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Measuring symptons and functioning in glioma patients

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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

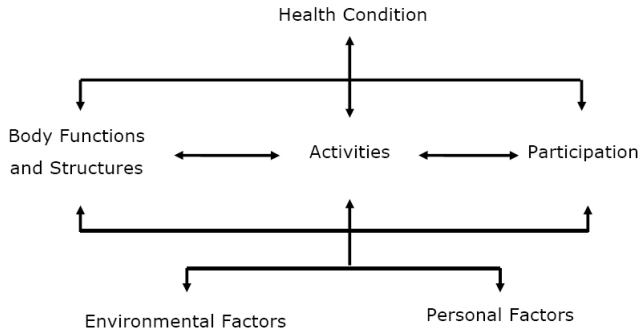

Figure 1. Representation of the model of disability according to the World Health Organization

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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