clinical practice, as such a system can calculate scale/domain scores and also visually display the results over time[28, 29]. To standardize psychosocial care, it would be desirable if one electronic system with graphic or calculating functions could be introduced in as much hospitals as possible. See also Table 3 for an overview of all recommendations.

As this study had a qualitative design, reported frequencies must be interpreted with caution. Given the relatively small number of patients included in the study, it was not possible to draw conclusions on possible differences in preferences of low- and high grade glioma patients. Patients and proxies were purposefully selected in order

Table 3. Recommendations assessment of patient-reported outcomes in Dutch neuro-oncological care

Question	Topic	Recommendations
1-2	Discussion of PRO results	We recommend that the nurse specialist discusses the results of the PROMs with the patients and the physician receives a short summary of this discussion, which can subsequently be used during their consultation.
3	Preference for topics	We recommend questionnaires about functioning in daily life and HRQoL.
4	Frequency of completing PROMs	We recommend to link PRO assessment to standard follow-up (MRI) visits of patients.
5	Preference to complete PROMs on paper or digitally	We recommend implementing an electronic data capture system in all hospitals to facilitate PRO assessment and interpretation. However, for those patients that are not willing to complete the questionnaires online, assessment on paper should be offered.
6	Ability to interpret PRO results	We recommend organizing a training (whether organized in person by the (inter)national working groups or via an e-learning) for HCPs in the interpretation and discussion of PROM results to standardize the neuro-oncological care.

to represent heterogeneity within this population, however the proportion of patient with different characteristics may be significantly different from the average glioma population. Another limitation is that selection bias may have occurred through the purposeful sampling and small sample size. Nevertheless, data saturation was reached with this population and conclusions would probably not have changed if we had recruited more participants. Patients who agreed to participate might be more interested in the completion of PROMs. Also, the number of patients and their reasons for non-participation were not systematically recorded, and not all specialist were willing to participate, resulting in the finding that not all hospitals represented all professionals backgrounds. However, we interviewed a heterogenous population including patients, proxies and HCPs, recruited from both general and academic hospitals throughout the Netherlands. Although the situation in the Netherlands may differ from other countries, for example with respect to the availability of a nurse specialist, the results highlight solutions that could possibly be considered to improve the care.

In conclusion, this study shows that routine assessment of PROMs is desirable by patients, proxies and HCP's in neuro-oncological care in Dutch hospitals. Overall, we recommend to routinely measure PROs in glioma patients using an electronic data capture system with a focus on functioning in daily life and symptoms, preferably assessed during standard follow-up moments and first discussed with the nurse specialist. A next step would be to implement routine monitoring of PROMs in glioma care and to evaluate its impact on the outcomes of patients as well as the perceived quality of care.

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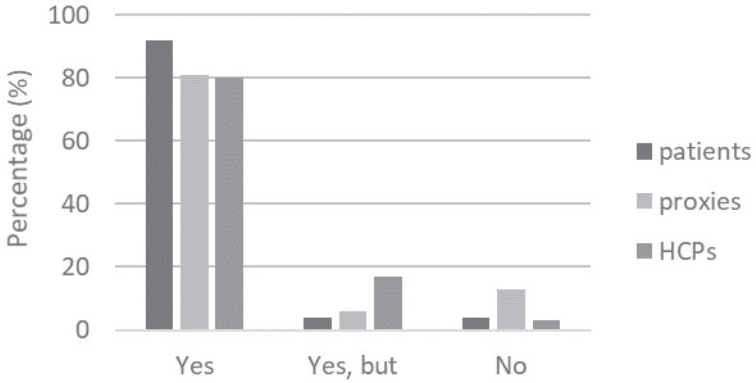
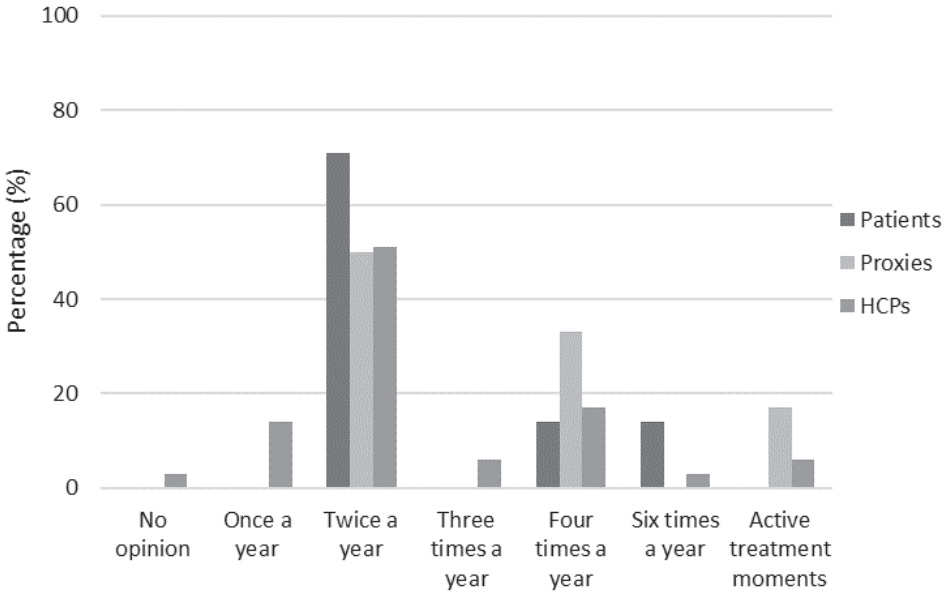
Supplemental material

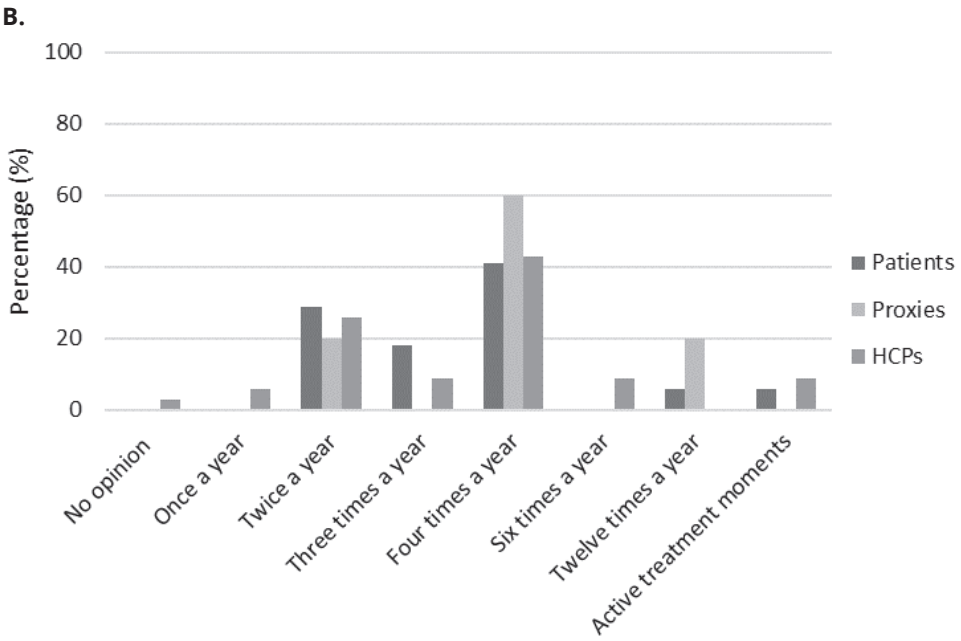


Supplementary Figure 1. Percentage of participants willing to discuss patient-reported outcome (PRO) results

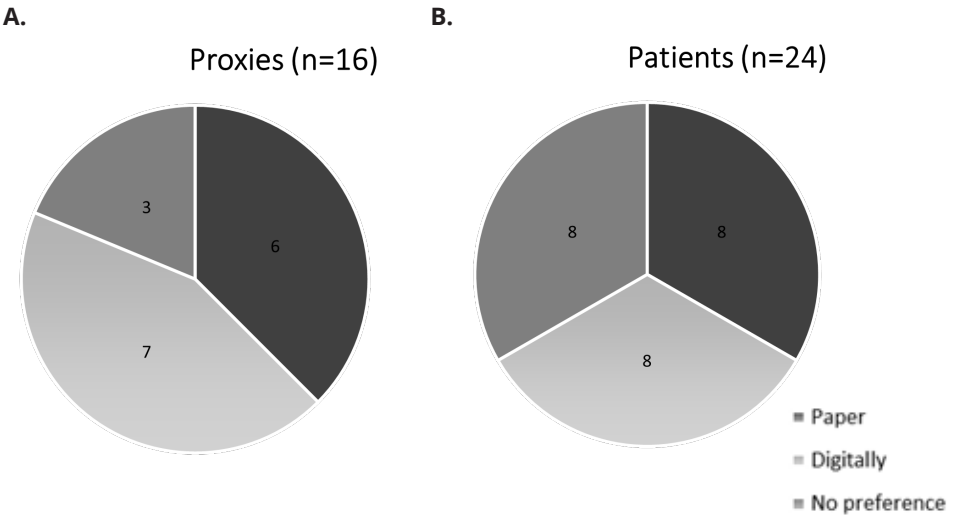
A.



Supplementary Figure 2A. Preferred frequency of completing PROMs, separately for low-grade glioma (A) and high-grade glioma (B) patients (see next page)



Supplementary Figure 2B.



Supplementary Figure 3. Preference to complete patient-reported outcomes (PROs) on paper or digitally, separately for patients (A) and proxies (B)

Supplementary Table 1. Reasons to discuss PRO results, separately for patients, their proxies and health care professionals

	Patients (n=24)	Proxies (n=16)	HCPs (n=35)
Generation of new or other information (n)	11	5	19
Focus on topics that are important for the patient (n)	2	4	17
To monitor and solve problems (n)	4	2	11
To improve the care of glioma patients (n)	2	0	6
Better communication between the patient and HCP (n)	1	1	0
Having someone to listen (n)	0	1	0
To better structure the consultation (n)	0	0	9

n = number

Supplementary Table 2. Reasons to discuss results with physician or nurse specialist, separately for patients, their proxies and health care professionals

	Patients (n=24)	Proxies (n=16)	HCPs (n=35)
Nurse specialist has more time and rest (n)	1	1	25
Nurse specialist is more accessible (n)	4	3	13
Nurse specialist has more experience with psychosocial topics (n)	1	2	12
Discuss results with the nurse specialist to relieve the physician (n)	1	0	5
Patient is the responsibility of the physician (n)	0	0	7
The nurse specialist has the role as case manager (n)	2	2	8
The physician has the role as case manager (n)	2	2	0
Physician has more (medical) knowledge (n)	4	4	0
More confidence in the physician (n)	2	0	0
Most frequent contact with the physician (n)	4	0	0
Most frequent contact with the nurse specialist (n)	4	2	0
More information for the physician (n)	3	0	0
Good contact with all HCPs (n)	1	1	0
Both have enough knowledge (n)	1	0	0

n = number

PART THREE

CHAPTER 6

Advance care planning (ACP) in glioblastoma patients: evaluation of a disease-specific ACP program and impact on outcomes

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Abstract

Background

The feasibility of implementing an advance care planning (ACP) program in daily clinical practice for glioblastoma patients is unknown. We aimed to evaluate a previously developed disease-specific ACP program, including the optimal timing of initiation and the impact of the program on several patient-, proxy- and care-related outcomes.

Methods

The content and design of the ACP program was evaluated, and outcomes including health-related quality of life, anxiety and depression, and satisfaction with care were measured every three months over a 15-month period.

Results

Eighteen patient-proxy dyads and two proxies participated in the program. The content and design of the ACP program was rated as sufficient. The preference for the optimal timing of initiation of the ACP program varied widely, however most of the participants preferred initiation shortly after chemoradiation. Over time, aspects of HRQoL remained stable in our patient population. Similarly, the ACP program did not decrease the levels of anxiety and depression in patients, and a large proportion of proxies reported anxiety and/or depression. The needed level of support for proxies was relatively low throughout the disease course, and the level of feelings of caregiver mastery was relatively high. Overall, patients were satisfied with the provided care over time, whereas proxies were less satisfied in some aspects.

Conclusion

The content and design of the developed disease-specific ACP program were rated as satisfactory. Whether the program has an actual impact on patient-, proxy- and care-related outcomes proxies remains to be investigated.

Introduction

The average incidence rate of glioblastoma, the most common and severe type of glioma, is approximately 3 per 100,000 persons per year[1,2]. With the introduction of multimodal treatment comprising surgery, radiotherapy and chemotherapy, the median survival of patients with glioblastoma increased but remains poor, i.e. approximately 15 months in a trial population[3].

During the disease course, many glioblastoma patients experience progressive neurological deficits such as seizures and motor deficits[4-6]. There may also be progression of cognitive dysfunction, which may subsequently interfere with the ability to make decisions about (future) care and treatment[7]. The poor median survival of glioblastoma patients in combination with the progressive neurocognitive decline warrants early involvement in treatment decision-making[8]. One way to involve patients in treatment decision-making is with advance care planning (ACP).

ACP is a process to involve patients and their proxies early in the disease trajectory in decision-making on future (palliative) care, also including end of life (EOL) care[9]. Currently, little is known about the effect of ACP on outcomes of glioblastoma patients, but it has been suggested that ACP could improve symptom control and enhance psychosocial support and EOL care planning[10]. Also, the quality of (EOL) care of patients could be improved. Previously, it has been shown that if glioma patients expressed their preferences for EOL care, these were often met[11]. Communicating their preferred place of death also resulted in more patients dying at that place[12], which was associated with dying with dignity[13]. Overall, these results suggest that ACP could potentially improve the quality of life and quality of care for glioblastoma patients.

Several ACP programs have been developed and implemented in various patient populations[9,14,15], and the effects are inconclusive. Positive effects that have been reported are empowerment, increased use of specialist palliative care and completion of advance directives, agreement between the preferred and delivered care, increased patient and family satisfaction with quality of EOL care, awareness of dying, and a reduction in stress, anxiety and depression in surviving relatives[9,14,16,17]. In contrast, other studies reported no impact of ACP on the level of health-related quality of life, patient satisfaction with care or shared decision-making, and that the delivered EOL care was not consistent with the patient's preferences[14,18].

Implementing an ACP program may be challenging. It was considered important that a program for glioblastoma should meet the demands of patients and their proxies with respect to the content of the program as well as the timing of implementation[19]. Previously, a disease-specific ACP program was developed specifically for glioblastoma patients, meaning that the content was customized for this patient population, e.g. with topics about anti-tumor and supportive treatment (e.g. corticosteroids and anti-

epileptic drugs), surrogate decision-making in case of incompetence, issues in the EOL phase (e.g. swallowing drowsiness), and caregiver burden. In addition, it was determined what the optimal timing of introduction of such a program would be. Even though the participants in that study[19] agreed on the program content, the optimal timing of introducing such a program was a matter of debate. Several patients and proxies indicated that early implementation of ACP is not preferred, however, it should also be considered that glioblastoma patients have a poor prognosis and might have a rapid decline in their cognitive functioning that could hamper decision-making later in the disease process. It was therefore suggested that the most optimal moment to offer the program was after the chemoradiation phase (approximately 3 months after the histopathological diagnosis), and that patients and proxies should be able to decide which topics are discussed.

The aim of the current study was to evaluate the previously developed ACP program in glioblastoma patients and their proxies[19], including re-evaluating the optimal timing of initiation, as well as the impact of the program on several patient-, proxy- and care-related outcomes such as health-related quality of life (HRQoL), feelings of anxiety and depression, caregiver needs and mastery, health resource utilization and satisfaction with care.

Methods

Study design and participants

This study comprised a longitudinal prospective feasibility study. Patients were eligible if they were (1) adults with a histologically confirmed glioblastoma, (2) visiting the outpatient clinic of the Haaglanden Medical Center, The Hague, a large tertiary hospital in the Netherlands, from October 2017 onwards, (3) able to understand the Dutch language, (4) considered competent to participate in an formal ACP program in a research setting as judged by the treating physician (there was no formal assessment of competence). In addition, proxies of patients that were recruited, were defined as a spouse, family member or close friend to the patient, providing most of the emotional and physical support to the patient.

Outcomes

Patients completed the cancer-specific European Organisation of Research and Treatment of Cancer (EORTC) quality of life C30 questionnaire (version 3.0) and the brain cancer-specific module, the QLQ-BN20, to assess their level of HRQoL[20-22]. Proxies

completed the Short-Form-36 to assess their level of HRQoL[23]. In addition, the Hospital Anxiety and Depression Scale (HADS) was administered to both patients and proxies to assess symptoms of anxiety and depression[24]. The Caregiver Mastery Scale[25] was administered to proxies to determine their level of mastery as informal caregivers, and the Caregiver Support and Needs Assessment Tool[26] was administered to evaluate in which areas of need the proxy required support.

To evaluate satisfaction with care, both patients and proxies completed a short-item list focusing on care in the outpatient clinic, based on items from the EORTC item library[27]. Health resource utilization of the patients was evaluated with a study-specific questionnaire. Other study-specific questionnaires were created to evaluate the content and structure of the ACP program and (changes in) wishes for treatment and EOL care over time. More detailed information on the used questionnaires can be found in Supplemental Files 1, and Supplemental Files 2-4 display the study-specific questionnaires.

Study procedures

By means of consecutive sampling, eligible patients and their proxies were invited for participation by the treating physician shortly after chemoradiation, but before adjuvant treatment, as this was considered the most optimal moment in the previous study[19] (details on the study design and patient population can be found elsewhere). If the patient and/or proxy agreed to participate, they received a study-specific folder with all topics that could be discussed within the ACP-program, which was developed in the previous study[19]. There were two scheduled ACP sessions, led by a trained facilitator (in this study the nurse specialist), which took place in the hospital. During the first session, the concept of ACP was introduced, and participants could indicate which topics they wanted to discuss in more depth. After the first session, participants were asked if they were interested in another ACP session, approximately four weeks later, in which additional questions and topics could be discussed. Patients were encouraged to complete an advance directive (AD) in their last ACP session, but this was not mandatory. During the follow-up period, patients were encouraged to contact the nurse specialist in case they had additional questions or if they wanted to inform the healthcare professionals that their wishes for treatment and EOL care had changed.

On the day of the first ACP session (i.e. baseline measurement), but prior to the actual discussion, participants were requested to complete several questionnaires (see 'outcomes'). Immediately after the ACP session(s), approximately four weeks after the baseline assessment, participants were requested to complete a questionnaire about the content and quality of the ACP program. At three months, and subsequently every three months with a maximum of 15 months follow-up, participants were also requested to complete several questionnaires related to their functioning and well-being, their perception of the quality of care received and health resource utilization

(see Figure 1 for an overview of the outcomes assessed at each time point). Approximately three months after the death of the patient, the proxy was contacted and asked to complete a questionnaire on the EOL care (these results will be reported separately). Lastly, the general practitioners (GPs) of the patients were contacted to evaluate if they were aware of the wishes of the patient and were able to act accordingly.

The study was approved by the medical ethical committee of the Haaglanden Medical Center, and all participants provided written informed consent before participation.

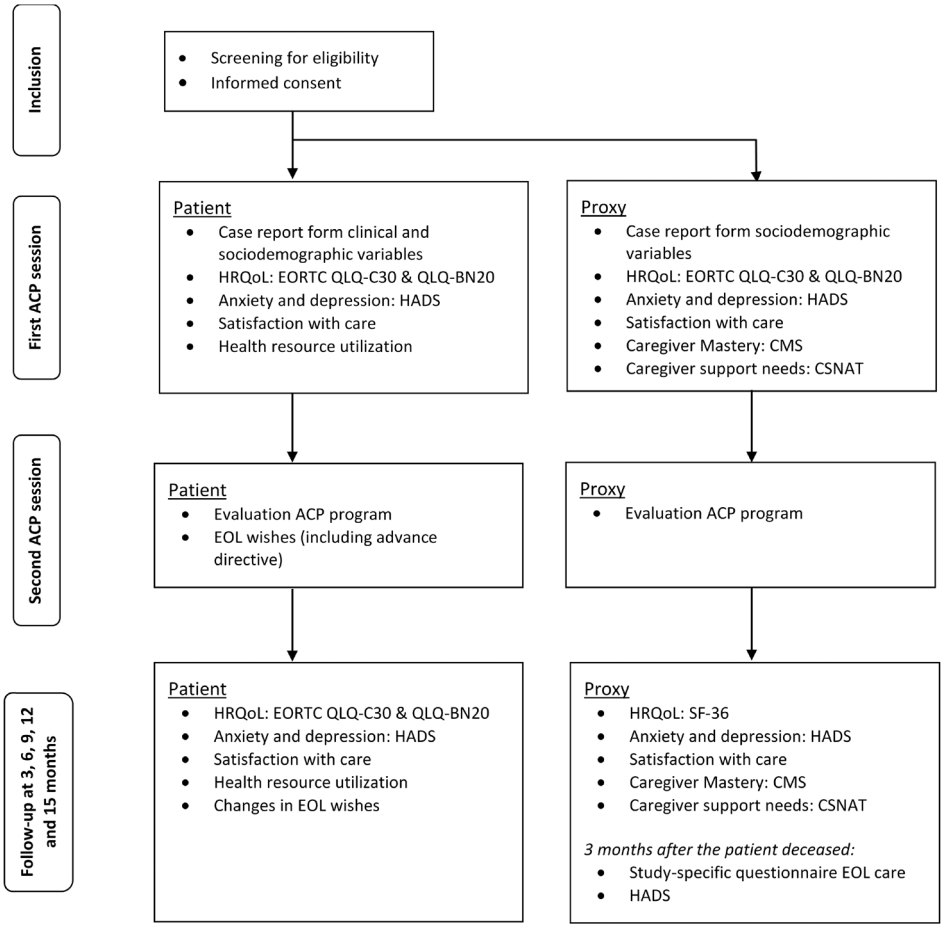

Figure 1. Overview of the assessments at each time point

Statistical analysis

Scores on the EORTC questionnaires, SF-36 and HADS were calculated according to their instruction manuals[23,28]. Due to the limited number of participants, descriptive statistics were used to describe the characteristics of the participants and the outcomes. For between and within group comparisons, students T-tests or Mann Whitney U tests were used, depending on the distribution of the tested variable. To analyze the data, IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY: IBM Corp) was used. A p-value <0.05 was considered to be statistically significant.

Results

Recruitment

A total of 31 eligible patient-proxy dyads were approached for participation between October 2017 and February 2018. Of these, 11 declined participation, four because this study was emotionally too burdensome, for two patient's their health status was too poor, two were not interested in participation, and three considered the topic of this study not relevant for their current situation. Patients who did not participate did not significantly differ from those who did participate in terms of sex (73% vs. 75% male, respectively, p=0.606), median age (65 vs. 56 years, p=0.212), median KPS score (90 vs. 80, p=0.528), and tumor type (95% vs. 91% glioblastoma IDH-wildtype, p=0.304).

Eighteen patient-proxy dyads participated in the ACP program, as well as two proxies without the patient. Therefore, aspects of the disease of a total of 20 patients were discussed. The majority of patients (75%) were male, diagnosed with glioblastoma IDH wildtype (95%), and with an unmethylated MGMT promotor (80%). The median age was 65 years (range: 45-77), with the majority of patients having a good performance status (KPS ≥70, 95%) and having no (65%) or mild (20%) cognitive symptoms. The median time since diagnosis was four months, and patients previously underwent a resection (70%) or biopsy (30%), and most patients received radiotherapy and chemotherapy (100% and 90%, respectively).

Most proxies were the partner of the patient (70%), and of female gender (75%), and they had a median age of 55 years (range:33-76). Median duration of their relationship was 36 years (range: 16-57), and most proxies (65%) were living together with the patient. See Table 1 for an overview of all baseline characteristics.

Evaluation ACP program

Patients

A total of 14/18 (78%) of the participating patients provided an evaluation of the ACP program, about one month after completion. The quality of the program was rated (on a 7-points Likert scale) as 'neither good nor poor' in 29%, and as 'somewhat good

Table 1. Sociodemographic and clinical characteristics of the participants

Baseline characteristics	Patients (n=20)	Proxies (n=20)
Age in years, median (range)	65 (45-77)	55 (33-77), *n=17*
Male sex, no. (%)	15 (75%)	5 (25%)
Educational level, no. (%)		
Low [0-4]	13 (65%)	11 (58%)
High [5-8]	6 (30%)	8 (42%)
Unknown	1 (5%)	1 (5%)
Religious, no. (%)		
Yes	8 (40%)	9 (45%)
No	9 (45%)	10 (50%)
Unknown	3 (15%)	1 (5%)
Religion important, no. (%)	n=8	n=9
Yes	5 (63%)	6 (67%)
No	2 (25%)	3 (33%)
Unknown	1 (13%	-
Tumor type, no. (%)		
Glioblastoma, IDH-wildtype	19 (95%)	-
Glioblastoma, NOS	1 (5%)	-
MGMT status, no. (%)		
Methylated	1 (5%)	-
Partial methylated	2 (10%)	-
Unmethylated	16 (80%)	-
Undetermined/missing	1 (5%)	-
KPS score, median (range)	80 (60-100)	-
≥70, no. (%)	19 (95%)	-
Cognitive status, no. (%)		
None	13 (65%)	-
Mild	4 (20%)	-
Moderate	3 (15%)	-
Severe	-	-
Time since diagnosis in months, median (range)	4 (4-8)	-
Disease status, no. (%)		
Active	2 (10%)	-
Stable	18 (90%)	-
Previous treatment, no. (%)		
Resection	14 (70%)	-
Biopsy	6 (30%)	-
Chemotherapy	20 (100%)	-
Radiotherapy	18 (90%)	-
Monoclonal antibodies	1 (5%)	-
Current treatment, no. (%)		
Chemotherapy	17 (85%)	-
Monoclonal antibodies	1 (5%)	-
No adjuvant treatment	1 (5%)	-
Relationship, no. (%)		
Partner	-	14 (70%)
Child	-	5 (25%)
Aunt	-	1 (5%)
Relationship In years, median (range)	-	36 (16-57)
Intensity contact, no. (%)		
Living together	-	13 (65%)
Daily	-	3 (15%)
Weekly	-	3 (15%)
Monthly	-	1 (5%)

to excellent' in 71%. Moreover, all patients felt that all important topics (related to the current situation, worries and fears, (supportive) treatment and preferred place of care and death[19]) were discussed, and did not identify missing topics. The acceptability of the topics, amount of provided information, number of ACP sessions, duration of the ACP session, and the functioning of the ACP facilitator were rated as acceptable to very acceptable in the large majority of cases (range: 85-100%; Figure 2A). Only one suggestion was made to improve the program, i.e. the use of a decision tree to visualize the care pathway.

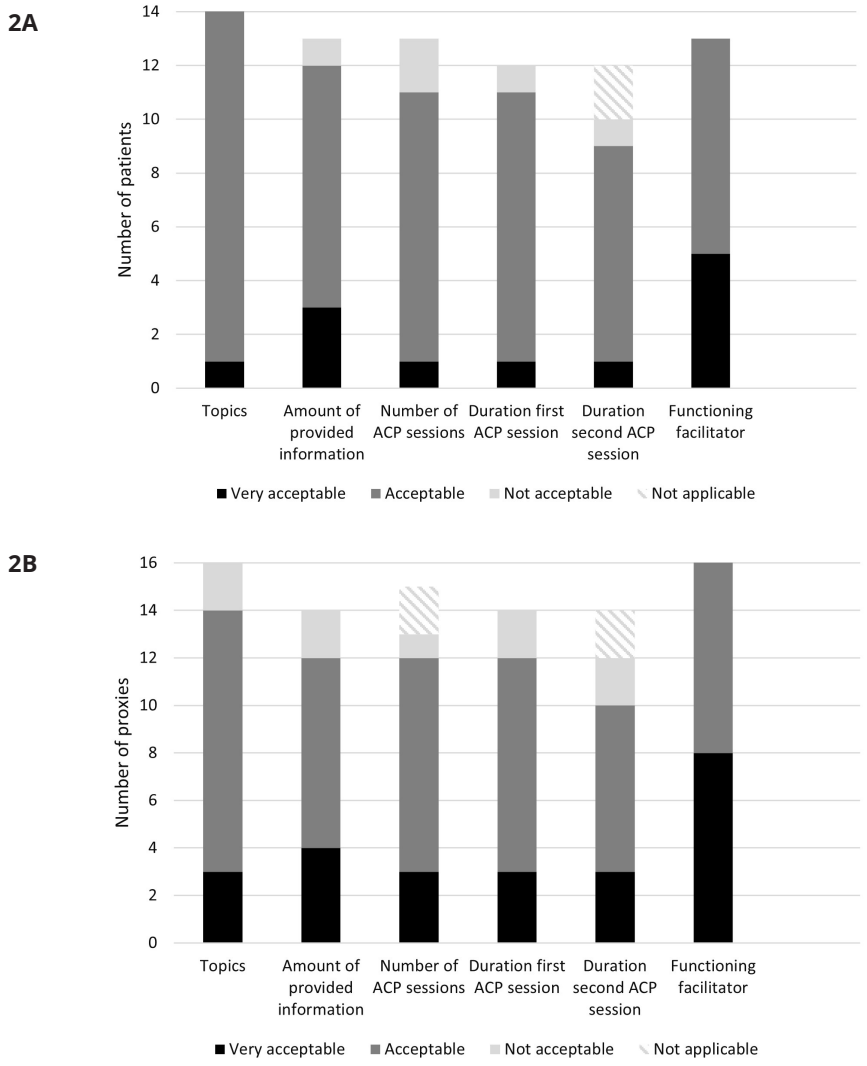

Figure 2. Acceptability of the ACP program according to patients (Figure 2A) and proxies (Figure 2B)

Responses with respect to the optimal timing of initiating the ACP program varied widely (Figure 3), with most patients preferring to introduce the program shortly after chemoradiation (about 16 weeks after the diagnosis; 5/14, 36%), during adjuvant chemotherapy (about 6 months after diagnosis; 3/14, 21%) or after adjuvant chemotherapy (about 9 months after diagnosis; 3/14, 21%).

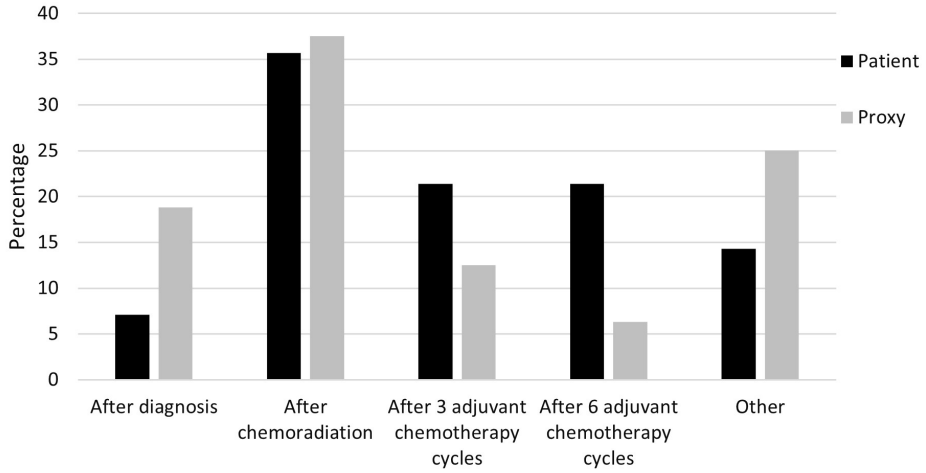

Figure 3. Preference of timing of initiation of the ACP program as rated by patients (n=14) and proxies (n=16)

Proxies

Seventeen out of 20 participating proxies (85%) provided an evaluation of the ACP program approximately one month after completion. Proxies rated the quality of the program as 'neither good nor poor' in 18% (3/17), and as 'somewhat good' to 'excellent' in 77% (13/17), with only one proxy (6%) rating the program as 'somewhat poor'. Thirteen out of sixteen (81%) of proxies indicated that all important topics were discussed, and the three proxies who indicated that not all topics were discussed did not provide information on missing topics. While the majority of proxies rated the acceptability of the topics, amount of provided information, number of ACP sessions, duration of the ACP session, and the functioning of the ACP facilitator as 'acceptable' or 'very acceptable' (range: 71-100%), there were some proxies rating some aspects (i.e. number and duration of ACP sessions) as 'not acceptable' (Figure 2B). Moreover, six patients suggested improvements for the ACP program, comprising separate sessions for patients and proxies, providing less information at once, asking participants which topics they want to discuss, and more focus on positive aspects of the disease (to maintain hope).

Similar to patients, the preference for the optimal timing of initiation of the ACP program varied widely (Figure 3). Three out of 16 proxies (19%) who provided information, preferred the time around diagnosis (shortly after surgery), 6/16 (38%) after chemoradiation (about 16 weeks after the diagnosis), 2/16 (13%) during adjuvant chemotherapy (about 6 months after diagnosis), 1/16 (6%) after adjuvant chemotherapy (about 9 months after diagnosis), and 4/16 (25%) proxies indicated that this should be flexible, and based on the wishes of the patient and proxy.

General practitioners

Eleven GPs (55%) completed the evaluation approximately 14 months after the patients/proxies started with the ACP program. Most (10/11, 91%) GPs indicated that all topics were addressed in the program. One GP reported that more information should be provided on the role of the GP during the disease trajectory. Eight GPs (73%) received the advance directive (AD) of the patients, and were aware of the content. In addition, 10/11 GPs indicated they (already) had intensive contact with the patient and proxy in which they discussed care preferences. Moreover, eight GPs indicated that it was possible to meet the wishes of the patients. Although most (64%) GPs were satisfied with the contact with the hospital, there were also some remarks. In general, the GPs felt that they were not sufficiently involved; they wished to be contacted more frequently and receive more information, with a clear transfer of information when the EOL phase starts.

Similar to patients and proxies, GPs were also not unanimous on the optimal timing of initiation of an ACP program, with 37% favoring around diagnosis, 18% immediately after chemoradiation, 9% after chemoradiation has finished, and 36% favoring an alternative time point. GPs felt that the timing should depend on the situation of the patient, but did indicate this had to be introduced as soon as possible.

Patient outcomes

Patient scores on the selected scales of the EORTC QLQ-C30 and QLQ-BN20 as well as the HADS for the baseline, 3-month and last assessment are presented in Table 2, and for all scales in Supplemental Table 1. In general, patients had significantly lower levels of functioning and more symptoms than the general population at baseline. Although the level of functioning increased between baseline and 3-months, these differences were not statistically significant. During the last assessment, the median level of physical functioning was significantly, but not to a clinically relevant extent[30], lower compared to baseline (73 vs. 80, p=0.008), while there were no significant differences for the other scales.

The median scores on the HADS anxiety and depression subscales did not differ significantly between the baseline, 3-month and last assessment (Table 2). Whereas

20% and 30% of patients reported possible anxiety and depressive disorder at baseline (score ≥8 points), respectively, this percentage was similar at the 3-month assessment (17% vs. 31%), but increased significantly to 46% and 54% at the last assessment (p=0.026 and p=0.039, respectively).

Proxy outcomes

Proxy scores on the SF-36 and HADS questionnaires at baseline, 3-months and during the last assessment are displayed in Table 3. Compared to the general population, proxies had significantly lower scores on the SF36 PCS (mean: 83 vs. 50, respectively) and MCS (mean: 69 vs. 44, respectively) at baseline. Also, proxies scored significantly lower on social functioning, mental health and vitality. At the 3-month assessment, none of the subscales or component scale scores of the SF-36 were significantly different compared to the baseline scores. At the last assessment, proxies did report significantly better physical functioning (mean: 92 vs. 84) and less bodily pain (mean: 83 vs. 77) than the baseline assessment. The median scores on the HADS anxiety and depression subscales did not differ significantly between the baseline, 3-month and last assessment. The percentage of proxies reporting possible anxiety and depressive disorder (≥8 points) changed from 56% and 29% at baseline, respectively, to 36% and 55% after three months and 39% and 39% at the last assessment.

The median CSNAT total score was similar over time, with a score of 5 out of 42 points at baseline and 3 points at both the 3-month and last assessment, indicating that the need of support was relatively low (Supplemental Table 2). In general, the need for support was higher at baseline (38% of proxies in need of at least a bit support on ≥1 item) compared to the 3-month and last assessment (28% and 26%, respectively; Supplemental Figure 1). Caregiver mastery as measured with the CMS was also similar over time, with a median score of 25 out of 35 (range 7-32) at baseline, and 27 (range: 9-33) and 26.5 (range: 9-35) at the 3-month and last assessment, with higher scores indicating less feelings of mastery (Supplemental Table 3).

Satisfaction with care

At baseline, patients rated the different aspects of care overall as 'good' to 'excellent' (mean 90%, range: 63-100%), with similar percentages at the 3-month (mean 92%, range: 70-100%) and last assessment (mean 92%, range: 82-100%; Supplemental Figures 2A-C). Only 'exchange of information between healthcare professionals' and 'provision of information about supporting organizations' were rated 'poor' at baseline by 10 and 15% of patients respectively, and 'exchange of information between healthcare professionals' was also rated as 'poor' after 3-months by 10%. The overall rating of the care received in the hospital was rated as 'good' to 'excellent' by 94% of patients at baseline, and 100% of patients at the 3-month and last follow-up (p=0.130 and p=0.274, respectively).

Table 2. Patient scores on the selected EORTC QLQ-C30 and QLQ-BN20 scales and HADS at baseline, 3 months and during their last assessment

	Baseline	Month 3	Last assessment	General population[29]
EORTC QLQ-C30				
Global health status				
Median (range)	67 (0-92)	63 (17-92)	58 (25-92)	
Mean (SD)	62 (27)	60 (23)	55 (22)	78 (17)*
No. of patients	18	14	15	
Physical functioning				
Median (range)	80 (13-100)	87 (20-100)	73 (8-100)*	
Mean (SD)	74 (26)	72 (28)	62 (32)	90 (15)*
No. of patients	18	13	15	
Role functioning				
Median (range)	67 (0-100)	50 (0-100)	83 (0-100)	
Mean (SD)	58 (35)	53 (35)	63 (38)	90 (15)**
No. of patients	18	13	13	
Emotional functioning				
Median (range)	71 (25-100)	88 (33-100)	67 (0-100)	
Mean (SD)	71 (23)	78 (20)	68 (28)	94 (16)**
No. of patients	18	14	15	
Cognitive functioning				
Median (range)	67 (0-100)	75 (0-100)	67 (0-100)	
Mean (SD)	66 (31)	69 (30)	67 (27)	90 (15)**
No. of patients	17	14	15	
Social functioning				
Median (range)	67 (0-100)	67 (0-100)	100 (0-100)	
Mean (SD)	68 (28)	63 (35)	73 (36)	90 (15)**
No. of patients	18	14	15	
EORTC QLQ-BN20				
Future uncertainty				
Median (range)	33 (8-92)	38 (0-100)	33 (8-100)	
Mean (SD)	39 (25)	43 (28)	42 (26)	N/A
No. of patients	18	14	14	
Communication deficit				
Median (range)	14 (0-100)	22 (0-100)	22 (0-100)	
Mean (SD)	29 (34)	35 (38)	36 (38)	N/A
No. of patients	18	14	15	
HADS				
HADS-anxiety				
Median (range)	4 (0-21)	4 (0-11)	6 (0-12)	
Mean (SD)	5 (5)	4 (3)	6 (4)	
No. of patients	15	12	13	
No. (%) score ≥8	3 (20%)	2 (17%)	6 (46%)	
HADS-depression				
Median (range)	3 (0-21)	4 (0-19)	9 (0-18)	
Mean (SD)	5 (6)	6 (6)	8 (6)	
No. of patients	17	13	13	
No. (%) score ≥8	5 (30%)	4 (31%)	7 (54%)	

*p-value <0.05 compared to baseline
**p-value <0.01 compared to baseline

Table 3. Proxy scores on the SF-36 subscales and summary scores and HADS at baseline, 3 months and during their last assessment

	Baseline	Month 3	Last assessment	General population[31]
SF-36				
Physical component score				
Median (range)	50 (31-65)	49 (19-60)	55 (36-61)	
Mean (SD)	50 (10)	47 (12)	53 (7)	83 (21)**[32]
No. of proxies	18	11	12	
Mental component score				
Median (range)	45 (17-62)	47 (16-62)	52 (16-61)	
Mean (SD)	44 (12)	47 (12)	44 (16)	69 (18)**[32]
No. of proxies	18	11	12	
Physical functioning				
Median (range)	95 (40-100)	90 (5-100)	95 (70-100)	
Mean (SD)	84 (21)	82 (26)	92 (10)*	85 (23)
No. of proxies	19	13	14	
Physical role functioning				
Median (range)	100 (0-100)	100 (0-100)	100 (0-100)	
Mean (SD)	75 (40)	66 (48)	77 (42)	80 (35)
No. of proxies	118	11	12	
Bodily pain				
Median (range)	74 (31-100)	62 (21-100)	92 (41-100)	
Mean (SD)	77 (25)	71 (26)	83 (22)*	81 (24)
No. of proxies	19	13	14	
Social functioning				
Median (range)	75 (25-100)	88 (13-100)	100 (25-100)	
Mean (SD)	72 (21)	67 (33)	81 (31)	85 (22)*
No. of proxies	19	13	14	
Mental health				
Median (range)	68 (8-96)	64 (4-100)	82 (4-96)	
Mean (SD)	65 (21)	61 (28)	66 (29)	76 (18)*
No. of proxies	19	13	14	
Emotional role functioning				
Median (range)	100 (0-100)	100 (33-100)	100 (0-100)	
Mean (SD)	70 (41)	81 (26)	72 (36)	83 (33)
No. of proxies	18	12	13	
Vitality				
Median (range)	70 (5-80)	55 (5-85)	66 (5-95)	
Mean (SD)	55 (27)	53 (26)	59 (27)	69 (19)*
No. of proxies	19	13	14	
General health perceptions				
Median (range)	67 (30-92)	67 (30-92)	72 (25-97)	
Mean (SD)	64 (18)	62 (20)	66 (23)	71 (21)
No. of proxies	19	13	14	

Table 3. Continued

	Baseline	Month 3	Last assessment	General population[31]
HADS				
HADS-anxiety				
Median (range)	9 (2-19)	5 (3-18)	6 (0-18)	
Mean (SD)	9 (5)	8 (6)	8 (6)	
No. of proxies	18	11	13	
No. (%) score ≥8	10 (56%)	4 (36%)	5 (38%)	
HADS-depression				
Median (range)	4 (0-20)	8 (0-202)	4 (0-20)	
Mean (SD)	6 (5)	8 (6)	7 (6)	
No. of proxies	17	11	13	
No. (%) score ≥8	5 (29%)	6 (54%)	5 (38%)	

*p-value <0.05 compared to baseline
**p-value <0.01 compared to baseline

Proxies were in some respects less satisfied with the provided care than patients, with 78% (range: 40-100%) still rating the care as 'good' to 'excellent' at baseline, and 87% at both the 3-month and last assessment (Supplementary Figures 3A-C). Particularly at baseline, 7/16 items were rated as poor by 5-20% of proxies, with 'the information provided on the overall supportive services available' rated as worst. This was the only item that was rated as 'poor' by 8% of proxies at the 3-month and last assessment. The overall rating of the care received in the hospital was rated as 'good' to 'excellent' by 90% of proxies at baseline, and 92% and 100% of patients at the 3-month and last follow-up, respectively (p=0.130 and p=0.02, respectively).

Health resource utilization

All patients had at least basic health insurance, with the majority (15/18, 83%) having additional insurances. Overall, health care usage was higher in the three months before baseline compared to the three months before the last assessment. The majority of patients had contact with the general practitioner (10/17, 59%), specialist in the hospital (16/17, 94%; mainly the neurologist) or other health care professionals (7/18, 39%; occupational therapist, physical therapist, psychologist, speech therapist, or massage therapist) in the three months before the baseline assessment. These percentages were 71% (10/14), 60% (9/15), and 20% (3/15) in the three months for the last assessment, respectively. None of the patients was treated in an inpatient clinic for medical or psychological problems in the three months before baseline, while one patient (1/14, 7%) was admitted to a rehabilitation center. In the three months before the baseline assessment, 41% (7/17) patients visited the emergency department for various reasons, and 50% (9/18) of patients was admitted to a hospital, while these

percentages were 13% and 13% in the three months before the last assessment. Lastly, the majority (14/18, 78%) of patients used medication (corticosteroids, anti-epileptic drugs and/or chemotherapy) in the three months before baseline, while this was 80% (13/15) at the last assessment.

Discussion

In this study we evaluated the previously developed disease-specific ACP program in glioblastoma patients and their proxies, including the optimal timing of initiation and the impact of the program on several patient-, proxy- and care-related outcomes. 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', and the overall quality was rated as 'somewhat good' to 'excellent' by most participants. These results suggest that the content and design of the currently available ACP program is sufficient. Some participants made suggestions for improvements, such as separate sessions for patients and proxies, providing less information at once, which could be considered on an individual basis, depending on the available time and resources. One of the reasons that participants in our study may have appreciated the program is that their treating nurse specialists were the facilitators, as previous research has shown that most patients prefer to have ACP discussions with their primary care physicians instead of surgeons or medical oncologists, because of trust and familiarity[33]. A similar relationship is expected between the patient and nurse specialist. Aspects that are important to include in ACP conservations are cultural aspects, taking sufficient time for the ACP conversations, and guiding patients in documenting their wishes. Still, about one third of the eligible patients did not want to participate for various reasons, of which being emotionally overwhelmed was the most common reason to decline[33]. A systematic review on experiences of patients with life-threatening or life-limiting diseases with ACP reported that, although patients also experienced benefits, ACP can be accompanied by unpleasant feelings[34]. The most important negative emotion was being confronted with having a life-limiting disease. It was suggested that the emotional burden could be lessened by introducing the program in group sessions[34]. In our ACP program, we aimed to reduce the emotional burden for patients and proxies by having them decide which topics they want to discuss. Even if not addressed, by presenting topics that could become an issue in the future (e.g. palliative sedation), we tried to trigger patients to at least think about these topics. A major limitation is that we did not record which topics were eventually discussed by the participants during the ACP sessions.

Similar to the results from the developmental phase[19], the preference for the optimal

timing of initiation of the ACP program varied widely. Although about one third of the participants in our study indicated that the program should be initiated shortly after chemoradiation, a large proportion suggested that the program should be initiated later in the disease trajectory. In studies in other populations, patients indicated that the optimal timing for the initiation of ACP was as early as possible[33,34], as they found it desirable to receive all relevant information as soon as possible and that it is better to deal with these issues in reasonable health. Early initiation of ACP is also considered important for glioblastoma patients, as they have an incurable disease and may experience a rapid decline in their cognitive functioning, hampering decision-making[7]. Neverthless, an important barrier for participation in such a program may be prognostic awareness, as about half of brain tumors patients is not fully aware of their poor prognosis[5]. The GPs participating in our study confirmed that it is important to offer ACP as soon as possible. Despite the variation in preference of optimal timing of initiation of the ACP program, we suggest to offer the program shortly after the chemoradiation before patients are cognitively too impaired, and mention the availability of the program in later disease stages (i.e. after 3 and 6 adjuvant chemotherapy cycles) to patients who declined before. Early initiation of such a program also allows that topics can be discussed at different moments in the disease course.

As also previously found, patients in our study had significantly lower levels of functioning and more symptoms compared to the general population[35,36]. Over time, aspects of HRQoL remained stable in our patient population. In the literature, the impact of ACP on HRQoL aspects was found to be contradictory. One large international RCT in 1117 patients with advanced cancer also did not find any impact of ACP on the level of HRQoL[14], while other studies found that the level of HRQoL was improved by introducing an ACP program[16,37]. Although glioblastoma patients typically experience a deterioration in HRQoL during the disease course[38-40], we cannot determine whether the ACP program helped to prevent this deterioration. Similarly, contrary to our expectations[16], the ACP program did not decrease the levels of anxiety and depression in patients over time. Instead, the number of patients with a possible anxiety or depression disorder was larger during the last assessment compared to baseline, which can be related to the progressive nature of the disease. The non-randomized study design, the possible selection of patients, and the small number of recruited patients and drop-out over time hampers to draw meaningful conclusions, warranting further investigation of the effectiveness of an ACP program on patient and proxy outcomes. It could also be argued that the currently used outcomes are not the most suitable for evaluating the impact of an ACP program, as these are influenced by many other aspects such as anti-tumor treatment, cognitive deterioration and societal and environmental factors. Currently, there is no consensus on the optimal outcome measure to evaluate the impact of an ACP program, and it is hypothesized that the

benefits of ACP are mainly related to the relational domain[14]. Perhaps mastery is a more suitable outcome, reflecting the belief that one is able to influence or control life events and that one is competent or effective in managing those events in order to produce desired outcomes[25]. Besides patient-related outcomes, outcomes related to the provided care and quality of care should also considered important, such as health care utilization and the use of anti-tumor treatment in the EOL stage.

Another outcome that was evaluated in this study is satisfaction with care. Overall, patients were satisfied with the provided care over time, whereas proxies were less satisfied. Particularly the exchange of information between healthcare professionals and the provision of information on support services were rated as poor. Provision of information could be enhanced by appointing a dedicated case manager or primary nurse, who could regularly ask patients and proxies about which information is needed[41] and who may facilitate the communication between different healthcare professionals in different settings (e.g. hospital and GP practice). Nevertheless, it should be recognized that in the international RCT described by Korfage et al.[14], but also in other studies[17], ACP did not have an impact on the perceived satisfaction with care. There is evidence though, that patients who participated in ACP conversations were more likely to receive palliative care and were more likely to have their preferences documented[14]. This was also observed in our study, in which most patients did document their wishes, which were also communicated to the GPs. The GPs indicated that these wishes could be met in 72%. It is unknown, however, whether this high rate of documented wishes is due to the ACP program, or due to the fact that this is a highly motivated population. Nevertheless, a previous study in glioblastoma patients has shown that patients who expressed their wishes more often died with dignity[13]. These findings suggest that some aspects of care can be improved with ACP.

Not only glioblastoma patients are affected by the disease and its treatment, but also their proxies. Caregivers are challenged to solve problems and make decisions when care changes, and not all of them are prepared for this[42]. We found that proxies 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. Over time, some aspects of HRQoL improved for proxies, such as better physical functioning and less bodily pain, suggesting that proxies became better in coping with the situation. We found that the needed level of support was relatively low throughout the disease course, and the level of feelings of caregiver mastery were relatively high. In general, the caregiver burden can be decreased by providing information and concrete advice[42,43], offering guidance[43], improving the communication between patients, proxies and their healthcare professionals[42], and by offering psychosocial support[42]. Several interventions are available to improve the knowledge of patients and caregivers[44], improve the caregivers'

level of social support, e.g. by offering support services[45], or establish caregiver mastery through a psychological intervention[46]. Although we did not find a change in outcomes for proxies over time in this non-randomized prospective study, it is premature to conclude that ACP does not have an impact at all. A previous controlled study in older people did find that relatives who received ACP had less stress, anxiety and depression compared to those that had not[16]. This underlines that a controlled study is needed to draw definite conclusions on the impact of ACP on the well-being of proxies.

In conclusion, the developed disease-specific ACP program is rated as acceptable by patients and proxies, suggesting that its current format is sufficient. Although not designed to evaluate the effectiveness of an ACP program on patient and proxy outcomes, the preliminary results of this feasibility study did not show an impact. To draw definite conclusions on the effect of ACP on outcomes of glioblastoma patients and their proxies, an international follow-study is needed, allowing to investigate cultural influences. Important aspects to consider in such a study are the most optimal design, the primary endpoint and the timing of introduction of an ACP program.

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Supplemental Table 1. Patient scores on the all EORTC QLQ-C30 and QLQ-BN20 scales at baseline, 3 months and during their last assessment

	Baseline	Month 3	Last assessment	General population[29]
EORTC QLQ-C30				
Global health status				
Median (range)	67 (0-92)	63 (17-92)	58 (25-92)	
Mean (SD)	62 (27)	60 (23)	55 (22)	78 (17)*
No. of patients	18	14	15	
Physical functioning				
Median (range)	80 (13-100)	87 (20-100)	73 (8-100)*	
Mean (SD)	74 (26)	72 (28)	62 (32)	90 (15)*
No. of patients	18	13	15	
Role functioning				
Median (range)	67 (0-100)	50 (0-100)	83 (0-100)	
Mean (SD)	58 (35)	53 (35)	63 (38)	90 (15)**
No. of patients	18	13	13	
Emotional functioning				
Median (range)	71 (25-100)	88 (33-100)	67 (0-100)	
Mean (SD)	71 (23)	78 (20)	68 (28)	94 (16)**
No. of patients	18	14	15	
Cognitive functioning				
Median (range)	67 (0-100)	75 (0-100)	67 (0-100)	
Mean (SD)	66 (31)	69 (30)	67 (27)	90 (15)**
No. of patients	17	14	15	
Social functioning				
Median (range)	67 (0-100)	67 (0-100)	100 (0-100)	
Mean (SD)	68 (28)	63 (35)	73 (36)	90 (15)**
No. of patients	18	14	15	
Fatigue				
Median (range)	39 (0-100)	50 (22.2-100)	33 (0-100)	
Mean (SD)	48 (29)	52 (26)	43 (31)	17 (20)**
No. of patients	18	14	15	
Nausea and vomiting				
Median (range)	0 (0-33.3)	0 (0-33)	0 (0-100)	
Mean (SD)	8 (12)	6 (11)	20 (32)	2.7 (10)
No. of patients	18	14	15	
Pain				
Median (range)	16.7 (0-67)	0 (0-50)	0 (0-67)	
Mean (SD)	19 (22)	10 (17)	12 (19)	15 (22)
No. of patients	18	14	15	
Dyspnea				
Median (range)	0 (0-67)	0 (0-33)	0 (0-67)	
Mean (SD)	9 (19)	13 (17)	16 (25)	7.1 (17)
No. of patients	18	13	15	
Insomnia				
Median (range)	33 (0-100)	0 (0-100)	33.3 (0-100)	
Mean (SD)	31 (33)	19 (31)	27 (31)	14 (23)*
No. of patients	18	14	15	
Appetite loss				
Median (range)	0 (0-67)	0 (0-100)	0 (0-67)	
Mean (SD)	19 (29)	17 (28)	20 (25)	3.3 (12)*
No. of patients	17	14	15	
Constipation				
Median (range)	0 (0-100)	16.7 (0-67)	33.3 (0-67)	
Mean (SD)	20 (32)	21 (25)	22 (24)	4.8 (14)
No. of patients	18	14	15	

Supplemental Table 1. Continued

	Baseline	Month 3	Last assessment	General population[29]
Diarrhea				
Median (range)	0 (0-67)	0 (0-33.3)	0 (0-33)	
Mean (SD)	9 (22)	5 (12)	7 (14)	3.9 (14)
No. of patients	18	14	14	
Financial difficulties				
Median (range)	0 (0-100)	0 (0-100)	0 (0-100)	
Mean (SD)	19 (31)	24 (33)	20 (30)	3.1 (13)*
No. of patients	18	14	15	
EORTC QLQ-BN20				
Future uncertainty				
Median (range)	33 (8-92)	38 (0-100)	33 (8-100)	
Mean (SD)	39 (25)	43 (28)	42 (26)	N/A
No. of patients	18	14	14	
Visual deficits				
Median (range)	6 (0-100)	22 (0-100)	28 (0-100)	
Mean (SD)	24 (31)	25 (28)	31 (30)	N/A
No. of patients	18	14	14	
Motor dysfunction				
Median (range)	17 (0-78)	11.1 (0-83)	22 (0-67)	
Mean (SD)	23 (24)	25 (29)	21 (20)	N/A
No. of patients	18	14	15	
Communication deficit				
Median (range)	14 (0-100)	22 (0-100)	22 (0-100)	
Mean (SD)	29 (34)	35 (38)	36 (38)	N/A
No. of patients	18	14	15	
Headache				
Median (range)	0 (0-33)	0 (0-33)	0 (0-100)	
Mean (SD)	6 (13)	10 (16)	16 (28)	N/A
No. of patients	18	14	15	
Seizures				
Median (range)	0 (0)	0 (0-33)	0 (0-33)	
Mean (SD)	0 (0)	2 (9)	2 (9)	N/A
No. of patients	18	14	15	
Drowsiness				
Median (range)	0 (0-100)	33.3 (0-100)	33.3 (0-100)	
Mean (SD)	28 (28)	28 (33)	29 (29)	N/A
No. of patients	18	13	14	
Hair loss				
Median (range)	0 (0-100)	0 (0-100)	0 (0-100)	
Mean (SD)	25 (36)	19 (31)	13 (30)	N/A
No. of patients	17	14	15	
Itchy skin				
Median (range)	0 (0-100)	0 (0-67)	0 (0-67)	
Mean (SD)	15 (31)	14 (22)	13 (21)	N/A
No. of patients	18	14	15	
Weakness of legs				
Median (range)	17 (0-100)	0 (0-67)	0 (0-33)	
Mean (SD)	31 (37)	18 (26)	11 (16)	N/A
No. of patients	18	13	15	
Bladder control				
Median (range)	0 (0-100)	0 (0-66.7)	0 (0-100)	
Mean (SD)	19 (31)	14 (22)	21 (31)	N/A
No. of patients	18	13	14	

*p-value <0.05 compared to baseline
**p-value <0.01 compared to baseline

Supplemental Table 2. Scores on the items of the Carer Support Needs Assessment Tool (CSNAT) at baseline and the 3-month and last assessment

	Baseline	Month 3	Last assessment
1) Understanding your relative's illness			
Median (range)	0 (0-3)	0 (0-3)	0.5 (0-3)
Mean (SD)	0.7 (0.9)	0.5 (0.9)	0.6 (0.8)
No. of proxies	18	13	14
2) Having time to yourself in the day			
Median (range)	0 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.7 (1)	0.3 (0.5)	0.2 (0.4)
No. of proxies	17	12	13
3) Managing your relative's symptoms			
Median (range)	1 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.9 (1)	0.3 (0.5)	0.3 (0.4)
No. of proxies	18	12	13
4) Your financial, legal or work issues			
Median (range)	0 (0-3)	0 (0-2)	0 (0-2)
Mean (SD)	0.7 (1)	0.5 (0.8)	0.5 (0.8)
No. of proxies	18	13	13
5) Providing personal care for your relative			
Median (range)	0 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.4 (0.9)	0.3 (0.5)	0.2 (0.4)
No. of proxies	16	12	12
6) Dealing with your feelings and worries			
Median (range)	1 (0-3)	0 (0-1)	0 (0-2)
Mean (SD)	0.8 (1)	0.5 (0.5)	0.6 (0.8)
No. of proxies	17	11	13
7) Knowing who to contact if you are concerned about your relative			
Median (range)	1 (0-3)	0.5 (0-2)	0 (0-2)
Mean (SD)	1.1 (1.1)	0.8 (0.9)	0.4 (0.9)
No. of proxies	18	12	14
8) Looking after your own health (physical problems)			
Median (range)	0 (0-2)	0 (0-0)	0 (0-1)
Mean (SD)	0.3 (0.7)	0 (0)	0.2 (0.4)
No. of patients	16	10	13
9) Equipment to help take care for your relative			
Median (range)	0 (0-2)	0 (0-1)	0 (0-1)
Mean (SD)	0.6 (0.7)	0.3 (0.5)	0.2 (0.4)
No. of proxies	16	12	13
10) Your beliefs or spiritual concerns			
Median (range)	0 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.3 (0.8)	0.1 (0.3)	0.1 (0.4)
No. of proxies	18	12	14
11) Talking with your relative about his or her illness			
Median (range)	0 (0-3)	0 (0-2)	1 (0-2)
Mean (SD)	0.6 (0.9)	0.4 (0.7)	0.7 (0.8)
No. of proxies	18	12	13
12) Practical help in the home			
Median (range)	0 (0-3)	0 (0-2)	0 (0-1)
Mean (SD)	0.7 (1)	0.2 (0.6)	0.2 (0.4)
No. of proxies	17	12	13

Supplemental Table 2. Continued

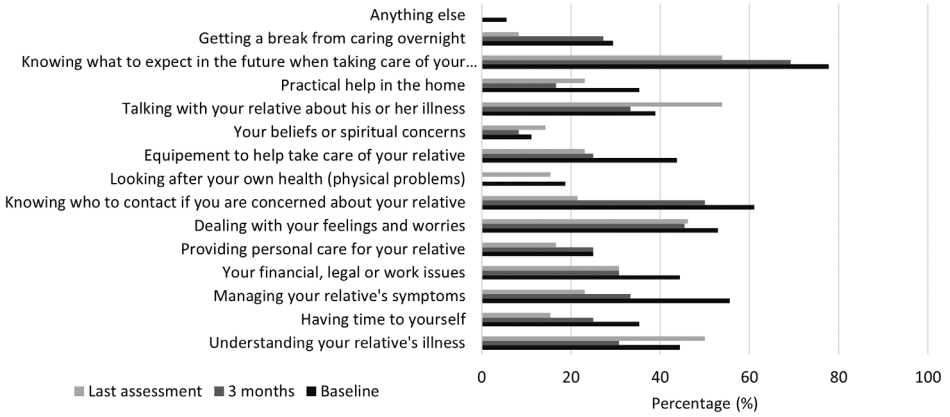
	Baseline	Month 3	Last assessment
13) Knowing what to expect in the future when taking care of your relative			
Median (range)	2 (0-3)	1 (0-3)*	1 (0-3)
Mean (SD)	1.5 (1)	0.9 (0.9)	0.9 (1.1)
No. of proxies	18	13	13
14) Getting a break from caring overnight			
Median (range)	0 (0-3)	0 (0-1)	0 (0-1)
Mean (SD)	0.5 (0.9)	0.3 (0.5)	0.1 (0.3)
No. of proxies	17	11	12
15) Anything else			
Median (range)	0 (0-2)	0 (0-0)	0 (0-0)
Mean (SD)	0.1 (0.5)	0 (0)	0 (0)
No. of proxies	18	5	8
Total CSNAT score			
Median (range)	5 (0-37)	3 (0-14)	3 (0-14)
Mean (SD)	7.7 (9.9)	4.6 (4.5)	4.9 (4.5)
No. of proxies	13	9	11

**p-value<0.05 compared to the baseline score*

Supplemental Table 3. Scores on the different items of the Caregiver Mastery Scale at baseline and the 3-month and last assessment

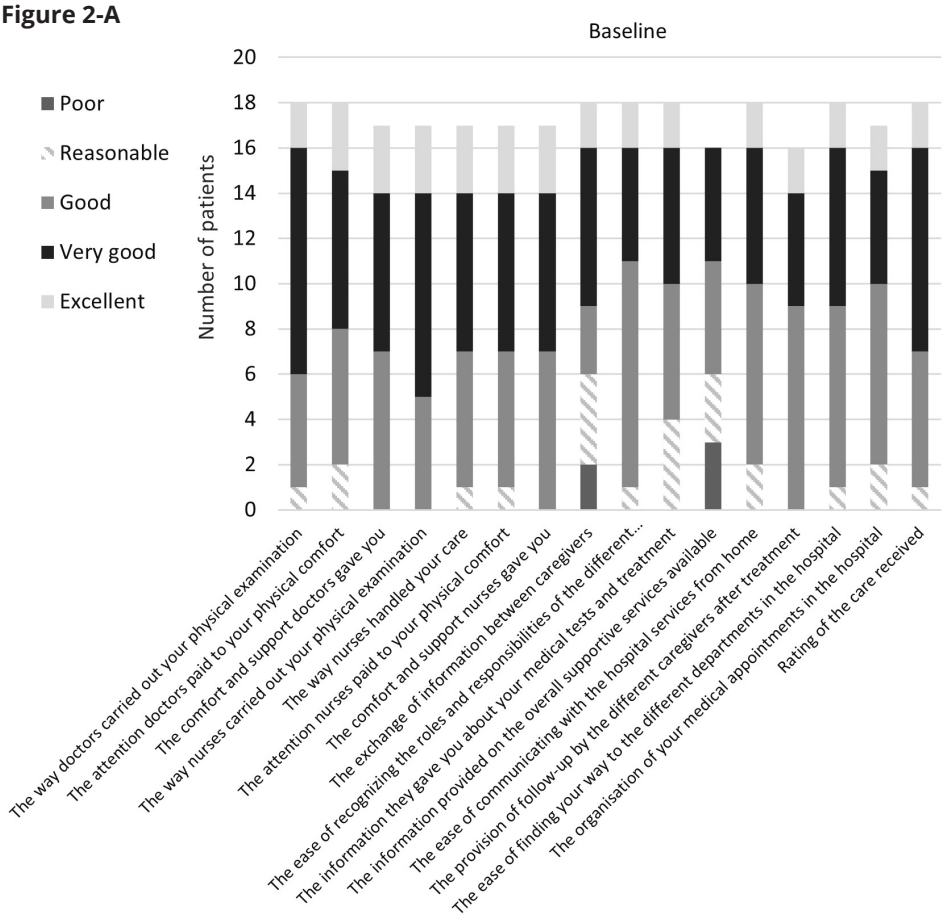
	Baseline	Month 3	Last assessment
1) You are usually certain about what to do in caring for your partner			
Median (range)	2 (1-15)	2 (1-4)	2 (1-4)
Mean (SD)	1.9 (0.9)	0.5 (0.9)	2.1 (1.1)
No. of proxies	18	13	14
2) No matter what you do as a caregiver, it never seems to be enough			
Median (range)	4 (1-4)	4 (1-5)	4 (1-5)
Mean (SD)	3.5 (0.9)	3.9 (1.1)	3.9 (1.1)
No. of proxies	18	13	14
3) In general, you are able to handle most problems in the care of your partner			
Median (range)	2 (1-5)	2 (1-5)	2 (1-5)
Mean (SD)	2.2 (1.1)	2.1 (1.1)	1.9 (1.0)
No. of proxies	18	13	14
4) You are not doing as well as you like as a caregiver			
Median (range)	4 (1-5)	4 (2-5)	4 (2-5)
Mean (SD)	3.7 (1.0)	3.9 (0.7)	3.9 (0.9)
No. of proxies	17	13	14
5) You feel that you have a great deal influence over the things that happen in caregiving			
Median (range)	2 (2-5)	2 (1-5)*	2 (1-5)
Mean (SD)	2.8 (1.1)	2.3 (1.3)	2.6 (1.4)
No. of proxies	17	13	14
6) You belief you are mastering most of the challenges in caregiving			
Median (range)	4 (1-5)	4 (1-5)	4 (1-5)
Mean (SD)	3.4 (1.2)	3.3 (1.3)	3.4 (1.3)
No. of proxies	18	13	14
7) You have lost some control of your life since your partner's illness			
Median (range)	2.5 (1-5)	2 (1-5)	2 (1-5)
Mean (SD)	2.8 (1.2)	2.5 (1.1)	2.4 (1.2)
No. of proxies	18	12	14
Total CMS score			
Median (range)	25 (7-32)	27 (9-33)	26.5 (9-35)
Mean (SD)	24.9 (5.6)	26.2 (6.1)	26.2 (6.5)
No. of proxies	17	13	14

*p-value<0.05 compared to the baseline score



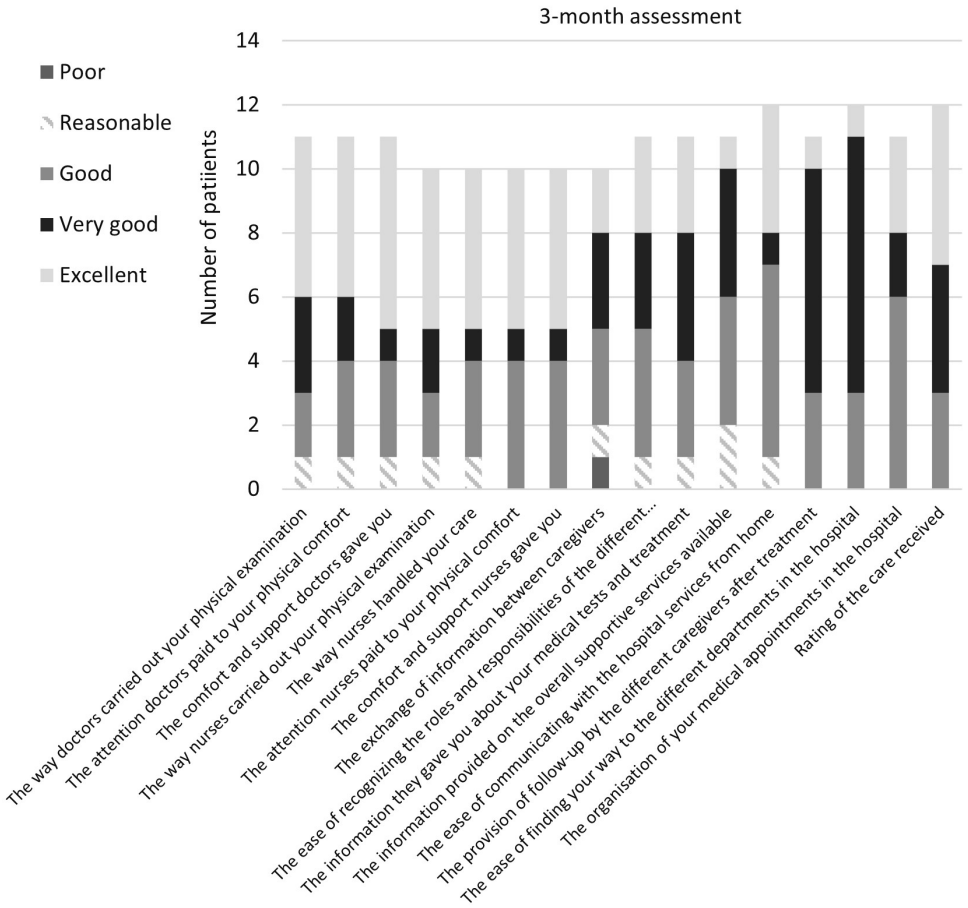
Supplemental Figure 1. The percentage of proxies indicating at least 'a bit more' need in support of different aspects as assessed with the CSNAT

Figure 2-A



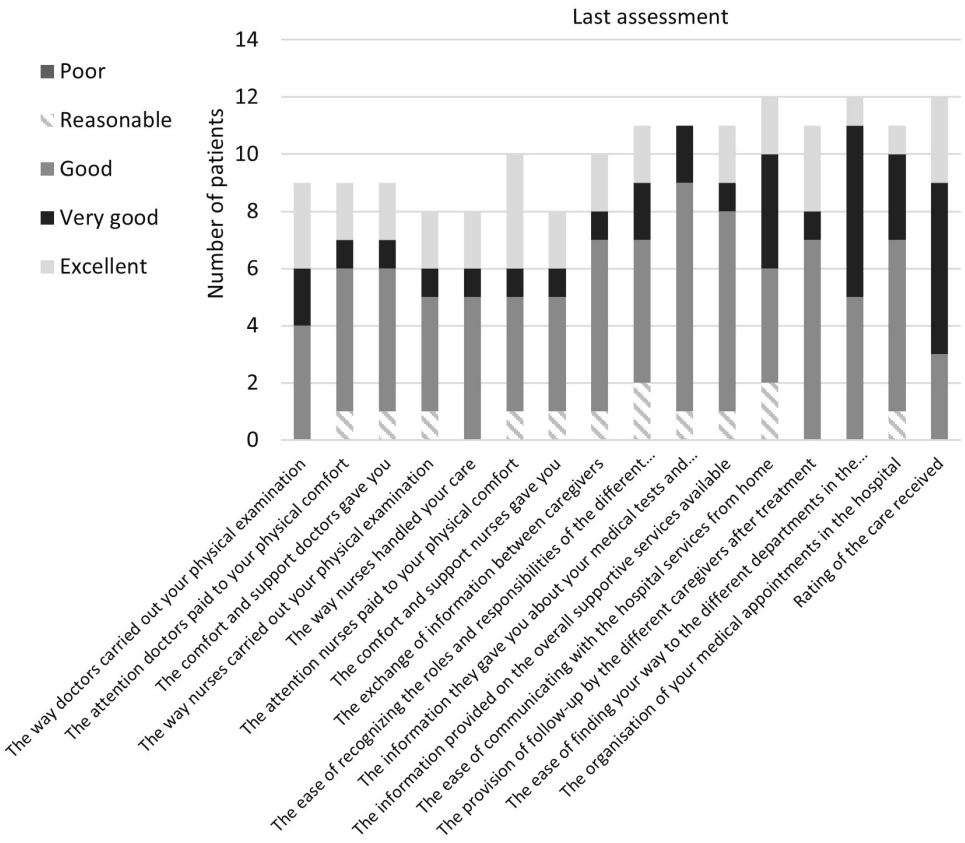
Supplemental Figure 2. Patient ratings of the satisfaction with care at baseline (Figure 2-A) and at the 3-month (Figure 2-B) and last assessment (Figure 2-C)

Figure 2-B



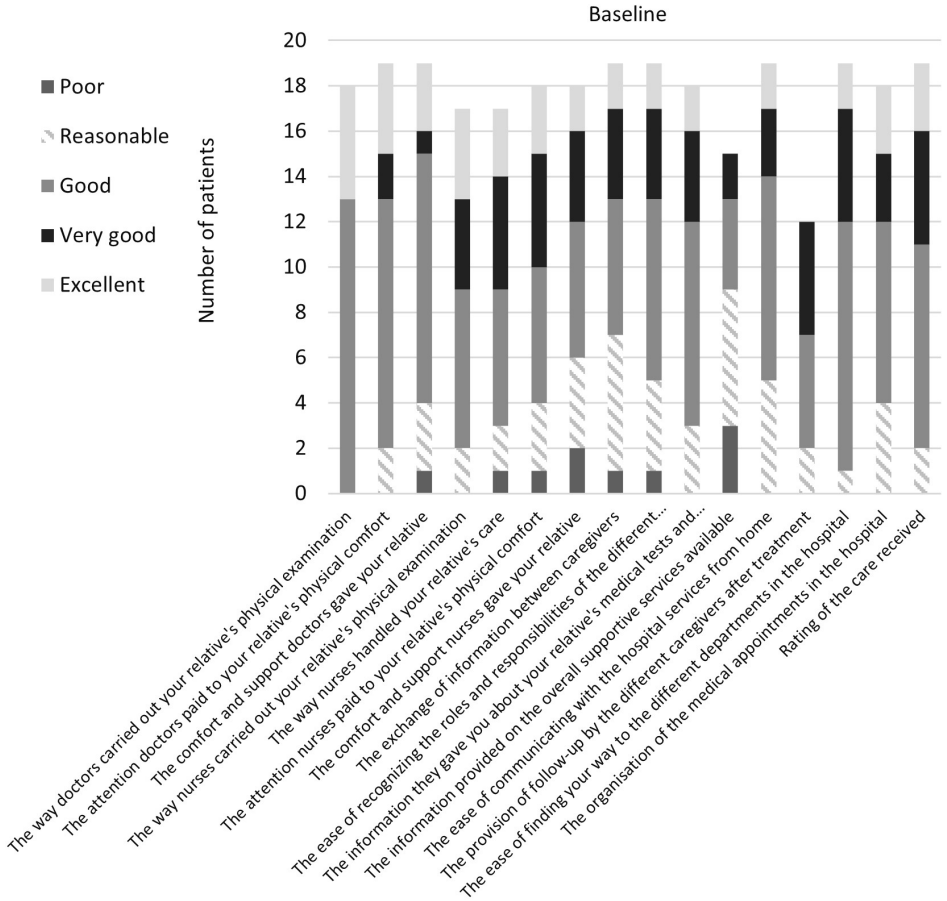
Supplemental Figure 2. Patient ratings of the satisfaction with care at baseline (Figure 2-A) and at the 3-month (Figure 2-B) and last assessment (Figure 2-C)

Figure 2-C



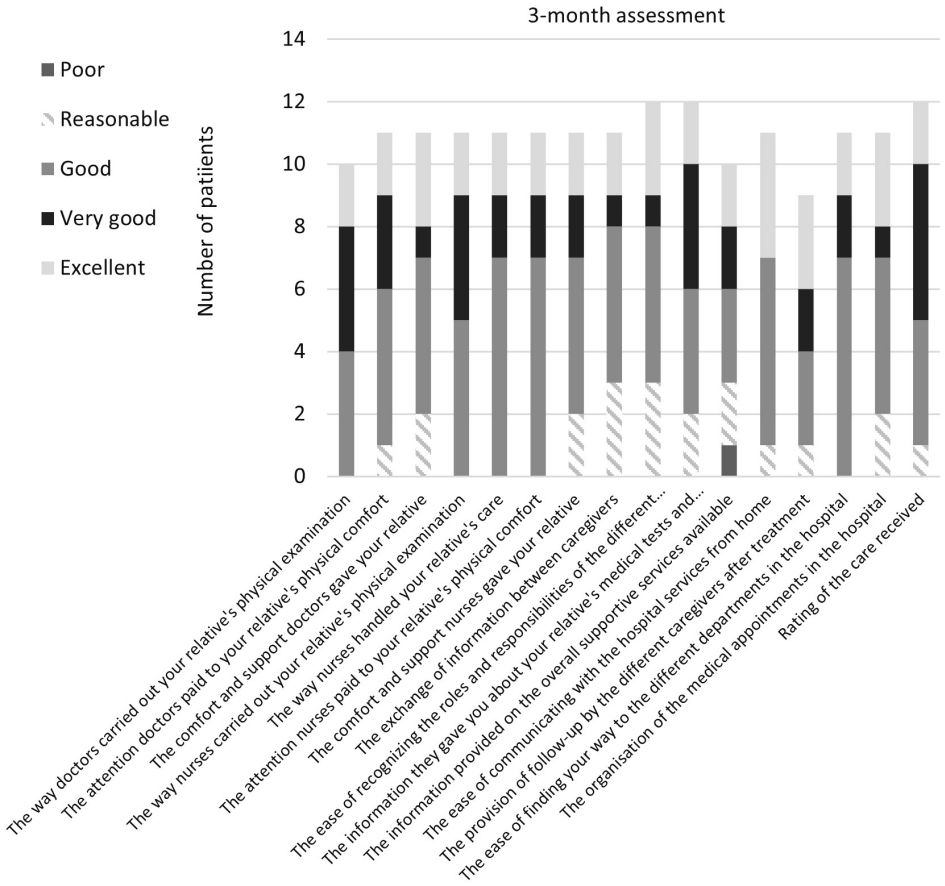
Supplemental Figure 2. Patient ratings of the satisfaction with care at baseline (Figure 2-A) and at the 3-month (Figure 2-B) and last assessment (Figure 2-C)

Figure 3-A



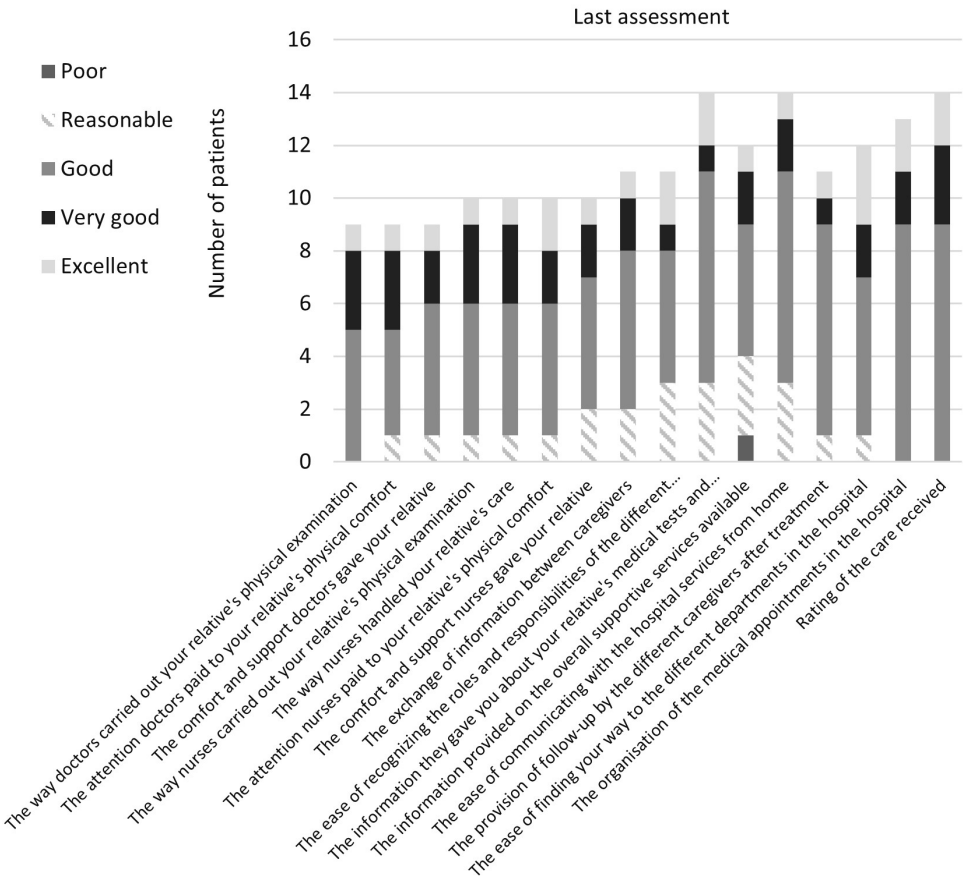
Supplemental Figure 3. Proxy ratings of the satisfaction with care at baseline (Figure 3-A) and at the 3-month (Figure 3-B) and last assessment (Figure 3-C)

Figure 3-B



Supplemental Figure 3. Proxy ratings of the satisfaction with care at baseline (Figure 3-A) and at the 3-month (Figure 3-B) and last assessment (Figure 3-C)

Figure 3-C



Supplemental Figure 3. Proxy ratings of the satisfaction with care at baseline (Figure 3-A) and at the 3-month (Figure 3-B) and last assessment (Figure 3-C)

Supplemental File 1.

Detailed description of the outcome measures

Health-related quality of life

To assess the patients' level of HRQoL, the European Organisation of Research and Treatment of Cancer (EORTC) quality of life questionnaire C30 (QLQ-C30, version 3.0) and brain cancer module (QLQ-BN20) were used[1-3]. The EORTC QLQ-C30 is a cancer-specific questionnaire comprising 30 items, resulting in five functional scales (physical, cognitive, emotional, role and social functioning), three symptom scales (fatigue, pain, nausea and vomiting), six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and a global health status score. The brain-specific QLQ-BN20 comprises 20 items, resulting in four symptom scales (visual disorder, motor dysfunction, future uncertainty and communication deficit) and seven symptoms assessed with a single item (headaches, seizures, drowsiness, itchy skin, hair loss, weakness of legs and bladder control). All items are scored on a 4-point Likert scale ranging from 'not at all' to 'very much', except for the items of the global health status score, which are scored on a 7-point Likert scale ranging from 'very poor' to 'excellent'. As specified in the EORTC scoring manual, raw item scores were aggregated and transformed into a linear scale ranging from 0 to 100. A higher score for the functioning scales represents better functioning, while a higher score for symptom scales represents worse functioning or a higher level of symptoms[4]. Differences in mean scale scores of at least 10 points were deemed clinically relevant for scales of the QLQ-BN20[5,6], while scale-specific minimal important differences (MIDs) were available for most of the scales of the QLQ-C30[7].

To assess the proxies' level of HRQoL, we used the Short-Form (SF)-36 questionnaire. This questionnaire consists of 36 items, organized into eight multi-item scales, assessing physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. In addition, the SF-36 yields two higher order component scores, the physical component score (PCS) and mental component score (MCS). A higher score represents better functioning[8]. As no MIDs were available for proxies, we set the MCID for the SF-36 domains also at 10 points, as the majority of reported MCIDs for the different domains were <10 points[9]. For the mental and physical component scales, MCIDs were set at 4.6 points and 3.0 points, respectively[10].

Anxiety and depression

To determine the level of anxiety and depressive symptoms in both patients and proxies, the Hospital Anxiety and Depression Scale (HADS) was used[11]. This

questionnaire comprises 14 items, resulting in an anxiety subscore and depression subscore. The total score ranges between 0 and 21 for each subscale, and a higher score indicates more problems. A score on a subscale ≥8 was considered indicative for borderline anxiety or depression[12].

Caregiver mastery

The Caregiver Mastery Scale was used to assess the level of mastery of the caregiver[13], i.e. the combined effects of the informal caregiver's self-perception and actual ability to successfully perform the activities of providing care. This questionnaire consists of seven statements for which the caregiver can indicate their perception on how well they were able to provide the necessary care. Scores are provided on a 5-point Likert-scale ranging from 'completely agree' to 'not agreeing at all'. Scores for each statement are added and a total score (range: 7-35) is calculated. A higher score indicates less feelings of mastery.

Caregiver support needs

The Care Support Needs Assessment Tool (CSNAT) was used to assess in which areas of need the informal caregiver requires support[14]. The questionnaires consists of 14 domains (i.e. broad areas of need, such as practical help at home or dealing with feelings and worries) in which carers commonly say they require support. All questions are scored on a 4-point Likert scale ranging from 'no', to 'a bit more', 'more' and 'much more' (scores 0-3). Scores on each item are added and a total score (range: 0-42) is calculated. A higher score indicates a higher need of support.

Satisfaction with care

A short-item list was created with items from the EORTC item library[15]. Most items were adapted from the EORTC PATSAT[16], which includes an outpatient module. Items were scored on a 5-point Likert scale ranging from 'bad' to 'excellent'. As specified in the EORTC scoring manual, raw item scores were aggregated and transformed into a linear scale ranging from 0 to 100[4]. A higher score indicates higher satisfaction with care. Both the patient and the proxy completed this questionnaire (see Supplemental File 3 for the selected questions).

Health resource utilization

A study-specific questionnaire (see Supplemental File 4) was created to assess health resource utilization of glioblastoma patients. In this questionnaire, the number (and days) of hospitalizations and consultations with healthcare providers (specialist, general practitioner, other medical providers) was collected, as well as used drug therapy.

Evaluation ACP program

Another study-specific questionnaire (see Supplemental File 5) was used to evaluate the content and structure of the ACP program. The patients and proxies assessed the overall quality of the program, as well as the quality of the facilitator. In addition, the topics and quantity of provided information were evaluated, the number and duration of the ACP sessions, and suggestions to improve the ACP program were requested.

The general practitioner of each patient also received an evaluation questionnaire, in which they also had to rate the timing, topics and quality of the ACP program. In addition, they were asked to indicate if they received an AD of the patient, if they were aware of the wishes of the patient in another way, if they were able to comply with these wishes, and whether the contact with the treating physicians in the hospital was satisfactory.

Patient wishes

To assess patient's wishes with EOL care, information on the number of completed ADs, changes in ADs over time, changes in wishes and preferred place of care/death were collected by the nurse practitioner, based on conversations with the patient during the follow-up period.

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Supplemental File 2.

Questions to measure satisfaction with care (patient version as example)

		Poor	Fair	Good	Very good	Excellent
How would you rate the doctors with respect to:						
1.	The way they carried our your physical examination (took your temperature, felt your pulse, etc.)?	1	2	3	4	5
2.	The attention they paid to your physical comfort?	1	2	3	4	5
3.	The comfort and support they gave you?	1	2	3	4	5
How would you rate the nurses with respect to:						
4.	The way they carried our your physical examination (took your temperature, felt your pulse, etc.)?	1	2	3	4	5
5.	The way they handled your care (gave your medicines, performed injections, etc.)?	1	2	3	4	5
6.	The attention they paid to your physical comfort?	1	2	3	4	5
7.	The comfort and support they gave you?	1	2	3	4	5
How would you rate the services and healthcare organisations with respect to:						
8.	The exchange of information between caregivers?	1	2	3	4	5
9.	The ease of recognizing the roles and responsibilities Of the different caregivers (doctors, nurses, physiotherapists psychologists, etc.) involved in your care?	1	2	3	4	5
10.	The information they gave you about your medical tests and treatment?	1	2	3	4	5
11.	The information provided on the overall support services available (social, psychological, physiotherapy dietitian services, support groups, etc.)?	1	2	3	4	5
12.	The ease of communicating with the hospital services from home?	1	2	3	4	5
13.	The provision of follow-up by the different caregivers (doctors, nurses, physiotherapists, psychologists, etc.) after treatment?	1	2	3	4	5
14.	The ease of finding your way to the different departments in the hospital?	1	2	3	4	5
15.	The organization of your medical appointments in the hospital?	1	2	3	4	5
16.	How would you rate the care you received?	1	2	3	4	5

Supplemental File 3.

Study-specific questionnaire to measure health resource utilization

1) In the last three months, have you contacted your general practitioner?

☐ No

☐ Yes, ☐☐☐ contact(s)

(Please sum all contacts, including contacts by phone)

2) In the last three months, did you have contact with a doctor in the hospital, without being admitted to the hospital?

(Examples of doctors are the neurologist, medical oncologist, neurosurgeon or rehabilitation specialist)

☐ No

	Doctor	Number of contacts
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐

3) In the last three months, have you contacted other healthcare professionals?

(Examples of other healthcare professionals are physiotherapists, occupational therapists, psychotherapists, social workers, alternative medicine practitioners, psychiatrists, or psychologists)

☐ No

	Healthcare professional	Number of contacts
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐
☐ Yes, namely:	_____	☐☐☐

4) In the last three months, have you received half-days or full days treatment for medical / psychological problems? A half-day or full-day treatment can vary from half a day to 5 days a week.

(Please sum all half-days and full days)

☐ No

☐ Yes, namely: ☐☐☐**,**☐☐ day(s)

In what kind of institution did you receive this care?
☐ University hospital
☐ Municipal hospital
☐ Psychotherapeutic institution
☐ Rehabilitation center
☐ Other institution, namely:_____

5) In the last three months, have you been admitted to a healthcare institution?
(This means at least one night in for example a hospital, nursing home, hospice, rehabilitation center)
☐ No
☐ Yes, namely ☐☐☐ times

In what kind of institution did you receive this care?
☐ University hospital
☐ Municipal hospital
☐ Psychotherapeutic institution
☐ Rehabilitation center
☐ Hospice
☐ Nursing home
☐ Other institution, namely:_____

6) In the last three months, did you visit the emergency department?
☐ No
☐ Yes, namely: ☐☐☐ times

Reason: _____
_____
_____
_____
_____

7) In the last three months, have you called the medical team (e.g. general practitioner, doctor in the nursing home or hospice, doctor in the hospital, psychiatrist, psychologist, nurse in the hospital, social worker) for information?
☐ No
☐ Yes, namely ☐☐☐ times

8) In the last three months, have you used medication?
*(Do **not** count the medicines that you received during a hospital stay, and neither count products such as contraception, vitamin supplements or alternative medicines)*

☐ No
☐ Yes, ☐☐☐ namely

Medicin (name or description	Dose*	Number of times a day	Number of days in the past 4 weeks

**If you do not know the dose, you can omit this question*

9) Do you have health insurance?

☐ Basic health insurance
☐ Basic health insurance + additional options
☐ Not insured

Supplemental File 4.

Study specific questionnaire to evaluate the ACP program (patient and proxy version)

1. In your opinion, what is the optimal time during the disease course to introduce the ACP program?
☐ After diagnosis (shortly after the operation)
☐ After chemoradiation (approximately 12-16 weeks after diagnosis)
☐ After 3 adjuvant chemotherapy (approximately 6 months after diagnosis)
☐ After 6 adjuvant chemotherapy cycles (approximately 9 months after diagnosis)
☐ Other, namely: _____

2. How would you rate the quality of the ACP program?

1	2	3	4	5	6	7
Poor			Neutral			Excellent

3. What is your opinion about the topics that are discussed within the ACP sessions?
☐ All important topics are discussed.
☐ Topics are missing, namely: _____

4. Was the ACP program acceptable?

	Very acceptable	Acceptable	Not Acceptable	Not applicable
a) Topics	☐	☐	☐	☐
b) Amount of provided information	☐	☐	☐	☐
c) Number of ACP sessions	☐	☐	☐	☐
d) Duration first ACP session	☐	☐	☐	☐
e) Duration second ACP session	☐	☐	☐	☐
f) Functioning facilitator	☐	☐	☐	☐
g) Other, namely:	☐	☐	☐	☐

5. Were there aspects that you encountered during the ACP sessions which you would suggest to change?

☐ No

☐ Yes, namely: _____

_____

_____

_____

Thank you for completing this questionnaire. Below you can provide additional comments.

_____

_____

_____

_____

_____

_____

_____

_____

_____

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.

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APPENDICES

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NEDERLANDSE SAMENVATTING

Een kwaadaardige hersentumor, primair of secundair, is een ernstige aandoening die een grote impact heeft op het leven van zowel patiënten als hun naasten. Deze impact beperkt zich niet alleen tot de verminderde levensverwachting, maar omvat ook de negatieve invloed van de ziekte en de behandeling op de gezondheidsgerelateerde kwaliteit van leven (*Health Related Quality of Life*, HRQoL) van patiënten. In dit proefschrift staan patiënten met een glioom centraal, een kwaadaardige primaire hersentumor die ontstaat uit de steuncellen van de hersenen. Van alle gliomen is het glioblastoom de meest voorkomende, maar ook de meeste agressieve variant.

Dit proefschrift richt zich op drie hoofdthema's:
1) prediagnostische symptomen en klachten bij glioompatiënten;
2) het meten van HRQoL van glioompatiënten;
3) het implementeren van een ziektespecifiek *advance care planning* (ACP) programma voor patiënten met een glioblastoom.

Deel 1 van dit proefschrift geeft allereerst een overzicht van de epidemiologie, pathofysiologie en de behandeling van hersentumoren en het meten van HRQoL. Vervolgens komen de symptomen en klachten die patiënten met een glioom ervaren in de periode voorafgaand aan de diagnose aan de orde. Uit eerder onderzoek is gebleken dat kennis over het volledige scala aan gezondheidsproblemen die patiënten in de periode voorafgaand aan de diagnose ervaren en het eventuele zorggebruik ten gevolge van deze problemen, schaars is. Een beter inzicht in symptomen en problemen in de prediagnostische periode zou patiënten, hun naasten en zorgverleners mogelijk kunnen helpen om een glioom in een eerder stadium te herkennen en te behandelen.

In **Deel 2** worden twee aspecten van het meten van HRQoL van glioompatiënten behandeld: (1) het effect van de timing van metingen van HRQoL op de daadwerkelijke uitkomsten en (2) de voorkeuren van patiënten, naasten en zorgverleners met betrekking tot het meten van HRQoL en het gebruik van HRQoL resultaten in de dagelijkse klinische zorg. Inzicht in de optimale timing van HRQoL metingen en in de implementatie van patiënt-gerapporteerde uitkomsten (*Patient Reported Outcomes*, PROs) in de klinische praktijk bij glioompatiënten in Nederland is beperkt. Meer kennis over het effect van de timing van de afname van vragenlijsten op HRQoL uitkomsten kan bijdragen aan het optimaliseren van de meetmomenten in klinische studies en in de dagelijkse praktijk. Daarnaast is het belangrijk om te weten hoe patiënten, hun naasten en zorgverleners aankijken tegen het afnamen van vragenlijsten en de terugkoppeling van de resultaten ervan als onderdeel van de reguliere zorg. De

perspectieven van álle gebruikers zijn nodig voor een succesvolle implementatie van patiënt-gerapporteerde meetinstrumenten in de zorg voor mensen met een glioom.
Deel 3 richt zich op een ziektespecifiek ACP-programma in de klinische zorg voor patiënten met glioblastoom en hun naasten. Er is steeds meer bewijs dat bij mensen met kanker in de laatste fase van het leven vroege palliatieve zorg effectief is ten aanzien van het verbeteren van aspecten van HRQoL, waaronder de stemming. Een vorm van vroege palliatieve zorg is ACP, een proces waarbij patiënten en hun naasten samen met behandelaren in een relatief vroeg stadium van de ziekte de doelen van de zorg in de laatste fase van het leven vaststellen, hetgeen patiënten de gelegenheid biedt om hun wensen en verwachtingen te definiëren[1]. Een tijdige inzet van ACP lijkt juist bij patiënten met een glioblastoom gerechtvaardigd, omdat zij een progressieve cognitieve achteruitgang kunnen doormaken, waardoor hun vermogen om beslissingen over de behandeling of zorg te nemen ernstig kan worden belemmerd[2-4]. Vroegtijdige betrokkenheid bij de besluitvorming lijkt daarom belangrijk[5], maar het is nog niet helemaal duidelijk wat de optimale manier is om ACP aan glioblastoompatiënten aan te bieden.

In de volgende paragrafen zullen de resultaten van de in dit proefschrift beschreven studies worden samengevat en besproken.

Prediagnostische symptomen bij glioompatiënten

In het algemeen, en in overeenstemming met eerder gepubliceerde studies over prediagnostische symptomen en klachten van hersentumorpatiënten, vonden de beide studies beschreven in **Deel 1** van dit proefschrift (**Hoofdstukken 2 en 3**) dat verschillende symptomen en klachten (zoals lichamelijke en mentale vermoeidheid, slaapstoornissen, hoofdpijn en stress) relatief vaak voorkomen vóórdat bij een patiënt een glioom wordt gediagnosticeerd[6, 7]. Eveneens in overeenstemming met de conclusies van eerdere studies[8-10], kwamen deze symptomen en verschijnselen echter niet vaker voor dan bij andere aandoeningen, waardoor het moeilijk is om patiënten met een glioom in een vroeg stadium te herkennen.
Deze conclusies zijn gebaseerd op twee studies met een verschillende opzet. Als eerste werd een case-control studie (**Hoofdstuk 2**) uitgevoerd, waarbij gebruik gemaakt werd van gegevens uit geanonimiseerde huisartsenregistraties. In deze studie werden de prevalenties van negen klinische symptomen waarmee glioompatiënten zich bij de huisarts kunnen presenteren in de vijf jaar voorafgaand aan de diagnose vergeleken met die van patiënten met andere aandoeningen van het centrale zenuwstelsel of met een geheel andere klacht / aandoening. In totaal werden 36 patiënten met een glioom en 72 gematchte controlepatiënten geïncludeerd (36 patiënten met andere aandoeningen van het centrale zenuwstelsel (CZS) en 36 “andere” patiënten,

gedefinieerd als de patiënten die niet voldeden aan de criteria voor de andere twee groepen, bv. patiënten met rugpijn of griep). In deze case-control studie werden geen verschillen in prevalenties van de klinische symptomen gevonden tussen de drie vooraf gedefinieerde groepen. Een uitzondering was een hogere prevalentie van motorische symptomen bij patiënten met andere aandoeningen van het CZS in vergelijking met de glioom- en "andere" patiëntengroepen (in de periode 60-24 maanden vóór de diagnose), en meer stemmingsstoornissen/angst bij patiënten met andere aandoeningen van het CZS in vergelijking met de "andere" groep (in de periode <6 maanden vóór de diagnose). Op grond van deze resultaten werd geconcludeerd dat patiënten met een glioom noch wat betreft het aantal noch het type prediagnostische symptomen konden worden onderscheiden van beide controlegroepen.
Een tamelijk breed scala van niet-specifieke problemen in het jaar voorafgaand aan de diagnose werd ook gezien in **Hoofdstuk 3**, waarin een cross-sectionele studie werd beschreven waaraan 59 patiënten met een glioom deelnamen. Het doel van de studie was de frequentie van het vóórkomen van prediagnostische symptomen en klachten vast te stellen, alsmede het daaraan gerelateerde zorggebruik. Met behulp van een studie-specifieke vragenlijst met in totaal 30 items werd vastgesteld dat patiënten in het jaar voor de diagnose een mediaan aantal van zes symptomen hadden ervaren, waarbij fysieke vermoeidheid, mentale vermoeidheid, slaapstoornissen, hoofdpijn en stress de vijf vaakst voorkomende waren. Zesentwintig van de 59 patiënten (44%) hadden in verband met ten minste één symptoom de huisarts bezocht. Patiënten die hun huisarts hadden geraadpleegd rapporteerden statistisch significant vaker spierzwakte dan patiënten die hun huisarts niet hadden geraadpleegd, terwijl er geen andere statistisch significante verschillen werden gevonden.

Hoewel de literatuur in het algemeen eensluidend is met betrekking tot de in het algemeen zeer aspecifieke klinische presentatie van patiënten met een glioom in de huisartspraktijk, wijken de resultaten van onze twee studies over de prediagnostische symptomen en klachten in de eerste lijn op een aantal punten af van eerder onderzoek over dit onderwerp. Zo moet worden opgemerkt dat eerdere studies patiënten met verschillende vormen van hersentumoren includeerden, terwijl aan onze studies alleen patiënten met een glioom deelnamen. In eerdere klinische studies met hersentumorpatiënten waarbij gebruik werd gemaakt van eerstelijns medische dossiers[8, 9], en in een systematische review over de symptomatische diagnose van kanker van het CZS in de eerstelijns gezondheidszorg[10], werd bevestigd dat hersentumorpatiënten zich met zeer diverse symptomen voor en/of op het moment van de diagnose kunnen presenteren, bijvoorbeeld met een eerste epileptische aanval, zwakte (als zelfgerapporteerde klacht), hoofdpijn, verwardheid, geheugenklachten, visusstoornissen of motorische zwakte bij lichamelijk onderzoek. Ook werd eerder al

vastgesteld dat patiënten met een glioom niet konden worden onderscheiden van patiënten met andere aandoeningen, met uitzondering van een eerste epileptische aanval, hetgeen vooral bij mensen ouder dan zestig jaar geassocieerd bleek te zijn met een verhoogd risico op een hersentumor[8-10]. Echter, in tegenstelling tot de bevindingen in deze eerdere studies, hebben wij *geen* verhoogde prevalentie van specifieke symptomen of klachten waargenomen bij glioompatiënten in vergelijking met patiënten met andere aandoeningen die de huisarts bezochten (**Hoofdstuk 2**). Bovendien bleek dat de symptomen en klachten van patiënten met een glioom die de huisarts bezochten redelijk vergelijkbaar waren met degenen die dat niet deden, met uitzondering van het vaker ervaren van spierzwakte door patiënten met een glioom die de huisarts wel bezochten (42%) in vergelijking met patiënten die dat niet deden (9%) (**Hoofdstuk 3**). Het is echter de vraag of dit verschil in prevalentie van spierzwakte voldoende klinisch relevant is om een huisarts in staat te stellen om patiënten met een mogelijk glioom te onderscheiden van patiënten met andere aandoeningen. Hoewel overwogen zou kunnen worden om in geval van spierzwakte nadere diagnostiek te verrichten, bijvoorbeeld beeldvormend onderzoek, is er ook literatuur die anders suggereert. Een belangrijke reden om af te zien van verdere diagnostiek ligt in de zeer lage incidentie van hersentumoren en de zwakke associatie tussen klachten en de aanwezigheid van een tumor[8-10]. Ter illustratie, een studie naar *direct-access Computerized Tomography* (CT) bij patiënten met chronische dagelijkse hoofdpijn (hoofdpijn ≥15 dagen per maand en langer dan 3 maanden)[11] rapporteerde dat gedurende de studieperiode van 8 jaar in totaal 4404 scans werden gemaakt. Hiervan leverden slechts 60 scans (1.4%) een waarschijnlijke pathofysiologische oorzaak van de hoofdpijn op, waarvan 22 een hersentumor betroffen (14 meningeomen, 1 laaggradig glioom, 4 hypofysetumoren, en 3 metastasen). Ook moet worden meegewogen dat bij snelgroeiende, agressieve hersentumoren het resultaat van beeldvormende procedures aanvankelijk negatief kan zijn. Dit wordt bevestigd in verschillende onderzoeken waarin bij patiënten die zich presenteerden met verschillende symptomen die mogelijk verband hielden met een hersentumor, aanvankelijk geen tekenen van een hersentumor werden vastgesteld, terwijl zij bij herhaalde beeldvorming uiteindelijk toch gediagnosticeerd werden met een hersentumor[12, 13]. Aangezien een glioom in bijna alle gevallen een ongeneeslijke ziekte is, zou een vroegere identificatie aan de ene kant kunnen leiden tot een vroegere behandeling, maar aan de andere kant ook tot een langere ziekteduur. Uit een recente studie bij incidenteel ontdekte glioblastomen bleek dat deze tumoren vaak klein waren en de patiënten goed functioneerden, en dat eerdere behandeling niet resulteerde in een langere progressie-vrije en algehele overleving[14].

Op basis van de twee *kwantitatieve* studies beschreven in dit proefschrift (**Hoofdstuk 2** en **Hoofdstuk 3**), kon geconcludeerd worden dat patiënten met een glioom zich met

aspecifieke symptomen en klachten presenteerden. Op dit gebied is ook *kwalitatief* onderzoek verricht. Bij kwantitatief onderzoek worden conclusies getrokken op basis van numerieke data (getallen) en statistiek, waarbij in kwalitatief onderzoek juist meningen en motivaties onderzocht en beschreven worden. Een kwalitatieve studie liet zien dat patiënten niet zozeer specifieke symptomen of klachten, maar wel andere subtiele veranderingen opmerkten, en dat familieleden deze veranderingen zelfs al eerder of vaker opmerkten dan de patiënt zelf, tot 6 maanden voor de diagnose[15]. Deze kwalitatieve studie inventariseerde ook de visie van patiënten op de mogelijkheden om het huisartsenbezoek te optimaliseren en zo de diagnostische vertraging te beperken. De belangrijkste conclusies waren dat vage klachten en symptomen een grondig onderzoek vereisen, en dat patiënten moeten worden aangemoedigd om deze tijdens het consult uitgebreid ter sprake te brengen, bijvoorbeeld aan de hand van een bijgehouden dagboek, en door patiënten de mogelijkheid te bieden terug te kunnen komen als zij ongerust zijn. De laatste jaren zijn er, onder andere in Nederland, verschillende campagnes gestart om patiënten te ondersteunen bij het voorbereiden van een bezoek aan hun arts, door hen te helpen nadenken over mogelijk relevante vragen[16]. Een goede voorbereiding kan de kwaliteit van het consult en mogelijk ook het diagnostisch proces ten goede komen. Ook werd in eerder onderzoek aanbevolen om niet alleen de patiënten, maar ook hun naasten bij het consult te betrekken[15]. In onze studie, gepresenteerd in **Hoofdstuk 3,** werden patiënten inderdaad gevraagd om de studie-specifieke vragenlijst samen met hun naasten in te vullen, om daarmee de kans op het missen van bepaalde klachten en symptomen te minimaliseren. Een beperking van onze studie was dat patiënten en hun naasten de vragenlijst niet onafhankelijk van elkaar invulden, maar juist gezamenlijk één vragenlijst, zodat we niet konden vaststellen of er eventuele discrepanties tussen hun antwoorden waren, om op grond daarvan de toegevoegde waarde van de betrokkenheid van naasten te bepalen.

Prediagnostische symptomen bij gliomen: Implicaties voor toekomstig onderzoek

Wat toekomstig onderzoek betreft geven de resultaten van beide in dit proefschrift beschreven studies, in combinatie met eerder gepubliceerde literatuur, aan dat de vroege identificatie van patiënten met glioom in de huisartsenpraktijk op basis van hun symptomatologie uiterst moeilijk lijkt. Met betrekking tot het beleid bij patiënten die zich presenteren met een breed scala aan aspecifieke klachten en symptomen, zou de toegevoegde waarde van het meer betrekken van naasten een onderwerp voor toekomstige studies kunnen zijn. In dergelijke studies kan worden nagegaan in hoeverre een beter en volledig overzicht van de klachten van de patiënten wordt verkregen als naasten worden betrokken, en kan ook worden nagegaan of en welke

verschillen er zijn in de ervaringen van patiënten en van hun naasten. Een grotere betrokkenheid van naasten bij de bezoeken aan de arts of andere zorgverleners kan mogelijk niet alleen van waarde zijn in de prediagnostische fase, maar ook bij patiënten bij wie uiteindelijk de diagnose glioom wordt gesteld. Met een vollediger inzicht in de gezondheidstoestand van de patiënt vóór de behandeling kunnen de effecten van de therapie en eventuele veranderingen in het klinische beloop mogelijk beter worden vastgesteld.

Prediagnostische symptomen bij gliomen: Implicaties voor de klinische praktijk

Wat de implicaties voor de praktijk betreft, vonden we in onze prospectieve studie (**Hoofdstuk 3**) dat de meerderheid van de patiënten met een glioom de huisarts niet bezocht in het jaar voorafgaand aan de diagnose, zelfs niet als ze symptomen hadden. Ook konden geen aanbevelingen worden gedaan om de vroege opsporing van een hersentumor te verbeteren, omdat de meeste prediagnostische symptomen en klachten niet vaker voor bleken te komen bij patiënten met een glioom dan bij patiënten met andere aandoeningen. Wel kan worden aanbevolen om bij patiënten die zich met een reeks van aspecifieke symptomen en klachten in de huisartsenpraktijk presenteren, altijd een grondig onderzoek uit te voeren. Meer voorlichting over prediagnostische symptomen bij een glioom zou huisartsen mogelijk kunnen helpen om bij dergelijke klachten een glioom als een mogelijke diagnose te overwegen, ook al is de incidentie laag. Het in een vroeger stadium overwegen van deze diagnose kan mogelijk leiden tot een snellere diagnose en behandeling, hoewel de impact hiervan op de levensverwachting onzeker is. Ook kan worden geadviseerd om bij een presentatie met een scala van aspecifieke klachten en symptomen zo mogelijk de naaste(n) van de patiënt te betrekken. Vooral eventuele veranderingen in persoonlijkheid of gedrag en cognitieve stoornissen worden misschien eerder opgemerkt door naasten dan door de patiënten zelf, terwijl deze verschijnselen relatief vaak voorkomen bij hersentumorpatiënten.

De toegevoegde waarde van meer publieksvoorlichting over de symptomen en klachten van hersentumoren is twijfelachtig, omdat de incidentie laag is en de symptomen veel overlap vertonen met die van aandoeningen die veel vaker voorkomen en minder ernstig zijn. Echter, omdat snelle en adequate behandeling ook voor andere aandoeningen van belang is, lijkt een meer algemeen publieksadvies om bij dergelijke problemen altijd naar de huisarts te gaan en het consult goed voor te bereiden (inclusief het maken van een overzicht van de problemen en relevante vragen), gerechtvaardigd.

Het meten van HRQoL van glioompatiënten

De studies beschreven in **Deel 2** van dit proefschrift hadden betrekking op het meten

van HRQoL in de klinische zorg voor glioompatiënten. **Hoofdstuk 4** beschreef een gerandomiseerde klinische studie bij patiënten met een glioom die de algemene kanker- en hersentumor-specifieke *European Organisation for Research and Treatment of Cancer* (EORTC) kwaliteit van leven vragenlijsten (QLQ-C30 en QLQ-BN20, respectievelijk) en de *Hospital Anxiety and Depression Scale* (HADS) op twee tijdstippen invulden. Het doel van het onderzoek was om te evalueren of HRQoL scores in klinisch relevante mate veranderden tussen het moment van de *Magnetic Resonance Imaging* (MRI) scan en voor of na het consult met de arts, ongeveer een week later, en of stemming hierin een rol speelde. Alle 100 gerekruteerde patiënten vulden de vragenlijsten in op de dag van de MRI-scan. Vervolgens vulden 49 van hen de tweede vragenlijst in vóór het consult met de arts ongeveer een week later, en 51 patiënten na het consult met de arts.

Over het algemeen toonde de studie geen verschillen in de HRQoL scores en symptomen van angst of depressie tussen de twee groepen; dit gold zowel voor de vergelijking op de twee meetmomenten zelf, als voor veranderingen over de tijd. Echter, als alle patiënten (n=100) gezamenlijk geanalyseerd werden, viel op dat een (aanzienlijk) deel van de patiënten een klinisch relevante verbetering of verslechtering in de loop van één week in een van de functionerings- of symptoomschalen toonden, namelijk tussen 8-58% per schaal. Slechts 3% van de patiënten had geen enkele klinisch relevante verandering op enige schaal van de HRQoL vragenlijst in de periode van één week.

De bevinding dat de HRQoL scores in deze studie niet beïnvloed werden door het afnamemoment, namelijk vóór of direct na het consult met de arts, was niet in overeenstemming met onze verwachtingen. Eerdere literatuur toonde namelijk aan dat het in onzekerheid verkeren over de uitkomst van diagnostische procedures (bv. een MRI) gepaard ging met meer angst en een slechter emotioneel welzijn[17]. Deze bevinding wekte de verwachting dat hogere angstniveaus en slechtere HRQoL scores, zoals bijvoorbeeld op het emotioneel functioneren, zouden worden gezien bij patiënten die de vragenlijsten invulden vóór het consult met de arts, in vergelijking met patiënten bij wie de afname na het consult met de arts plaatsvond. Aan de andere kant was ook te verwachten dat een slechte MRI-uitslag een negatieve invloed had op de HRQoL scores bij de patiënten die de vragenlijst na het consult met de arts invulden. Dat wij dit in onze studie geen effect zagen van het meetmoment zou mogelijk kunnen liggen aan het feit dat de meeste patiënten in onze studie (90%) een relatief stabiele ziekte hadden, en de mogelijke impact van de angst voor een slechte uitslag dan wel depressieve gevoelens na daadwerkelijk een slechte MRI-uitslag op hun functioneren ook beperkt was. Hoewel het tijdstip van de afname van vragenlijsten ten opzichte van de MRI uitslag geen invloed had op de scores, werden dus wel klinisch en statistisch significante veranderingen van HRQoL scores gezien in de tijdsperiode van één week. Dit was een nogal onverwachte bevinding in een populatie waarin de meerderheid

(radiologisch) stabiele ziekte had. Mogelijk werd de mate waarin deze fluctuaties optraden beïnvloed door de gezondheidsstatus van de patiënt, omdat het aantal HRQoL schalen waarop klinisch relevante veranderingen werden gezien lager was bij patiënten met een betere Karnofsky Performance Scale (KPS) score en patiënten die chemotherapie voor de tumor ondergingen in de periode van het invullen van de vragenlijsten[18]. Deze laatste bevinding strookt met de verwachting dat wanneer er wel behandeling plaatsvindt, of daarin verandering optreedt, er ook in een relatief korte tijdsperiode veranderingen in HRQoL kunnen optreden. In ander onderzoek rapporteerden patiënten met andere vormen van kanker inderdaad voor 9/15 schalen van de EORTC QLQ-C30 een slechtere gezondheidstoestand één week na toediening van chemotherapie in vergelijking met de dag van toediening, hetgeen de impact van de behandeling weerspiegelt[19]. Het feit dat wij klinisch relevante veranderingen vonden in een korte tijdsperiode van slechts een week, bij patiënten die klinisch en radiologisch stabiel waren en waar geen veranderingen in de behandeling plaatsvond, is reden tot nader onderzoek. Een tijdsvenster van één week is namelijk belangrijk bij de analyse van gegevens uit klinische studies, om de korte termijn impact van de behandeling op het functioneren en het welzijn van de patiënten te bepalen. Gewoonlijk worden in klinische studies zogeheten '*completion time windows*' gedefinieerd, die de periode weergeeft waarin een HRQoL-vragenlijst moet worden ingevuld, die kan wisselen van 1 week (in het geval dat men acute toxiciteit wil meten) tot bijvoorbeeld 3 maanden (in het geval men op de lange termijn een effect wil meten). Dit wordt gedaan om zoveel mogelijk vragenlijsten te includeren op een bepaald meetmoment in de studie, omdat in de praktijk altijd afwijkingen van het gestelde tijdstip plaatsvinden (bijv. omdat een patiënt de vragenlijst te laat ontvangt of terugstuurt). Eerder is een studie gedaan waarin de impact van de grootte van het *completion time window* is onderzocht in patiënten met kleincellig longkanker of colorectale kanker die behandeld werden met chemotherapie[20]. Er werd vastgesteld dat de verschillen in de definitie van het tijdvenster resulteerden in statistische en potentieel klinisch relevante verschillen. Hoewel niet in onze studie, kunnen conclusies van vergelijkingen van behandelingen worden beïnvloed door de definitie van een tijdvenster. Zorgvuldige overweging van een tijdvenster is daarom noodzakelijk, waarbij zelfs tijdvensters van één week als potentieel problematisch worden beschouwd.

In **Hoofdstuk 5** werd een studie naar het perspectief van glioompatiënten, hun naasten en neuro-oncologische zorgprofessionals op de uitvoerbaarheid van het routinematig meten van patiënt gerapporteerde uitkomsten (PRO) in de klinische praktijk beschreven. Over het algemeen waren alle deelnemers positief over de mogelijkheid om vragenlijsten routinematig af te nemen[21]. Deze conclusie is gebaseerd op kwalitatieve data; er werden semi-gestructureerde interviews afgenomen bij glioompatiënten

(n=24), hun naasten (n=16) en zorgprofessionals uit acht Nederlandse neuro-oncologie centra (n=35). Het bleek dat de meerderheid van de patiënten, hun naasten en de zorgprofessionals bereid waren om de resultaten van PRO-metingen te bespreken tijdens de reguliere follow-up bezoeken, waarbij het thuis invullen van de vragenlijsten, ongeveer een week voor het consult, de voorkeur had. Er bleek geen duidelijke voorkeur te zijn voor het ofwel op papier of online invullen van de vragenlijsten. Hoewel zorgverleners het liefst zouden zien dat de resultaten met de verpleegkundig specialist worden besproken, was slechts een derde van de patiënten en naasten het hiermee eens, met name omdat de meeste van hen de arts als voornaamste gesprekspartner zagen. Het functioneren in het dagelijks leven werd volgens alle drie de groepen als een erg belangrijk onderwerp in de evaluatie gezien[21].

Dat patiënten, hun naasten en professionals over het algemeen positief waren over het routinematig gebruik van PRO-uitkomstmaten in de neuro-oncologische praktijk **(Hoofdstuk 5)** is in lijn met bevindingen van eerdere studies, die concludeerden dat patiënten bereid zijn om routinematig PRO-uitkomstmaten in te vullen en dat het gebruik ertoe leidt dat relevante patiëntuitkomsten ook inderdaad vaker aan bod komen tijdens de consulten[22-25]. Bij de interpretatie van de resultaten van eerdere studies moet wel rekening gehouden worden met het feit dat deze onderzoeken in andere landen werden uitgevoerd, bij andere patiëntenpopulaties, en dat vooral werd gekeken naar situaties waarbij de arts (en niet een andere professional) de PRO-uitkomsten met de patiënt besprak. Ten aanzien van de implementatie van de routinematige afname van PRO-uitkomstmaten in de klinische praktijk in Nederland laten de resultaten van het onderzoek beschreven in **Hoofdstuk 5** zien dat het erg belangrijk is om de voorkeuren en wensen van álle stakeholders daarbij te betrekken.

Het meten van HRQoL bij glioompatiënten: Implicaties voor toekomstig onderzoek

Wat betreft de implicaties van de bevindingen beschreven in dit proefschrift voor toekomstig onderzoek naar het niveau van HRQoL van glioompatiënten, kan een aantal aanbevelingen worden gedaan. Allereerst moet een zorgvuldige selectie van instrumenten plaatsvinden op basis van de specifieke aspecten van de gezondheidstoestand die gemonitord of geëvalueerd moeten worden, bijvoorbeeld epileptische aanvallen of lichamelijk functioneren. Vervolgens moet worden nagegaan of hiervoor gevalideerde vragenlijsten beschikbaar zijn, waarbij ook moet worden meegenomen dat er instrumenten zijn die zich richten op één enkel aspect of juist meerdere dimensies van de gezondheidstoestand omvatten. Als er geen gevalideerd instrument beschikbaar is, kan eventueel een studiespecifieke vragenlijst worden ontwikkeld. Hiervoor zou gebruik kunnen worden gemaakt van items uit bestaande itembibliotheken, bijvoorbeeld de *EORTC Item Library*, of de *Patient Reported Outcome*

Measurement Information System (PROMIS) Item Bank. Als het niet mogelijk is om bestaande items te selecteren, kunnen nieuwe items worden ontwikkeld. Bij een zelf ontwikkelde vragenlijst is een onderzoek naar de psychometrische eigenschappen (bv. betrouwbaarheid, validiteit) noodzakelijk en zullen de resultaten met de nodige voorzichtigheid moeten worden geïnterpreteerd.
Momenteel zijn de meeste meetinstrumenten die gebruikt worden om het perspectief van de patiënten te meten binnen de neuro-oncologie statisch van aard, dat wil zeggen dat ze bestaan uit een vaste set items, die door alle patiënten allemaal moeten worden ingevuld. De relevantie van bepaalde items kan echter verschillen tussen patiënten; zo zal een item over betaald werk alleen van toepassing zijn op werkende patiënten. Bovendien kan de relevantie van bepaalde items in de loop van de tijd veranderen binnen individuele patiënten. Symptomen zoals haaruitval en misselijkheid zijn bijvoorbeeld meer van toepassing in de behandelfase terwijl in de maanden en jaren na de behandeling cognitieve klachten of beperkingen bij de terugkeer naar betaald werk op de voorgrond kunnen staan[26]. De eerdergenoemde itembibliotheken kunnen hiervoor een oplossing bieden: de huidige beschikbare vragenlijsten kunnen worden aangevuld met zogenaamde '*single- of multi-item*' schalen uit de itembibliotheek. Om de belasting van het invullen van extra vragen(lijsten) te beperken is het voor sommige instrumenten mogelijk een CAT (*Computerized Adaptive Testing*) versie aan te bieden. Hierbij worden de vragen die aan een patiënt worden voorgelegd afgestemd op de antwoorden op eerdere vragen. Dit zorgt voor minder en relevantere vragen voor een individuele patiënt en daarmee een vermindering van de responslast, terwijl de vergelijkbaarheid van de schaalscores gewaarborgd is. Voorbeelden van een dergelijke aanpak zijn de PROMIS[27] of de EORTC CAT[28].

Een juiste selectie van PRO-meetinstrumenten is ook belangrijk voor de vergelijkbaarheid van resultaten van verschillende studies. In veel studies wordt gekozen voor een combinatie van ziektespecifieke en generieke vragenlijsten, waardoor zowel vergelijkingen binnen als tussen patiënten met verschillende aandoeningen mogelijk zijn. In de studie die is beschreven in **Hoofdstuk 4** werd bijvoorbeeld een uitgebreide set instrumenten gebruikt om HRQoL te meten, bestaande uit de hersentumor-specifieke EORTC QLQ-BN20 en de kanker-specifieke EORTC QLQ-C30 vragenlijsten. Daarnaast werden vragenlijsten gericht op specifieke aspecten van de gezondheid meegenomen, zoals de HADS voor stemming (i.e. angst en depressie). In **Hoofdstuk 2** werd gebruik gemaakt van een zelf ontwikkelde vragenlijst over de aanwezigheid van prediagnostische symptomen en zorggebruik, omdat er geen geschikte bestaande vragenlijst beschikbaar was. Deze werkwijze maakte het wel moeilijker om de resultaten direct te vergelijken met die van andere studies.
Om de vergelijkbaarheid tussen studies te vergroten, zouden idealiter in alle studies

dezelfde uitkomsten en meetinstrumenten gebruikt moeten worden. Om dit te realiseren heeft de werkgroep *Response Assessment in Neuro-Oncology Patient Reported Outcomes (RANO-PRO*) een zogenaamde '*Core Set*' van uitkomsten vastgesteld, die in alle klinische studies bij hooggradige glioompatiënten moeten worden gemeten[29]. Deze *Core Set* stelt welke domeinen van uitkomsten gemeten zouden moeten worden, maar geeft geen aanbevelingen wat betreft specifieke meetinstrumenten, waardoor er alsnog variatie in de selectie van meetinstrumenten en problemen bij de interpretatie en/of samenvoeging van gegevens uit meerdere studies kan optreden. Er zijn ook voorbeelden van *Core Sets* die gedetailleerdere aanbevelingen geven ten aanzien van het gebruik van specifieke meetinstrumenten, zoals de sets die zijn ontwikkeld door het *International Consortium for Health Outcomes Measurement (ICHOM*) initiatief[30-32]. Voor kanker zijn er momenteel ICHOM sets beschikbaar voor het meten van uitkomsten bij patiënten met colorectale kanker, borstkanker en gevorderde prostaatkanker.
Naast de inhoud van PRO-meetinstrumenten is ook de timing van de follow-up metingen van belang. In tegenstelling tot de *RANO-PRO Core Set* bieden de *Core sets* van het ICHOM-initiatief ook een tijdlijn met aanbevolen tijdstippen voor afname van de meetinstrumenten. Uiteraard moeten bij het vaststellen van de meetmomenten altijd aspecten zoals de aard van de patiëntenpopulatie en de onderzoeksvraag worden meegewogen. Bij het vaststellen van de meetmomenten moet ook gelet worden op het tijdsframe van de te gebruiken instrumenten (bv. of deze vragen betrekking hebben op de dag van invullen, de afgelopen week of maand). Idealiter loopt de planning van follow-upmetingen synchroon met de standaard follow-up momenten in de klinische zorg, zodat de resultaten niet alleen waardevolle gegevens voor onderzoek kunnen opleveren, maar ook bruikbaar zijn in de individuele patiëntenzorg.

Naast standaardisatie van de selectie van de uitkomsten, meetinstrumenten en de timing van metingen is ook standaardisatie van de dataverzameling en de statistische analyses nodig. Naast het verzamelen van de gegevens uit vragenlijsten, dient ook een nauwkeurige registratie van (a) prognostische variabelen plaats te vinden, zoals bijvoorbeeld de tumorgraad of leeftijd (case-mix variabelen), en (b) een systematische registratie van behandelingen. Met behulp van deze informatie kunnen resultaten van vergelijkingen tussen populaties nauwkeuriger geïnterpreteerd worden, omdat met deze variabelen gecorrigeerd kan worden voor case-mix variatie en verschillen in behandeling. Ook de grote verscheidenheid aan analysetechnieken die momenteel worden gebruikt bij de evaluatie van patiënt-gerapporteerde gegevens van glioompatiënten[33] kan mogelijk leiden tot verschillende interpretaties van studieresultaten[34]. Standaardisatie van analysetechnieken met betrekking tot bepaalde onderzoeksdoelstellingen is daarom gerechtvaardigd. Momenteel wordt daarom het SISAQOL-project (*Setting International Standards in Analyzing Patient-Reported Outcomes*

and Quality of Life Endpoints Data) uitgevoerd, dat tot doel heeft om aanbevelingen voor de analyse en interpretatie van PROs in klinisch kankeronderzoek te formuleren[35].
Naast aanbevelingen voor de inhoud, de timing en analyse van patiënt-gerapporteerde metingen binnen de neuro-oncologie, is ook ruimte voor verbetering van de kwaliteit van het rapporteren van de methode, resultaten en interpretatie. Bij het publiceren van studies die gebaseerd zijn op gegevens die routinematig in de dagelijkse praktijk zijn verzameld, is bijvoorbeeld het gebruik van richtlijnen voor het rapporteren van observationele studies, zoals de rapportagerichtlijnen van *The International Society of Quality of Life Research (ISOQOL)*[36] of de STROBE *(STrengthening the Reporting of OBservational studies in Epidemiology*) richtlijnen[37] aan te bevelen.
Ten slotte is het meeste onderzoek bij glioompatiënten gericht op het functioneren en het welzijn van de patiënten zelf. Hoewel het belang hiervan evident is, mag de impact van de aandoening op de naasten van de patiënten niet worden onderschat. Naasten van glioompatiënten worden ook getroffen door de ziekte, hetgeen tot uiting kan komen in een verminderd niveau van HRQoL[38, 39]. Omdat onderzoek op dat gebied relatief schaars is, kan worden aanbevolen om ook de gevolgen van de ziekte en de behandeling op het functioneren en het welzijn van naasten van glioompatiënten grondiger te bestuderen.

Het meten van HRQoL bij glioompatiënten: Implicaties voor de klinische praktijk

Door de HRQoL van een patiënt met vaste regelmaat te monitoren, kunnen behandelaars eventuele veranderingen in de gezondheidstoestand van een patiënt eerder herkennen en daar beter op inspelen[40, 41]. Routinematige monitoring van HRQoL gegevens maakt zorgverleners in het algemeen meer bewust van het belang daarvan en ondersteunt hen om tijdens het consult specifiek díe onderwerpen aan te snijden die op dat moment belangrijk zijn voor de patiënt[24, 42]. Eerder onderzoek liet inderdaad zien dat routinematige monitoring van de HRQoL van kankerpatiënten een gunstige invloed had op de communicatie tussen de arts en de patiënt, en resulteerde in gezondheidswinst voor patiënten met betrekking tot hun algemene kwaliteit van leven[25].
Routinematige monitoring van HRQoL brengt, ondanks de voordelen, ook praktische uitdagingen met zich mee, bijvoorbeeld op het gebied van de manier van gegevensverzameling (papier of elektronisch) en bij- en nascholing van zorgverleners ten aanzien van de interpretatie van de resultaten[43]. Met betrekking tot de afname van vragenlijsten heeft digitale afname de voorkeur, omdat op die manier de schaalscores direct kunnen worden berekend en visueel kunnen worden gepresenteerd, wat de interpretatie vergemakkelijkt. Niettemin gaf in onze studie ongeveer een derde van de patiënten aan de vragenlijst liever op papier te willen ontvangen, vooral om reden van

het gemak[21]. We hebben niet onderzocht of en in hoeverre het ervaren gemak verband hield met specifieke vaardigheden, in het bijzonder bij degenen die de voorkeur gaven aan papier. Het is belangrijk om te onderkennen dat een deel van de patiënten mogelijk niet over de benodigde (computer)vaardigheden beschikt of een visuele of motorische handicap heeft die hen belemmert bij het invullen van digitale vragenlijsten. Om de kwaliteit van zorg voor alle patiënten te kunnen garanderen is het daarom belangrijk om patiënten die extra ondersteuning nodig hebben bij het invullen van vragenlijsten te herkennen en hen de juiste alternatieven of begeleiding aan te bieden.
In de studies in dit proefschrift is niet ingegaan op de vraag of en in hoeverre patiënten zelf toegang zouden willen hebben tot de uitkomsten van de vragenlijsten, om hun gezondheidstoestand in de loop van de tijd zelf te kunnen monitoren. Om dat mogelijk te maken is een systeem nodig waarbij schaal- en samenvattingsscores op lekenniveau worden berekend en gepresenteerd. Ook moeten er duidelijke afkappunten beschikbaar zijn voor situaties waarin extra of eerdere klinische consulten nodig zijn, waarbij hetzij de patiënt zelf of de zorgprofessional wordt gewaarschuwd indien een bepaald aspect meer aandacht verdient[44, 45].

Advance care planning (ACP)

In de loop van de ziekte kan de progressieve cognitieve achteruitgang het vermogen van glioompatiënten om beslissingen over hun behandeling en/of de zorg te nemen ernstig belemmeren[4]. Het is daarom belangrijk om glioompatiënten en hun naasten al vroeg in het ziektetraject bij de besluitvorming over toekomstige (palliatieve) zorg in de laatste fase van hun leven te betrekken[5]. Een manier om dit te bereiken is met *Advance Care Planning (ACP)*[46]. **Deel 3** van dit proefschrift betrof de evaluatie van de proefimplementatie van een ACP-programma bij glioblastoom patiënten in een Nederlandse neuro-oncologische setting. Eerder werd een ziektespecifiek ACP-programma ontwikkeld, waarvan de inhoud en het moment van implementatie in het ziektetraject waren gebaseerd op de uitkomsten van een focusgroep met zorgprofessionals en op semigestructureerde interviews met individuele patiënten met een glioblastoom en hun naasten (van zowel levende als overleden patiënten)[47]. Hoewel de deelnemers aan deze kwalitatieve studie het eens waren over de voorgestelde inhoud van het ACP-programma, was het optimale moment van het aanbieden van een dergelijk programma een punt van discussie. De resultaten gaven aan dat het waarschijnlijk het meest geschikt zou zijn om het programma wel al kort na de diagnose aan te bieden, maar om patiënten en hun naasten te laten beslissen welke onderwerpen met betrekking tot de laatste levensfase zij zouden willen bespreken[47].
De haalbaarheid van het implementeren van een dergelijk ACP-programma én de impact van het programma op verschillende patiënt-gerelateerde en zorg-gerelateerde

uitkomsten werd geëvalueerd in een volgende stap, die is beschreven in **Hoofdstuk 6**. Dit betrof een longitudinale, prospectieve studie waarvoor 20 glioblastoom patiënten en (indien beschikbaar) hun naasten werden gevraagd voor deelname in één neuro-oncologisch centrum. Alle patiënten en hun naasten kregen elk twee ACP-sessies werden aangeboden, die werden gefaciliteerd door een getrainde verpleegkundige. Tijdens de sessies reflecteerden de gespreksleider, de patiënt en/of zijn/haar naasten op de doelen, waarden en overtuigingen van de patiënt, en bespraken ze onderwerpen zoals de gewenste tumor- of ondersteunende behandeling, en de voorkeur voor de plaats van levering van zorg in de eindfase en bij het sterven. De deelnemers werd aangeraden om hun wensen over de gewenste zorg in de laatste fase van hun leven vast te leggen in een zogenaamde *Advance Directive* (AD; wensenformulier), maar dit was niet verplicht. De evaluatie van het ACP-programma bestond uit studiespecifieke vragenlijsten die betrekking hadden de inhoud en de opzet van het ACP-programma, en gevalideerde vragenlijsten die zich richtten op het functioneren en welzijn van zowel patiënten als naasten, de tevredenheid over de verleende zorg en het zorggebruik De metingen vonden elke 3 maanden plaats tot een maximum van 15 maanden.
Uit de evaluatie van het ACP-programma bleek dat de meerderheid van de patiënten en hun naasten de verschillende aspecten van het ACP-programma (zoals de onderwerpen, het aantal sessies, de duur van de sessies, en het functioneren van de gespreksleider), als voldoende beoordeelden, terwijl de algemene kwaliteit door de meeste deelnemers als enigszins goed tot uitstekend werd beoordeeld. Deze resultaten suggereren dat de inhoud en opzet van het huidige beschikbare ACP-programma voldoende is. Vergelijkbaar met de bevindingen in de ontwikkelingsfase[47], liepen de voorkeuren voor het optimale tijdstip van het aanbieden van het ACP-programma nogal uiteen. Hoewel patiënten en naasten in een vroeg stadium nog niet altijd open blijken te staan voor het bespreken van moeilijke onderwerpen (zoals palliatieve sedatie en plaats van zorg in de laatste levensfase en overlijden), gaven zorgverleners aan dat het toch belangrijk is om gesprekken hierover zo vroeg mogelijk aan te gaan vooral vanwege de mogelijk snelle achteruitgang in cognitief functioneren van glioblastoompatiënten, waardoor de besluitvorming mogelijk wordt belemmerd[2-4]. Hoewel patiënten in de studie significant meer functionele beperkingen en symptomen ervaarden dan de algemene bevolking[48], bleef hun niveau van HRQoL over het algemeen relatief stabiel tijdens de follow-up. Relatief veel patiënten rapporteerden angst en/of depressie, en hun aantal nam toe in de loop van de tijd. Over het algemeen waren de patiënten tevreden over de verleende zorg, terwijl de naasten minder tevreden waren, vooral over de informatie die werd gegeven over de beschikbare (aanvullende) zorg. Wat de naasten betreft, vonden we dat zij significant lagere scores rapporteerden op de fysieke en mentale domeinen van HRQoL dan de algemene bevolking, en een groot deel van de naasten rapporteerden angst en/of depressie

tijdens het ziekteverloop. Deze resultaten benadrukken de impact van de ziekte op het functioneren en het welzijn van de naasten. Desondanks was hun behoefte aan ondersteuning relatief laag gedurende het ziektebeloop, en hun gevoel van controle over de situatie relatief hoog.

Deze studie draagt bij aan het groeiende inzicht in de effectiviteit van interventies op het gebied van palliatieve zorg in een vroeg stadium[49, 50]. De effectiviteit van ACP, in termen van meer tevredenheid bij de familie en minder stress, angst en depressie bij nabestaanden, is eerder aangetoond door middel van gerandomiseerde klinische studies (RCT's) bij onder andere oudere patiënten[51] en bij patiënten met eindstadium congestief hartfalen of nierziekte[52]. Tot voor kort was onderzoek naar het effect van ACP bij patiënten met hersentumoren schaars. Een eerder gepubliceerde studie suggereerde dat vroegtijdige en gestructureerde ACP de ervaren HROoL en symptomen van hersentumorpatiënten zou kunnen verbeteren[53], hoewel dit niet direct werd onderzocht. Andere studies, specifiek bij glioompatiënten, vonden dat tijdige bespreking van de mogelijkheden van zorg in de laatste levensfase resulteerde in meer patiënten die uiteindelijk op de plaats van hun voorkeur stierven en een positief effect had op gevoelens van waardig sterven[54, 55]. In onze studie vonden we dat het percentage patiënten dat gevoelens van angst of depressie had toenam tussen de eerste en de laatste beschikbare beoordeling, terwijl dit niet het geval was voor de naasten. Er zijn echter veel factoren die, afgezien van de ACP-interventie, gevoelens van angst en depressie kunnen beïnvloeden, waaronder persoonlijke en omgevingsfactoren. Het belangrijkste is echter dat de niet-gerandomiseerde studieopzet, in combinatie met de kleine steekproef, het trekken van conclusies over de precieze impact van het ACP-programma op glioblastoom patiënten en hun naasten eigenlijk niet toelaat.

Advance Care Planning: Implicaties voor toekomstig onderzoek

De relatief positieve resultaten van de longitudinale studie naar de implementatie van een ziektespecifiek ACP-programma voor glioblastoom patiënten **(Hoofdstuk 6)** rechtvaardigt de noodzaak van een grotere, gecontroleerde studie, met betrokkenheid van meerdere centra, zo mogelijk uit meerdere landen. Door een grootschaligere en internationale opzet kan rekening worden gehouden met mogelijke verschillen in cultuur en godsdienst, hetgeen factoren zijn die de acceptatie en effectiviteit van een dergelijk programma kunnen beïnvloeden[56-58]. Er moet ook aandacht worden besteed aan de juiste selectie van patiënten en naasten die belangstelling hebben voor en baat kunnen hebben bij de interventie. In onze studie zag ongeveer een derde van de voor deelname in aanmerking komende patiënten van deelname aan het programma af, van wie de meesten aangaven dat een dergelijk programma emotioneel te moeilijk was of dat het onderwerp levenseinde voor hen nog niet relevant was.

Om de kwaliteit van de interventie te waarborgen, moeten de gespreksleiders een passende opleiding krijgen en moeten hun werkwijzen regelmatig worden geëvalueerd. Wat betreft de meting van potentiële uitkomsten, is de vraag of HRQoL of angst en depressie de meest geschikte primaire uitkomsten zijn voor een interventie zoals ACP. Mogelijk is het passender om tevredenheid te meten over díe specifieke aspecten van de zorgverlening waarop het ACP-programma zich richt. Het kan daarbij bijvoorbeeld gaan om de ervaren autonomie, betrokkenheid bij klinische beslissingen en het gevoel controle of regie te hebben over de zorgverlening[49, 60]. Voordat het onderzoek wordt voortgezet lijkt daarom een verdere verkenning van de optimale studieopzet, timing en keuze van primaire uitkomstmaten aan te bevelen.

Advance Care Planning: Implicaties voor de klinische praktijk

De literatuur en de resultaten van de studies die zijn uitgevoerd om de uitvoering van een ziektespecifiek ACP-programma bij glioblastoom-patiënten te ontwikkelen en te evalueren[47], onderstrepen het belang van passende zorg en ondersteuning in de laatste levensfase. Eigenlijk moeten de zorg en ondersteuning voor glioblastoompatiënten vanaf het moment van de diagnose tot en met het sterven worden gezien als een continuüm, met verschillen in de nadruk op specifieke aspecten tijdens het gehele traject. De uitvoering van de longitudinale studie, die in de dagelijkse praktijk werd ingebed, maakte ook duidelijk dat er verschillende aspecten zijn waarmee rekening moet worden gehouden. Omdat de meeste patiënten die afzagen van deelname aan het programma aangaven dat de reden hiervan was dat zij het emotioneel te belastend vonden, en op grond van het eerdere onderzoek naar ACP bij glioblastoom[47], konden patiënten en naasten die wel deelnamen zelf beslissen welke onderwerpen ze wilden bespreken. Niettemin kregen patiënten wel een overzicht van alle mogelijke onderwerpen die in de toekomst voor hen relevant zouden kunnen worden (bv. palliatieve sedatie), hetgeen patiënten er mogelijk toe aanzette om toch al over deze onderwerpen na te denken. Wat de timing van het programma betreft, lijkt het het meest passend om het programma aan te bieden na de chemoradiatie, en voor degenen die op dat moment geen belangstelling hebben, de beschikbaarheid van het programma in een later stadium opnieuw te noemen, bijvoorbeeld na 3 en 6 adjuvante cycli chemotherapie.

Het is ook belangrijk te beseffen dat de naasten een belangrijke rol spelen in het ziekteproces, en dat zij andere vragen en zorgen kunnen hebben dan de patiënt, die ook aandacht behoeven. De zorgprofessionals die het ACP-programma verzorgen moeten daarom goed voorbereid zijn op de vragen van naasten en hen zo veel mogelijk bij het proces betrekken. Naast het verstrekken van informatie en concrete adviezen[61, 62], zijn er verschillende interventies specifiek voor naasten beschikbaar, gericht op het overbrengen van kennis[63], het vergroten van sociale steun[64] of het gevoel van regie

door middel van een psychologische interventie[65].
Vanuit organisatorisch oogpunt is het belangrijk om rekening te houden met de menskracht en middelen, met name de tijd, die nodig zijn om de interventie aan te kunnen bieden. Allereerst moeten de gespreksleiders geschoold worden. Daarnaast moeten patiënten en naasten die mogelijk baat kunnen hebben van de interventie worden geselecteerd, er moet contact met hen worden opgenomen en zij moeten voldoende worden geïnformeerd. Vervolgens moet de interventie daadwerkelijk worden aangeboden, waarbij gespreksleiders ook beschikbaar moeten zijn voor vragen en problemen tussen de geplande sessies in. Bovendien moet het programma aansluiten bij de zorg die reeds wordt verleend door zorgprofessionals die betrokken zijn bij palliatieve zorg in de eerstelijnsgezondheidszorg, zoals de huisarts, en professionals die werkzaam zijn in de thuiszorg, verpleeghuizen of hospices.

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CURRICULUM VITAE

Marthe Peeters was born on April 21nd, 1994 in Leiden and raised in Voorschoten. After graduating from the Stedelijk Gymnasium in Leiden, she studied Medicine at Leiden University.
After obtaining her Bachelor's degree in Medicine, she started a research internship at the department of Neurology in the Leiden University Medical Center in September 2015 under supervision of prof.dr. Martin J.B. Taphoorn and dr. Linda Dirven. The aim of this research project concerned prediagnostic symptoms in glioma patients.
During her clinical internships, from May 2016- April 2018 (coschappen), she continued her research at the department of Neuro-oncology. From 2018 to 2020, she worked full-time as PhD student and the results of her research internship and her PhD project are described in this thesis.

In August 2020, she continued her study Medicine and obtained her Master's degree on February 26th, 2021. Since then, she worked as a physician not in training (ANIOS) at the departments of Urology at Alrijne Hospital in Leiderdorp and LUMC.

Marthe lives with her partner Peter van Dam in Voorhout.

LIST OF PUBLICATIONS

Fritz L, Peeters MCM, Zwinkels H, Koekkoek JAF, Reijneveld JC, Vos MJ, et al. Advance care planning (ACP) in glioblastoma patients: Evaluation of a disease-specific ACP program and impact on outcomes. Neurooncol Pract. 2022;npac050.

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