Neurocognitive functioning and health-related quality of life in patients with brain tumors: impact of tumor- and treatment-related factors

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Part I

Introduction

1

General introduction and outline

Introduction

Epidemiology and classification of brain tumors

Brain tumors can be classified as either primary, such as gliomas which originate from the glial cells in the brain, or as secondary, in which case systemic tumors (mainly from lung, melanoma, renal cell, breast, and colorectal cancer) metastasize to the brain.

In the Netherlands, gliomas have an incidence of 5.9 per 100,000 persons,[1] resulting in approximately 1000 new cases per year. Traditionally gliomas were divided into either of four grades, primarily based on their histopathology (World Health Organization (WHO) 2007 classification of gliomas). Grade I and II gliomas are classified as low-grade glioma, and grade III (anaplastic glioma) and grade IV (glioblastoma multiforme) as high-grade glioma.[2] Standard treatment for grade I glioma, which are often pediatric tumors, consists of surgery. Although most of these patients are cured after treatment, a substantial number suffers from late effects such as depression and social difficulties, and performs on an intelligence level below average[3]. Grade II gliomas are often slowly-growing but infiltrate the surrounding brain tissue. Despite treatment with (early) surgery, increasingly followed by adjuvant radiotherapy and/or chemotherapy, these tumors do recur and can eventually evolve into grade III or IV glioma. These high-grade gliomas, with glioblastoma as the most prominent and aggressive subtype, are rapidly growing tumors infiltrating the surrounding brain tissue. Treatment for grade III glioma consists of surgery (often) followed by radiotherapy and chemotherapy.[4] For glioblastoma multiforme, standard treatment is surgery, followed by radiotherapy with concomitant and six cycles of adjuvant chemotherapy[5]. In 2016 the WHO classification of gliomas has been updated by the additional inclusion of molecular genetics, which resulted in major adjustments in classification and, consequently, treatment of specific glioma patients[6,7]. For patient groups presented in this thesis, the WHO 2007 classification was used, categorizing patients based on tumor histopathology.

Median overall survival for grade II glioma ranges from 4.7 to 9.8 years,[8] for anaplastic gliomas from 19 to 42 months,[9,10] and for glioblastoma patients from only 9 to 15 months.[1,5]

With an incidence of cancer ranging between 306.3 to 429.9 per 100,000 persons, and 9-45% of cancer patients developing brain metastases, secondary brain tumors far outnumber gliomas.[11-13] In the past decades, the incidence of brain metastases has increased, possibly due to prolonged survival as result of better control of the primary tumor and better neuro-imaging techniques to detect brain metastases.[12,14,15] Treatment for brain metastases is in most cases palliative only and treatment choice depends on the age and condition of the patient, as well as the primary tumor type. Radiotherapy has an important role in treatment and encompasses both whole-brain radiotherapy (WBRT) and stereotactic radiotherapy (SRT). Currently, SRT is the

preferred treatment for patients with one to three brain metastases, while WBRT is often applied in case of more than three metastases.[16] At the moment, several trials are under development to evaluate SRT in patients with more than four brain metastases,[17] since WBRT is assumed to be more harmful in terms of risk of late neurotoxicity than focal treatment.[18,19] Surgery can equally be applied in case of a solitary brain metastasis, depending on location and mass effect. Recent developments resulted in a variety of new treatment options for the primary tumor, including treatments based on the molecular genetics of a tumor and targeted therapies. These treatments may also have an effect on brain metastases. Indeed, immunotherapy and targeted tumor treatment have found to be effective for brain metastases, with metastases from melanoma being a prominent example.[20,21]

The median overall survival of patients with brain metastases ranges considerably, from 2.6 to 15 months,[22,23] with long term survivors becoming more frequent due to new systemic cancer treatments.

As most patients with glioma or brain metastases cannot be cured, treatment not only aims at prolonging survival, but also at maintaining or improving patients' functioning and well-being. Indeed, prolonged survival may not be meaningful if patients suffer from many problems or limitations in daily life functioning. A shorter survival duration without compromised functioning and well-being may in that case be preferred. In contrast to other cancer patients, brain tumor patients are characterized by impairments in neurocognitive functioning, which may be caused by both the tumor and its treatment. Impaired neurocognitive functioning may have a negative impact on the performance of activities in daily life as well as health-related quality of life (HRQoL) and should therefore be a key aspect in the treatment of brain tumor patients. This thesis focuses on the impact of having a brain tumor and receiving specific anti-tumor treatment on neurocognitive functioning and HRQoL.

The concepts of neurocognitive functioning and health-related quality of life

Neurocognitive functioning (NCF) comprises all aspects of human thinking, including reasoning and planning, attention, memory, speed of information processing, language, visuospatial abilities, and executive functions. These functions may be closely related to the integrity of specific brain areas (e.g. arcuate fasciculus involved in language) or merely to cortical and subcortical connections in the brain, resulting in networks subserving specific functions such as attention. Neurocognitive impairment is a deterioration of one or several cognitive functions, which is particularly seen after changes within the brain due to neurological illnesses or brain injury.

Quality of life is defined by the WHO as 'a person's perception of their physical, cognitive and affective state, as well as their perception of their interpersonal

relationships and social roles'.[24] Quality of life is thus a multi-dimensional concept that is self-reported. In brain tumor research both the terms 'quality of life' and 'health-related quality of life' (HRQoL) are used interchangeably. In the latter however, quality of life is related to the impact of illness or health specifically. In this thesis we will therefore use the term HRQoL.

The definition of the WHO on quality of life includes the persons' perception of their cognitive state. This is reflected in the inclusion of cognitive complaints in many HRQoL questionnaires. Although the concordance between cognitive complaints and objectively measured NCF is only moderate,[25,26] previous research has shown that NCF is associated with various functioning scales of HRQoL questionnaires, including role limitations and mental health.[27,28] Neurocognitive impairments also impact HRQoL in more indirect ways by negatively influencing return to work, interpersonal relationships and leisure activities.[29]

Assessment of NCF and HRQoL

NCF can be objectively assessed with a variety of tests, ranging from short cognitive screening instruments to comprehensive standardized test batteries specifically designed to assess neurocognitive function in various domains. The patient's perception on how he or she is functioning can be assessed with subjective measures such as questionnaires.

In many randomized controlled trials (RCTs), NCF has been included as a secondary outcome, for which often screening instruments such as the Mini Mental State Examination (MMSE) were used, as they are short and simple in terms of administration and limited in costs. However, these instruments are not sensitive for detecting more subtle neurocognitive impairment in brain tumor patients, nor for detecting (subtle) changes over time.[30,31] To obtain more reliable and informative results on NCF, a test battery should cover all relevant cognitive functions, should be repeatable and sensitive to change, should have standardized administration procedures, published normative data should be available, and the maximum administration time ideally should not exceed 40 minutes.[32,33] To optimize NCF evaluation in clinical trials in brain tumor patients, suggestions have been made for implementing a standardized test protocol meeting most of the above criteria, for example by the response assessment in neuro oncology (RANO) group,[34,35] and others.[36,37] This test protocol assesses verbal memory, processing speed and aspects of executive functioning, and is included in recent RCTs of the EORTC and Radiation Therapy Oncology Group (RTOG), among others.[32] However, this protocol does not include other relevant neurocognitive functions.[38,39] As NCF is the primary outcome in the studies in this thesis, we made use of a comprehensive test battery comparable to earlier studies, covering all relevant neurocognitive functions (such as memory,

executive functioning, attention and information processing speed) for brain tumor patients.[26,40,41]

Assessment of HRQoL in brain tumor research is typically done with validated self-report questionnaires, such as the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire C30 (EORTC QLQ-C30)[42,43] or the Functional Assessment of Cancer Therapy (FACT),[44] often complemented by brain tumor specific questionnaires such as the EORTC Brain Module (QLQ-BN20)[43] or FACT-Brain. In the current studies we have used the EORTC QLQ-C30 and QLQ-BN20, which both have good psychometric properties.[45]

NCF and HRQoL in brain tumor patients

Patients with brain tumors may experience both disease-specific and more general symptoms. Indeed, brain tumor patients often experience neurological symptoms and deficits, such as hemiparesis, sensory deficits or aphasia, epilepsy,[46,47] changes in personality[48] and neurocognitive impairments.[49,50] In addition, fatigue[51] and depression[52] are frequently reported.

Neurocognitive impairments can be the first presenting sign of a brain tumor,[49,53] but may also develop later in the disease trajectory, i.e. at disease progression.[54] In rapidly growing high-grade gliomas, neurocognitive impairments might initially be overshadowed by more pronounced neurological deficits.[26] Mainly more widespread neurocognitive functions such as memory, attention, executive functioning and processing speed are hampered in brain tumor patients.[40,55]

Although it has been shown that neurocognitive impairment is associated with the presence of a brain tumor,[56,57] it is still not clear how brain tumors exactly affect discrete cognitive functions, and what aspects of the tumor (e.g. location or size, speed of growth) have a predominant impact on NCF. Similarly, it is still unclear what the precise impact is of anti-tumor treatment, such as resection, radiotherapy and chemotherapy, on NCF. Several studies have found that treatment with (various doses of) radiotherapy with or without chemotherapy resulted in impaired memory and attention in glioma patients.[41,55,58,59] However, the impact of other treatments (such as SRT or chemotherapy) on short- and long-term discrete neurocognitive functions and HRQoL are less well known.[60,61] Finally, also epilepsy and use of supportive treatment such as anti-epileptic drugs and corticosteroids can negatively influence NCF.[62]

As NCF is essential for human functioning, neurocognitive dysfunction has a profound impact on daily functioning and HRQoL of both brain tumor patients and their proxies (i.e. relatives or close friends of the patient).[55,63] Since the treatment of gliomas and brain metastases is in most cases not curative but aimed at prolonging life, maintaining patients' functioning and well-being during the survival time is essential for patients and their proxies. This holds true for patients with relatively

short survival times, such as glioblastoma and brain metastatic patients, but also for patients with longer survival, because patients with low-grade glioma are often relatively young and late effects of treatment may adversely impact their functioning over time. For clinical decision making, in which the potential benefit of treatment in terms of prolonged survival should be weighed against possible negative impact of treatment on NCF and HRQoL, insight in the specific roles of tumor- and treatment related factors is essential. Also, counselling patients regarding (neurocognitive) impairments or a negative impact on HRQoL, and offering patients adequate (cognitive) rehabilitation for their impairments, can be optimized when knowing the patient's NCF and HRQoL characteristics.

Aim and outline of this thesis

The primary aim of this thesis is to improve knowledge about the frequency, type and nature of (impaired) NCF in both primary and secondary brain tumor patients during the entire disease course. With this information, treatments can be optimized and personalized. A secondary aim is to shed more light on the impact of a brain tumor and its treatments on short- and long-term HRQoL of brain tumor patients. In addition, a tertiary aim is to evaluate the impact of neurocognitive outcomes on clinical decision making.

In part II, the short- and long-term effects of the tumor and anti-tumor treatment on NCF and HRQoL are explored, thereby providing information about the different and unique impact of the tumor and its treatment on these functions. NCF is measured with tests for verbal and working memory, attention, executive functioning, psychomotor function, information processing speed and visuoconstructive abilities, and HRQoL with the EORTC QLQ-C30 and BN20 questionnaires. Chapter 2 addresses the effects of the tumor itself and of resective surgery on NCF in patients with high-grade glioma, by evaluating NCF preceding and after surgery, but before subsequent anti-tumor treatment. In chapter 3, the impact of SRT, a focal form of radiation, on short-term NCF and HRQoL in patients with one to three brain metastases is investigated. These patients are tested prior to SRT, and three and six months after SRT. Also MRI scanning is included to correlate changes in metastatic disease to NCF and HRQoL. While NCF and HRQoL are assessed at *group* level in chapter 3, these are investigated on the *individual patient* level in chapter 4. In this study, changes in all neurocognitive domains and HRQoL scales for each individual patient are combined. Chapter 5 focusses on the long-term (> 8 years) effects of radiotherapy and chemotherapy on HRQoL and NCF in anaplastic glioma patients.

In part III, the association between NCF and tumor location (chapter 6) and

between NCF and resection cavity location (i.e. the space that is left after the surgical removal of a tumor; chapter 7) in low- and high-grade glioma patients are described. To study this association, we did use tumor localization maps, to obtain more detailed information about the relationship between discrete neurocognitive functions and tumor- or resection locations.

Part IV consists of a systematic review on the level of reporting of neurocognitive outcomes in randomized controlled trials on brain tumor patients. With adequate reporting of neurocognitive data, the outcomes of these studies can contribute in determining the net clinical benefit of a treatment, meaning that the benefits of a treatment in terms of improved survival are weighed against possible side-effects of the treatment on a patients' functioning. This information may be useful for clinical decision making.

Finally, in part V a summary and discussion of the main findings is provided, together with methodological challenges encountered and future directions for research.

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