Long-Term Neurocognitive Outcomes in Post-Radiotherapy Low-Grade Glioma Patients

Merethe Blandhol
S3472051

University College Groningen

Bachelor's Thesis

Word count: 9894

Abstract

Low-grade glioma (LGG) is a type of primary brain tumor that usually affects relatively young and otherwise healthy patients. The tumor is often slow-progressing, and the majority of patients survive for over 5 years after initial diagnosis. However, there is no cure for LGGs and treatment primarily focuses on extending progression-free survival. One of the standard treatment modalities for managing LGGs is the use of radiotherapy (RT). However, LGG patients often struggle with cognitive decline following RT and other treatment modalities, which impacts their quality of life post-treatment. Investigating different tumor and treatment characteristics that influence neurocognitive outcomes in this patient group is therefore an important part in ensuring that an increased survival does not compromise quality of life. This thesis looks at three main characteristics in a LGG patient group (n=17), namely the influence of radiotherapy treatment volume (CTV), tumor location (left vs. right hemisphere), and time interval after radiotherapy on neurocognitive function. Additionally, overall cognitive functioning of the LGG group is examined through a comparison to a group of healthy controls. Correlational analysis revealed that overall the LGG patient group performed significantly worse ($Z > -2.04$, $p < 0.05$) on 9 out of 11 neuropsychological assessments compared to a group of healthy controls (n=18), with attention and processing speed, immediate and delayed recall, visuoconstructive abilities, and language being affected. CTV volume negatively correlated ($r_s = -0.527$, $p = 0.03$) with performance on the Rey Complex Figure Test (CFT), and interval between RT treatment and neuropsychological assessment was negatively correlated ($r_s = -0.584$, $p = 0.014$) with performance on phonetic fluency scores. Patients with left-sided tumors performed significantly worse on the Rey Auditory Verbal Learning Task immediate recall trial ($Z = -2.198$, $p = 0.028$), and on semantic fluency measures for trial 1 ($Z = -2.204$, $p = 0.028$) and trial 2 ($Z = -2.110$, $p = 0.035$) compared to patients with right-sided tumors. This exploratory study suggests that there are significant deficits in neurocognitive functioning in LGG patients, and that attention and processing speed, immediate and delayed recall, visuoconstructive abilities, and language are functions that may be influenced by treatment and tumor factors. With more extensive research this could prove valuable information to guide patient follow-up, preservation of function, and to improve patient quality of life.

Acknowledgements

A sincere thank you to Drs. Hiske van der Weide and Sandra Rakers for all the guidance, wisdom and support throughout this process.

To all the people at the Radiotherapy and Neuropsychology departments at the UMCG who made my participation in this research possible, thank you for welcoming me with open arms.

Lastly, thank you Dr. Roland Chiu for making my participation in this project possible.

Table of Contents

General introduction

Low-grade glioma (LGG) is a type of slow-progressing brain tumor that has a comparably long average survival period after initial diagnosis (Oberheim Bush & Chang, 2016). Despite its relatively slow progression, the tumor is not curable and eventually leads to malignant development and death (Dixit & Raizer, 2017). Those diagnosed with LGGs are usually young to middle-aged adults who are otherwise in good clinical condition (Klein, 2012). Due to the relatively young age of patients, and the slow-progression of the tumor, it is important for treatment plans to balance efforts to increase lifespan with efforts to preserve quality of life for the patient.

Treatment options for LGG patients include surgical intervention, radiotherapy, and chemotherapy, which are often given in combination. Radiotherapy is one of the treatment modalities that is important in the management of tumor progression. However, at what point during the disease course radiotherapy is most beneficial is uncertain, since administration of radiotherapy has shown to cause adverse effects on neurocognitive functioning (NCF) of the patient (Taphoorn & Klein, 2004). Neurocognitive decline in LGG patients is not limited to side-effects of radiotherapy, but can also be caused by the tumor itself, epilepsy, chemotherapy, or surgical intervention (Klein, 2012). Investigations into how treatment options like radiotherapy affect cognitive function could therefore be important in order to establish risk-benefit calculations and possible areas of therapeutic improvement. It can also be valuable when implementing new treatment techniques like proton-based radiotherapy, which targets the treatment in such a way that a larger portion of healthy brain tissue is spared from radiation.

A decrease in NCF is not only one of the most relevant adverse effects of radiotherapy but is also associated with a decreased health-related quality of life (HRQOL) (Taphoorn & Klein, 2004). In some cases, patients are unable to live independently due to post-treatment decline, and some patients experience severe mental or physical fatigue (Struik et al., 2009). Often, it is measures of overall survival, progress-free survival, and objective response to treatment as measured by MRI and CT scans that are in focus when evaluating treatment options (Taphoorn & Klein, 2004). Consequently, a consideration for the clinical presentation of neurocognitive deficits and HRQOL of the patient is often lacking. Research focusing on how radiotherapy treatment factors influence NCF and HRQOL is therefore needed to holistically develop optimal future treatments.

This thesis is based on a collaborative cross-sectional research project with the Radiotherapy and Neuropsychology departments at the University Medical Center Groningen (UMCG). The data used was collected from existing patients who had been previously treated for low-grade gliomas and who, at the time of the study, had a stable non-progressing tumor. The project also includes extensive radiological imaging, however, this thesis will focus only on neurocognitive outcomes with regards to general tumor and radiotherapy characteristics. As a pilot study, the project aims to investigate correlations between neurocognitive function post-treatment, neurophysiological characteristics, radiotherapeutic factors, and tumor characteristics. With future research, this investigation might provide insight into various treatment factors that influence long-term outcomes in diffuse LGG patient groups.

Background/Literature Review

Low-Grade Gliomas

Glioma is a type of primary brain tumor that arises from mutations in different neuroglial cells including oligodendrocytes, astrocytes, and microglial cells (Purves et al., 2001). These supporting cells provide several vital functions such as maintaining the ionic milieu of nerve cells, modulating synaptic uptake, and aiding in neuronal development and recovery (Purves et al., 2001). Different tumor types, stemming from different glial cells, have different prognosis and malignancy grades. Low-grade gliomas (LGGs) are gliomas graded as either grade I or grade II on the World Health Organization (WHO) scale for classification of brain tumors (Forst et al., 2014) and is the least malignant group of tumors. The grade II gliomas involve different types, such as astrocytomas, oligodendrogliomas, and oligo-astrocytomas or mixed gliomas (Pan & Prados, 2003). This thesis focuses specifically on diffuse LGGs, which includes astrocytomas and oligodendrogliomas grade II.

Epidemiology

The overall incidence of gliomas in the Netherlands is estimated to be around 6.5 cases per 100,000 person-years for men, and approximately 4.4 in women (van der Sanden, Schouten, van Dijck, van Andel & Coebergh, 1998). Diffuse LGGs are relatively rare and account for around 15% of all gliomas (Bauchet, 2017) and approximately 5% of all primary brain tumors (Sepúlveda-Sánchez et al., 2018). The tumor type often presents in relatively young and otherwise healthy patients (Rasmussen et al., 2017), with peak incidence occurring between 35 and 44 years (Dixit & Raizer, 2017). Incidence of diffuse LGGs varies across different tumor histologic types and various patient characteristics but is estimated to be around 1/100,000 persons per year (Bauchet, 2017).

Histology

One molecular feature found in diffuse LGG is mutations of the isocitrate dehydrogenase (IDH) enzyme 1 and 2, and it is thought that these mutations initiate gliomagenesis and may be of prognostic significance (Cohen, Holmen & Colman, 2013). Further, the 1p/19q co-deletion is another molecular feature that is required for the diagnosis of oligodendrogliomas (Di Muzio & Saber, 2020), and refers to complete deletion of the short arm of chromosome 1, along with the deletion of the long arm on chromosome 19 (Kim et al., 2019). The presence of this genetic deletion (Kinjo, Hirato & Nakazato, 2008) has shown to indicate an improved prognosis and better response to treatment in some patient groups (Jenkins et al., 2006).

Symptomatology

Low-grade gliomas most often present with seizures, but other symptoms can include headaches, cognitive or behavioral changes, and focal neurological deficits (Klein, 2012). These symptoms are often caused by increased intracranial pressure or invasion of the tumor into functional tissue (Forst et al., 2014). In 70-90% of patients, onset of seizure activity is the primary symptom that leads to an initial diagnosis (Smits, 2019) and anti-epileptic drugs are often administered as a part of overall treatment to control seizure activity. Due to the slow-progressing nature of the tumor, functional disruption is often not seen at the initial onset of the disease, as cortical plasticity allows for some functional reorganization in the brain (Smits, 2019). Some cases of LGGs, known as incidental asymptomatic LGGs, present without

symptoms and are only discovered during screening procedures for other complaints (Opoku-Darko et al., 2017).

Prognosis

Despite the relatively slow progression of LGG tumors, treatment is often difficult due to the diffuse infiltration into adjacent brain tissue. The general outcome of LGGs is malignant transformation of the tumor to a high-grade glioma and consequent death (Dixit & Raizer, 2017). Estimated median survival rates are around 13 years with aggressive treatment (Oberheim Bush & Chang, 2016) and 5-year overall survival rates are between 58% and 72% in randomized studies (Smits, 2019). Patient outcome is often predicted using molecular tumor markers, but non-pathological prognostic factors also include tumor size and the extent of surgical resection. Mutated IDH enzymes, co-deletion of the 1p/19q chromosome, and minimal neurocognitive deficits at diagnosis are all factors that correlate with a better prognosis (Smits, 2019).

Standard of Care

Standard of care for LGG patients involves an initial surgery with the aim of obtaining a histological diagnosis from a biopsy and, if possible, maximal safe resection (Sepúlveda-Sánchez et al., 2018). A gross-total resection is not always feasible due to the diffuse infiltration of the tumor and its frequent location in functional tissue (Jooma, Waqas & Khan, 2019). Initial surgical resection is often considered beneficial for increasing overall survival and delaying degeneration compared to observation (Duffau, 2014). Radiotherapy (RT) is also part of the standard management for LGGs and is used to minimize tumor progression, though there is controversy around the optimal timing of administration and radiation dose (Van den Bent et al., 2005). Chemotherapy is also recommended as a supplementary post-surgical treatment, with specifically Procarbazine, Lomustine, and Vincristine (PCV) showing improved overall survival compared to only RT treatment (Buckner et al., 2016).

Radiotherapy

Which combination of treatment approaches are used and their exact timings depend on several factors such as patient age, performance status, and location and type of tumor (Klein, 2012). For young, relatively asymptomatic patients, a more conservative approach using observation might be favored over aggressive treatment (Klein, 2012). The optimal treatment methods for overall survival and progression-free survival has been a topic of controversy in the management of LGGs (Pan & Prados, 2003). Radiotherapy is one of the treatment modalities that has been in focus, with questions regarding risks associated with radiation toxicity, optimal radiation dose, and the timing of treatment being central (Postma et al., 2002).

Modern photon-based radiotherapy is widely used in clinical practice and delivers a relatively precise radiation dose to the tumor (Levin et al., 2005). However, healthy brain tissue surrounding the tumor is also exposed to radiation, which poses a risk for radiation-induced damage and the development of second malignancies in these areas (Levin et al., 2005). Radiation doses are measured in Gray (Gy) and are normally between 50 and 54 Gy for the management of LGGs (Oberheim Bush & Chang, 2016). In randomized trials with LGG patients, those who received radiotherapy directly after surgery had an increase in progression-free survival with 2 years compared to the observation group, but overall survival was not

significantly increased (Oberheim Bush & Chang, 2016). Studies investigating treatment factors such as the timing of radiotherapy usually lack information on patient neurocognitive functioning and quality of life, and little is known about the influence on these factors. Consequently, treatment teams often struggle to balance an aggressive/early treatment approach that will limit tumor progression and increase overall or progression-free survival, with reduced neurotoxicity and conservation of neurocognitive function.

Neurocognitive Function in LGG Patients

Neurocognitive functioning (NCF) refers to different cognitive domains, including learning and memory, executive function, attention, language and perceptual-motor function (Buchbinder et al., 2018). Studies of NCF in LGG patients often only look at functioning post-treatment or earliest at the time of diagnosis (Baumfalk et al., 2017). Thus, information on the extent of cognitive decline caused by the tumor itself is limited and is expected to be underestimated (Duffau, 2014). However, research suggests that cognitive impairment occurs in the majority of treatment-naïve glioma patients, though significant deficits are more common in high-grade gliomas (Baumfalk et al., 2017). For example, assessments of patients' verbal working memory performance pre-treatment have shown that there were impairments present from the tumor alone (Duffau, 2014). Deficits in neurocognitive functioning in glioma patients are often subtle, and therefore require sensitive and domain-specific neuropsychological assessments (Baumfalk et al., 2017).

Neurocognitive Function Post-Radiation

Radiation-induced cerebral damage is a side-effect of radiotherapy and is characterized by vascular abnormalities, demyelination, inflammation, gliosis, white matter lesions, and local necrosis (Makale et al., 2016)(Swennen et al., 2004). Further, there is increasing evidence suggesting that radiotherapy induces cognitive decline in patients (Taphoorn & Klein, 2004) and that NCF outcomes should be central measurements for evaluating treatment plans (Klein, 2012). Yet, long-term follow-up studies indicate that LGG patients treated with radiation only show evidence of cognitive decline 12 years post-treatment when compared to non-radiated LGG patients, but that this difference is not seen in earlier comparisons (Douw et al., 2009). This indicates that radiation or other treatment-induced NCF deficits may develop gradually over time.

There is also evidence to support that specific structures, such as the hippocampus, are subject to dose-dependent atrophy following radiation, which could explain consequent deficits in memory (Seibert et al., 2017). Structural changes and damage to the brain following radiation is often assessed using neuroimaging techniques such as magnetic resonance imaging (MRI) scans (Taphoorn et al., 2002). Diffusion-tensor imaging (DTI) is a non-invasive MRI technique used to evaluate the effect of radiotherapy on white matter (Connor et al., 2016) and is a valuable technological advancement in the monitoring of neurophysiological changes. Susceptibility weighted imaging (SWI) is another MRI technique that can be used to detect microvascular damage (Mittal, Wu, Neelavalli & Haacke, 2009). Both these sequences were used in the study outlined in this thesis, along with other techniques.

Risk of radiation-induced brain damage, such as white matter lesions and atrophy, has been shown to increase with whole-brain radiotherapy and with increased age of the patient (Swennen et al., 2004). Long-term follow-up studies have shown that LGG patients who

received radiotherapy showed a progressive decline in their attentional functioning compared to non-radiotherapy LGG patients, and that cognitive dysfunction was associated with radiological abnormalities (Douw et al., 2009). They have also shown worse memory performance in irradiated patient groups, which correlated with leukoencephalopathy (Surma-aho et al., 2001). Though there is evidence supporting the connection between radiation-induced changes in the brain and deficits in cognitive function (Postma et al., 2002), no clear causal link has yet been established. However, there is stable evidence that radiotherapy contributes to neurocognitive deficits post-treatment, and that radiation to functional areas may cause specific deficits at certain radiological doses (Gondi, Hermann, Mehta & Tomé, 2012).

Functional Brain Anatomy

Neuropsychological assessment can be used to objectively measure cognitive functioning without relying on subjective patient self-reports through questionnaires. Cognitive domains that are measured in neuropsychological assessments include, amongst others, executive functions, memory, language processing, and processing speed (Buchbinder et al., 2018). These domains can be associated with different functional regions and networks in the brain. Depending on tumor location and extension, these functional regions and networks are exposed to radiation and are at risk for damage that might result in impairment. Yet, not all functions have distinct locations, and some areas involve multiple functions, making a firm distinction between functional regions difficult (Ogden, 2005). Primary functional areas that directly control a specific function are often defined as “eloquent tissue”, and regarded as prioritized areas to preserve during radiotherapy or surgical intervention (Di Muzio & Deng, 2020). However, some disagree that a harsh distinction between eloquent and non-eloquent tissue can be made and that all tissue has certain functional value (Duffau, 2014).

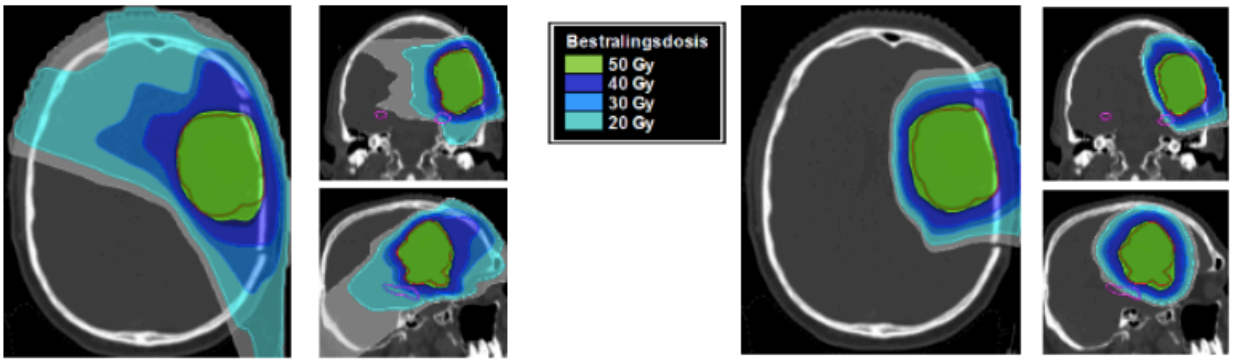
Some specific functional areas that could be relevant in preserving NCF in LGG patients are the prefrontal cortex, the left temporal lobe, and the hippocampus. The prefrontal cortex is involved in a series of executive functions such as planning, organization, and abstract thinking (Ogden, 2005). The hippocampus, located in the medial temporal lobes, is involved in several vital functions such as memory formation (Solomon, 2020). The left temporal lobe is also the site of several language functions such as verbal learning and is the location of Wernicke’s area, which is central for language comprehension (Ogden, 2005). It is also home to the fusiform face area (FFA), which is involved in facial recognition (Ogden, 2005).

Proton-based Radiotherapy

New forms of radiotherapy treatment, such as proton-based therapy (PBT), show promising potential to spare the amount of healthy brain tissue exposed to radiation (Thurin et al., 2018) and preserve neurocognitive function (Pulsifer et al., 2015). This new form of RT is considered standard care for pediatric brain tumor patients, and selected adult patients with low-grade brain tumors in the Netherlands (Durante, 2018). Today, there are three proton therapy centers in the Netherlands, including the Groningen Proton Therapy Center of the University Medical Center Groningen. Compared to traditional photon therapy, PBT has an energy-dependent range in tissue, meaning that it does not radiate beyond a certain point, known as the Bragg peak, and can be adjusted such that surrounding tissue is spared to a larger degree (Jhaveri et al., 2018). This also decreases the number of beams needed compared to photon

therapy, where a combination of different beam angles is needed to ensure enough radiation reaches the tumor (Grau, Durante, Georg, Langendijk & Weber, 2020).

Figure 1. *Illustration of radiation dose distribution in the brain with photon-based RT and proton-based RT (Courtesy of University Medical Centre Groningen)*



Photon-based RT

Proton-based RT

In *figure 1* the difference in dose distribution between PBT and standard photon-based RT is shown and clearly illustrates a more focal distribution of radiation dose in PBT patients. In the diagrams, radiation dose is color-coded, with the green area representing the highest radiation dose (50 Gy) and the red line marking the clinical target volume (CTV). With this increased precision, clinicians may be able to optimize the therapeutic ratio for RT and provide a safer treatment option (Jhaveri et al., 2018). It also has the potential to spare specific brain regions such as the hypothalamic-pituitary (HPA) axis, which could help prevent endocrine dysfunctions (Taku, Gurnell, Burnet & Jena, 2017). In a prospective study, LGG PBT patients showed no overall cognitive decline and quality of life measures remained stable in a 5-year average follow-up (Shih et al., 2015). Similar results have been found in PBT patients in a more recent preliminary 2-year follow-up study (Dutz et al., 2020). A better understanding of the neurotoxicity of radiotherapy treatment and correlations between localized radiation, specific deficits, and radiation doses could help optimize future proton-based radiotherapy.

Quality of Life

A deficit in neurocognitive functioning is shown to negatively affect the health-related quality of life (HRQOL) of both the patient and their close relationships (Baumfalk et al., 2017). HRQOL is defined by the WHO as an individual's perception of their position in life, with emphasis on the context of the individual's culture, expectations, values, and goals (WHO, 2020). Impairments in functioning have been shown to influence social and professional functioning and self-care in patients (Klein, 2012), with some patients struggling to live independently or hold jobs. Low-grade glioma patients also often experience fatigue (Struik et al., 2009), frustration, anxiety and worry about their condition (Mullens et al., 2018), complaints that are often linked with quality of life (Randazzo & Peters, 2016). Since assessment of HRQOL is often time-consuming and troublesome to administer for both patient and doctor, it has not been widely used in clinical practice as an outcome measure (Klein, 2017). However, there is increasing consensus that HRQOL measures should be prioritized in the evaluation of clinical outcomes in LGG patients (Gabel et al., 2019) and that QOL measures can be used to support patient needs over the course of their disease (Mullens et al., 2018).

Research Question

This thesis will primarily concern itself with a general investigation of the long-term neurocognitive outcomes in diffuse low-grade glioma patients. Due to restrictions in time and scope, radiological data will not be considered in detail, but the focus will instead be on assessments of several cognitive domains and their relation to important radiotherapeutic measures. The main research question will therefore be:

What are the long-term neurocognitive outcomes in stable post-treatment radiotherapy low-grade glioma patients and how do outcomes relate to important radiotherapeutic variables?

More specifically, this thesis will discuss three sub-questions that relate to specific neurocognitive functions and clinical characteristics. The first question concerns the overall neurocognitive outcomes of the post-treatment group in comparison to a healthy control group, and whether there are significant overall differences in performances.

1. *Are there significant differences in neurocognitive functioning between the post-treatment group and healthy controls?*

Secondly, the effect of tumor volume, as measured by the clinical target volume (CTV) for radiotherapy, and the interval between the end of radiotherapy and the time of neurocognitive testing will be considered with regards to outcome in overall cognitive processing speed. This is because previous research on the effects of radiation have shown to contribute to white-matter changes (Connor et al., 2016)(Walker et al., 2014), which could indicate that neuronal connections are weakened and overall processing speed declines (Borghesani et al., 2013). The first sub-question will therefore be:

2. *Is there an effect of clinical target volume and/or the interval between radiotherapy and neurocognitive testing on cognitive processing speed?*

The last sub-question will look at lateralization of tumor location, and whether tumors located in either the left or the right hemisphere impact specific performance scores post-treatment. In particular, it is interesting to see whether tumors in the left hemisphere of patients correlates with significant decreases in verbal memory scores, as the left temporal lobe is associated with language functions and verbal memory. In the majority of people, the left hemisphere is dominant for language, though this has shown to vary with individual factors such as left- or right-handedness (Knecht et al., 2000). Consideration of patient dexterity is therefore important when considering this question. Thus, the third sub-question is:

3. *Are there significant differences between tumor location in left vs. right cortical hemispheres on verbal memory scores?*

Hypotheses

The first hypothesis concerns the main research question on the long-term neurocognitive outcomes in post-treatment LGG patients.

1. *Long-term neurocognitive measures in post-treatment LGG patients will show significant deficits in all neuropsychological domains when compared to healthy controls.*

This main hypothesis is based on previous research indicating the presence of neurocognitive deficits normally occurs months or years following radiotherapy treatment. The second hypothesis on the effects of clinical target volume (CTV) and interval between radiotherapy and neuropsychological assessment on overall processing speed is as follows:

2. *Larger clinical target volumes and longer intervals between radiotherapy and neuropsychological assessment are both associated with lower scores on cognitive domains associated with mental processing speed.*

This hypothesis is based on indications from other studies that white matter lesions and overall atrophy are known side-effects of radiotherapy, and have also been linked to the slowing of processing speed (Kuznetsova et al., 2015). With increased CTV volume, more of the brain is exposed to radiation which could result in increased lesions and atrophy. Further, damage might present gradually over time, indicating that an increased interval since radiotherapy would show worse outcomes.

Lastly, the third hypothesis predicts the relationship between tumor lateral location and performance on verbal memory scores:

3. *Patients with tumors located in the left-hemisphere will perform significantly worse on verbal memory and semantic fluency measures compared to patients with right-hemisphere tumors.*

From looking at what is known about functional neuroanatomy, the left hemisphere and particularly the left temporal lobe is associated with functions related to verbal learning, memory, and language comprehension and production. It is therefore hypothesized that the functional location of important regions such as Wernicke's area in the left-hemisphere will cause significant differences between the left- and right-sided patient groups.

Methods and Materials

Study characteristics

The study outlined is a cross-sectional pilot study involving LGG patients that had previously received radiotherapy treatment and had a stable tumor during follow up at the UMCG. Eligible patients were informed of the study and asked to participate. The additional investigational procedure that was required was an extension of the scheduled follow-up MRI where research sequences were used to gather data on white matter integrity and microvascular damage. Following this, patients completed a neuropsychological assessment as well as fatigue and quality of life questionnaires. Primarily, the aim of the study is to investigate correlations between certain clinical factors and neuropsychological outcome post-treatment, and that any results obtained can be used to guide further prospective research in larger populations, including LGG patients currently treated with proton therapy. It is therefore not the aim that the results obtained from this small sample size will be generalizable, but rather that they provide a good basis for future research, understanding of methodology, and help create a research collaboration between the radiotherapy and neuropsychology departments.

Specifically, this thesis will correlate neuropsychological performance scores with lateral tumor location (left vs. right lateral hemisphere), interval between radiotherapy treatment and neurocognitive testing (Interval RT-NCF), and the amount of brain tissue, clinical target volume (CTV), that is the focus for radiotherapy. The neurocognitive functioning of LGG patients will also be compared to that of a healthy control group to establish whether there are significant deficits in functioning overall.

Participants

Patients were recruited for the study via the radiotherapy registration at the University Medical Centre Groningen, and only patients with lower-grade gliomas were asked to participate. Two participants with anaplastic oligodendrogliomas were included in the study as their prognosis was comparable to the other LGGs. Further, only patients with a stable or non-progressing tumor and who had received radiotherapy treatment minimum 1 year prior were eligible for the study. Out of 40 eligible patients asked to participate, 19 gave informed consent to participate, whilst 21 (52.5 %) declined due to the extra MRI time required.

A group of healthy controls was used to compare scores on neuropsychological assessments. This group consisted of 18 participants who were recruited using convenience sampling, with the requirement that they would be matched with the treatment group.

Neuropsychological Assessment

In order to assess neurocognitive functioning in post-treatment groups, a set of neuropsychological tests for different cognitive domains was performed. The following tests were administered to patients in this study to assess neurocognitive function. Some of the neuropsychological tests are Dutch adaptations of other tests, and all tests were performed in Dutch.

Rey's Auditory Verbal Learning Test (RAVLT)

The Rey's Auditory Verbal Learning Test (RAVLT), also known as the 15-word test (WT15), consists of three different levels of recall to measure overall verbal memory imprinting, recall, and recognition (Rey, 1964). First, participants are presented with 5 immediate recall trials where the words are first presented and then participants are asked to repeat the words from the list that they recall. After around 20 minutes, a delayed recall trial is performed where participants are asked to reproduce as many words they can, without the words being presented again. Lastly, participants are presented with a list of 30 words, half of which are words from the original list and the other half are new words. Participants are asked to indicate, with a yes or a no, which words they recognize from the original word list. Scores are calculated based on the amount of correctly recalled or recognized words.

The results of the different trials indicate performance on short-term auditory-visual memory, rate of learning, retention of information, and possible deficits in memory and learning. In previous research, the test has indicated that learning and delayed recall were associated with activity in the medial prefrontal cortex and hippocampus, whereas recognition was associated with the thalamus and caudate nucleus, especially in the left hemisphere (Ferreira Correia & Campagna Osorio, 2013).

Trail Making Task (TMT)

In the trail making task (TMT), patients are assessed in visual attention and task switching in a two-part subtest setup (Arbuthnott & Frank, 2000). The first part (A) is a measure of attention and general processing speed, whilst part (B) measures attention, general processing speed, and mental flexibility. The first part (A) consists of 25 circles distributed on a piece of paper each labeled with a number between 1 and 25. Patients are instructed to connect the circles by drawing a line between them using a pencil, as fast as possible, in ascending order without interruption or lifting the pencil from the paper. Any error made by the patient is verbally corrected by the instructor and the patient must rectify the mistake. The total time it takes to accurately connect all circles is measured.

Part (B) has a similar set-up to part (A), but instead of only consisting of numerical values the circles alternative between numbers and letters. The patients are instructed to connect the circles in ascending order, alternating between ascending numbers and letters (i.e. 1-A-2-B-3-C). The same error-correction protocol is in place and the total time taken is recorded. A combination score (BA) is calculated by subtracting the raw score of A from the raw score of B (B-A). Thus, BA corrects for processing speed and attention and is a more accurate measure of mental flexibility.

Symbol Digit Modalities Test (SDMT)

The SDMT test measures attention and processing speed and involves a simple substitution task, where participants are asked to translate symbols into numbers using a reference key provided (Benedict et al., 2017). This task is given a time limit of 90 seconds, and responses are given orally. With this test, cognitive domains such as attention, perceptual processing speed, motor speed, and visual scanning are assessed. The test is often used in clinical settings to assess cerebral dysfunction associated with brain injury, stroke, brain tumors, and neurological disorders. It is also sensitive to changes in neurological status over time, making it a useful tool to track disease progression and evaluate interventions (Kiely, Butterworth,

Watson & Wooden, 2014). Each individual score is calculated by adding the total number of correctly numbered symbols.

Rey Complex Figure Test (CFT)

The Rey complex figure test (CFT) is used to assess visuospatial constructive abilities (McKinlay, 2011). Participants are first asked to copy a complex geometrical figure (see *figure 2*), usually followed by a delayed reconstruction from memory after a planned distraction. For the study outlined in this thesis, only the first part of the test was performed – namely the copy version. Consequently, visuospatial constructive abilities were measured, but not visual memory. The drawings are assessed on 18 scoring units using a standardized score sheet, where placement and accuracy are judged on a scale from 0 (inaccurately drawn, incorrectly places, omitted, unrecognizable) to 2 (accurately drawn, correctly placed), with the overall score ranging from 0 to 36.

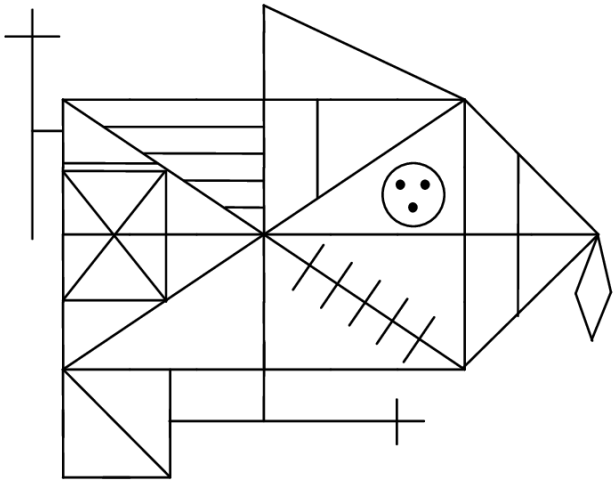


***Figure 2**. Complex geometrical figure used in the Rey Complex Figure Test (Canham, Smith & Tyrrell, 2000)*

Letter Fluency Test

The letter fluency test is a Dutch version of the English controlled oral word association test (COWAT) (Benton, Hamsher & Sivan, 1983), and is primarily an assessment of verbal fluency and executive function. Participants are asked to name as many words starting with a particular letter as they can within one minute, for three different letters. Since words are grouped by their first letters, and not by their meaning, the task is good for measuring phonetic fluency (Patterson, 2011). In the Dutch translation there are three different test versions. These are created by using three different initial letters with increasing levels of difficulty based on their frequency in the dictionary (Schmand, Groenink & den Dungen, 2008). Scoring is done by counting the number of correct responses given for each letter within a time limit and adding the scores together. Numbers, repetitions of the same word with a different suffix, and proper nouns are not counted as correct responses.

Woordopnoemen

The Woordopnoemen test is a Dutch version of the semantic verbal fluency (SVF) test and measures verbal fluency, semantic memory, lexical access ability, and a range of executive functions relating to inhibition and task switching (Shao, Janse, Visser & Meyer, 2014). The

task consists of two parts, and is a part of the Groninger Intelligence Test (GIT). In the first part of the test, participants are given one minute to name as many different animals as they can without repeating words. The second part repeats the same procedure, but instead of animals participants are asked to name as many occupations as they can. The total number of correct responses are collected for each category and compared to normative data to indicate performance. Compared to the letter fluency task, the semantic fluency test is a closer measure of conceptual memory and requires the participant to actively assess the meaning of each word (Oriá, Costa, Lima, Patrick & Guerrant, 2009).

Dutch Multifactor Fatigue Scale (DMFS)

The Dutch multifactor fatigue scale (DMFS) (Visser-Keizer, Hogenkamp, Westerhof-Evers, Egberink & Spikman, 2015) was used as a method of assessment for how patients were impacted by fatigue, the nature of the fatigue they experienced, and how they cope with this. This was included as an indication of patient experiences with fatigue, as a common side-effect of different treatment modalities. Five different domains were recorded, namely impact, consequences, mental fatigue, physical fatigue, and coping. High scores for the first four domains indicate the high presence, impact and consequences of fatigue in the patient's life (Visser-Keizer, Hogenkamp, Westerhof-Evers, Egberink & Spikman, 2015). Low scores on coping also indicates the presence of fatigue symptoms and a high score indicates that the patients has little fatigue symptoms or is managing well with their complaints. Overall coping score does not correlate with the other domains, meaning it is a separate measure for how well the patient copes with fatigue (Visser-Keizer, Hogenkamp, Westerhof-Evers, Egberink & Spikman, 2015). Each domain is scored on a 1-5 scale, and total scores depend on the number of items for each domain. The minimum and maximum scores for each domain is as follows: Impact (11-55), Consequences (9-45), Mental fatigue (7-35), Physical fatigue (6-30), and Coping (5-25).

Statistical Analyses

Statistical analyses were performed using SPSS version 25 and a significance level of $p < 0.05$ was used for all tests. Due to small sample-sizes for both the treatment (n=17) and control (n=18) groups, non-parametric tests were used for analysis. The two groups (treatment/control) were first compared and checked for statistically significant differences in age, educational level, dexterity, and gender. For age an independent samples t-test was used, for educational level a Kruskal Wallis test, and for gender and dexterity chi-square tests were used.

A Mann-Whitney U-test was used to compare neurocognitive function in the treatment and control groups. Spearman correlations were performed for two of the treatment factors that were targets for analysis: Clinical target volume (CTV), and interval between radiotherapy and neuropsychological assessment (EndRT-NCF). For tumor location (left vs. right lateral hemisphere) a Mann-Whitney U-test was used to compare the two groups (left vs. right) on neurocognitive performance. An additional Mann-Whitney U test was performed to check whether there were significant differences between left- and right-hemisphere tumors on the interval between RT and NCF.

Results

Patient Characteristics

In total 19 patients were recruited for the study, but only 17 were used for analysis since data from two patients was not completed. This data was then compared to a group of 18 healthy controls and an analysis on difference in demographics was conducted. All tests revealed a non-significant ($p > 0.05$) value, indicating that there the two groups were well matched. An overview of participant characteristics and the comparisons of different demographics between the groups is shown in *table 1*. Educational level was graded on a 7-point scale according to years of education (YoE) in the Dutch system, with the following scales: 1 = primary school (<6 YoE), 2 = finished primary school (6-8 YoE), 3 = did not finish secondary school (7-8 YoE), 4 = finished secondary school (9 YoE), 5 = finished secondary school (10-11 YoE), 6 = finished secondary school (12-16 YoE), and 7 = university degree (>16 YoE).

Table 1. *Participant Characteristics*

	HC	LGG-Patients	Difference	
Variable	(*n*=18)	(*n*=17)	F/X^2	*p*
Age, M(SD)	52.8 (8.24)	47.7 (9.31)	F = .456	.093
Gender (Male), n (%)	7 (38.9%)	11 (64.7%)	X^2 (1, *n*=35) = 2.33	.127
Education, M(SD)	6.05 (0.80)	5.35 (1.16)	$X^2(1) = 2.89$	.089
Dexterity (Right), n(%)	17 (94.4%)	17 (100%)	X^2 (1, *n*=35) = .972	.324
Epilepsy, n(%)				
Yes	0 (0%)	15 (88.2%),		
No	18 (100%)	2 (11.8%)		

- HC = Healthy controls, LGG = Low-grade glioma, Age = mean age at neurocognitive testing

An overview of different tumor characteristics in the patient group is shown in *table 2*. There was an even distribution of left- vs. right-sided tumors (10-7) and the majority of tumors were grade II, with an even distribution between astrocytomas and oligodendrogliomas.

Table 2. *Overview Tumor Specifics, n (%)*

TUMOR CHARACTERISTICS	**n (%)**
LOCATION (HEMISPHERE)	
LEFT	10/17 (58.8)
RIGHT	7/17 (41.2)
LOCATION (LOBE)	
FRONTAL	6/17 (35.3)
TEMPORAL	6/17 (35.3)
PARIETAL	2/17 (11.8)
INSULA	3/17 (17.6)
TUMOR TYPE AND HISTOLOGY GRADE	
ASTROCYTOMA IDH-MUTATED GR II	8/17 (47.1)
OLIGODENDROGLIOMA GR II	6/17 (35.3)
OLIGODENDROGLIOMA GR III	3/17 (17.6)

Table 3 displays treatment specifics such as radiation dose, number of resections and interval between RT and neuropsychological assessment. Most patients underwent a single resection,

and were treated with chemotherapy (PCV) in addition to RT. Both CTV volume and the interval since RT showed a large range of values between patients.

Table 3. *Overview Treatment Specifics*

TREATMENT SPECIFICS	M (±SD)	MIN	MAX	N(%)
DOSE RT	53.3(3.37)	50.4	59.4	
INTERVAL RT-NCF	40.5(18.1)	22	89	
NUMBER OF RESECTIONS	1.29(0.77)	0	3	
CHEMOTHERAPY (PCV)				
PCV				15/17 (88.2%)
No chemotherapy				2/17 (11.8%)
CTV VOLUME	183.8(97.5)	58.17	471.01	

**Dose in Gray (Gy), Interval RT-NCF in months, CTV volume in cc/cm^3*

Neuropsychological Performance Compared to Healthy Controls

The analysis revealed that the treatment group performed significantly worse ($p < 0.05$) on the RAVLT immediate recall and delayed recall, TMT A and TMT B, SDMT, Rey CFT, letter (phonetic) fluency task, and Woordopnoemen (semantic fluency) compared to the healthy controls. However, the LGG group did not perform significantly worse on the RAVLT recognition trial (Z = -1.138, p =.255) and the trail making task combined score (TMT B/A) (Z = - .910, p = .363).

Table 4. *Difference in performance control vs. treatment, raw scores M (±SD)*

DOMAIN/TEST	HC (n=18)	LGG-Patients (n=17)	Difference		
			U	*Z*	*p*
Attention and Processing Speed					
SDMT	56.56 (6.14)	43.35 (12.18)	47.5	-3.192	.001**
TMT A	29.56 (10.29)	40.65 (14.08)	62.0	-3.006	.003**
TMT B	64.89 (19.44)	105.53 (54.87)	84.5	-2.262	.024*
TMT B/A	2.27 (0.67)	2.52 (0.84)	125.5	- .910	.363
Memory					
RAVLT Immediate recall	47.17 (10.03)	34.94 (14.15)	69.0	-2.774	.006**
RAVLT Delayed recall	9.5 (2.57)	6.41 (3.87)	77.5	-2.511	.012*
RAVLT Recognition	28.72 (1.57)	27.06 (3.42)	120.0	-1.138	.255
Visuoconstructive Abilities					
CFT Rey	33.14 (2.36)	30.50 (4.69)	91.5	-2.043	.041*
Language					
Letter Fluency	40.06 (10.76)	24.41 (9.51)	42.0	-3.667	.000**
Woordopnoemen I	24.22 (3.96)	17.59 (5.36)	52.5	-3.323	.001**
Woordopnoemen II	19.0 (4.06)	13.47 (5.90)	64.0	-2.780	.005**

- HC = Healthy controls, LGG = Low-grade glioma, Woordopnoemen I = animals, II = occupations
- * = $p < 0.05$, ** = $p < 0.01$

Analysis of Treatment Factors

Clinical Target Volume (CTV)

For clinical target volume, a significant negative correlation, r_s = -0.527, p = 0.03, n = 17, was found with results for the Rey Complex Figure test (CFTrey), with larger CTV volumes generally performing worse. For other neuropsychological assessments there were no significant correlations between performance and clinical target volume.

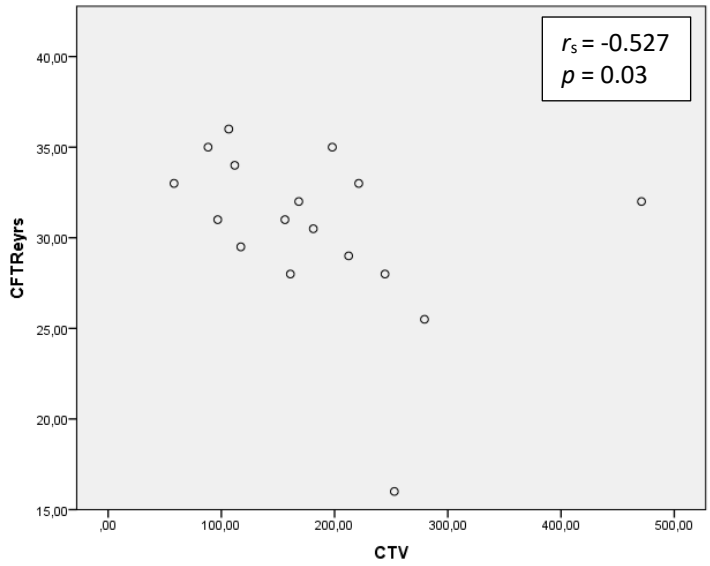


Figure 3. *Scatter plot of relationship between clinical target volume (CTV) and performance on the Rey Complex Figure Test (CFTRey).*

The data was also visually inspected to see whether tumors with a larger CTV happened to be located in the parietal lobe, which would be expected with a lower performance in visuospatial abilities as measured by the CFTrey. However, there was no obvious over-representation of parietal tumors in the high-CTV cases.

Radiotherapy and Neuropsychological Assessment Interval

Correlational analysis for performance scores and differences in intervals between the last RT treatment and the time of neuropsychological assessment (in months) revealed a significant negative correlation (r_s = -0.584, p = 0.014, n = 17) for letter (phonetic) fluency scores.

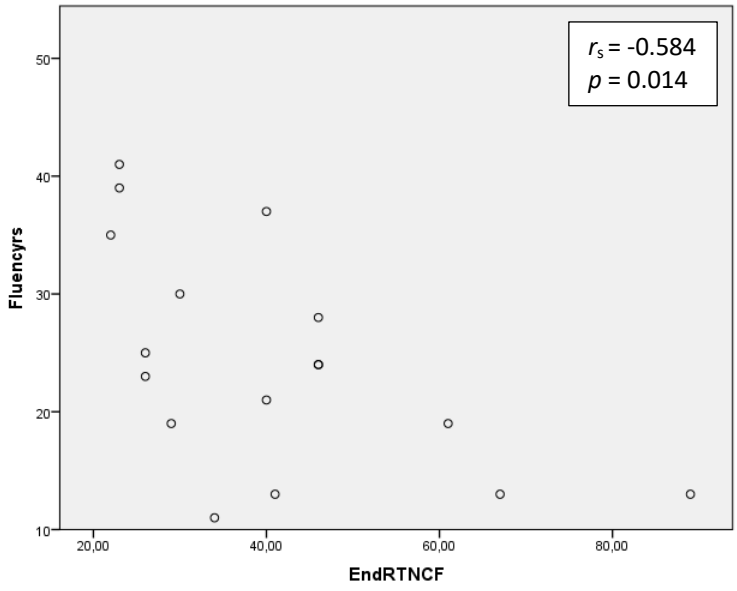


Figure 4. *Scatter plot for letter fluency scores and the interval, in months, between the end of radiotherapy treatment and the time of neuropsychological assessment.*

For all other neuropsychological assessments there were no significant correlations with interval. An additional analysis was performed to check whether there were significant differences between left- and right-hemisphere tumors on interval. The test revealed no significant differences, indicating that performance on the letter fluency test could not be explained by an overrepresentation of left-sided tumors in the longer intervals.

Tumor location

An overview of differences in performance between patients with left- and right-sided tumors can be found in table *5*. For lateral tumor location, patients with a left-sided tumor performed significantly worse (Z = -2.198, p = 0.028) on the RAVLT immediate recall (WT15IR) trial and the semantic fluency (Woordopnoemen) tasks than patients with a right-sided tumor. The differences in scores between the groups (left vs. right) for immediate recall is visualized in a boxplot in *figure 5*. Immediate recall scores for one patient with a left-sided tumor was abnormally high compared to the rest of the location group, indicating that this score is an outlier. However, this patient's performance was not an outlier on other assessments, and though their educational level was high, it was not the highest among participants.

Table 5. *Differences in performance between right- and left-sided tumors, raw scores M (±SD)*

	Left-sided	Right-sided	Difference		
DOMAIN/TEST	(*n*=10)	(*n*=7)	*U*	*Z*	*p*
Attention and Processing Speed					
SDMT	40.0 (14.2)	48.14 (6.84)	21.0	-1.368	.171
TMT A	39.50 (14.7)	42.29 (14.1)	34.5	- .049	.961
TMT B	110.4 (59.4)	98.57 (51.4)	31.5	- .342	.733
TMT B/A	2.71 (0.89)	2.24 (0.72)	22.5	- 1.222	.222
Memory					
RAVLT Immediate recall	29.6 (13.95)	42.6 (11.27)	12.5	-2.198	.028*
RAVLT Delayed recall	5.4 (4.12)	7.86 (3.24)	20.5	-1.429	.153
RAVLT Recognition	26.3 (3.92)	28.14 (2.41)	24	-1.114	.265
Visuoconstructive Abilities					
CFT Rey	30.95 (3.26)	29.866.47)	32	-.294	.769
Language					
Letter Fluency	22.4 (10.33)	27.29 (8.04)	22	-1.273	.203
Woordopnoemen I	15.1 (4.36)	21.14 (4.81)	12.5	-2.204	.028*
Woordopnoemen II	11.1 (5.57)	16.86 (4.85)	13.5	-2.110	.035*

- Woordopnoemen I = animals, II = occupations, * = $p < 0.05$

Further analysis revealed no significant difference between left- and right-sided tumors for CTV volume (Z = -1.695, p = 0.097), with right-sided tumors having marginally larger CTV volumes. All patients, except for two, received PCV chemotherapy treatment in addition to radiotherapy. The two that did not receive PCV or any other chemotherapy both had left-sided tumors. However, these two participants did not have significantly lower or higher

performance scores compared to the rest of the left-sided group. There was no significant difference in the number of resections for either tumor location.

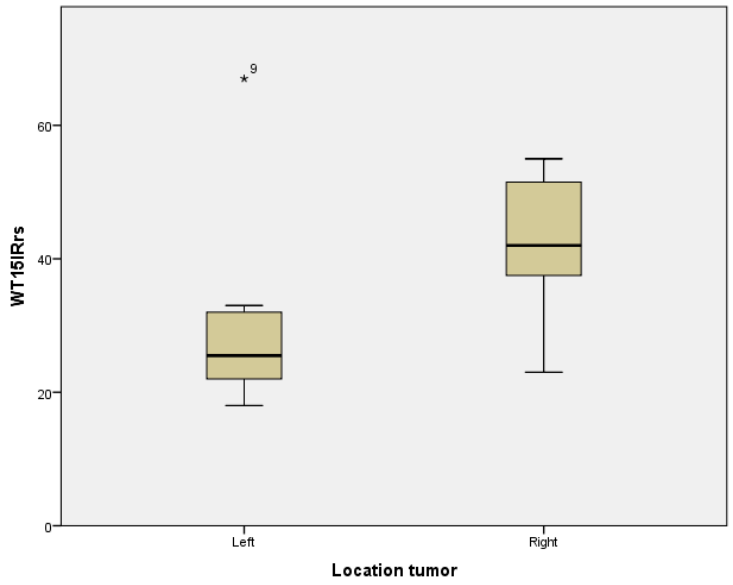


Figure 5. *Box-plot showing scores from immediate recall trials of the RAVLT for patients with a left- or right-sided tumor.*

Performance on the Woordopnoemen semantic fluency task was also significantly worse for both animal (Z = -2.204, p = 0.028) and occupation (Z = -2.110, p = 0.035) trials in the left-sided patients compared to the right-sided group.

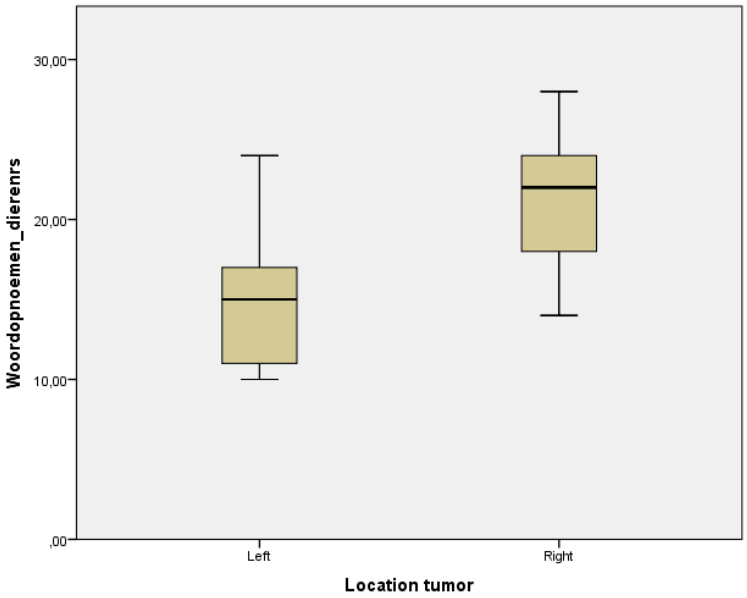


Figure 6. *Boxplot of semantic fluency performance for the animal condition in both tumor locations.*

In the occupational trial of the semantic fluency test participant number 4 was an outlier in the left-sided group with a significantly higher score, but was not an outlier in other assessments.

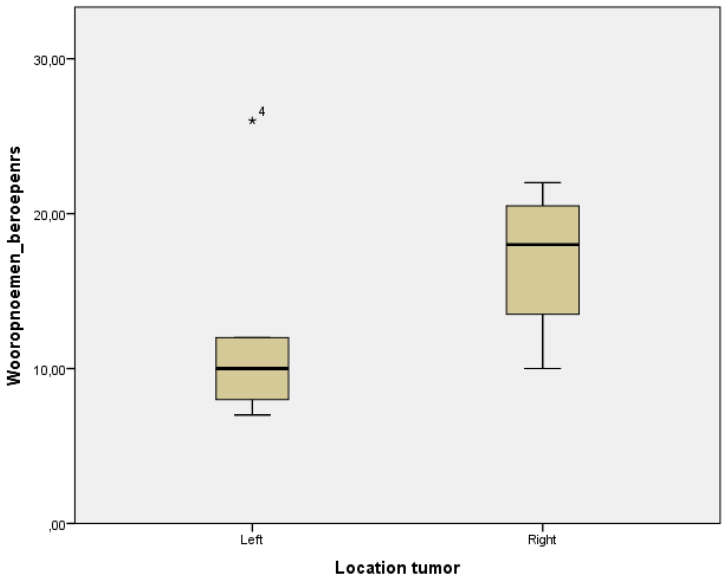


Figure 7. *Boxplot of semantic fluency test for the occupation condition for tumor location.*

Fatigue

For the DMFS, 11 out of 16 (68.8%) patients who completed the questionnaire scored “high” or “very high” on the impact scale, indicating that fatigue had a big impact on their life. For consequences the number of “high” or “very high” was 8/16 (50%), with 7 other patients scoring “above average”. 10 patients (62.5%) had indications of “high” or “very high” mental fatigue, but only 4 patients (25%) scored in these categories for physical fatigue. On the coping measure, most patients (81%) scored “average” or higher, with only 3 patients scoring below. This indicates that most patients in the study experienced severe mental fatigue, and that this fatigue has severe impact on their life, but that most cope with fatigue relatively well.

Discussion

The study outlined in this thesis is primarily an exploratory investigation into different possible factors that influence long-term neurocognitive function in LGG patients. Despite the small sample size (n=17), some of the analyses revealed statistically significant results ($p < 0.05$), and the overall significantly poor performance of LGG patients in comparison to healthy controls indicates that paying attention to cognitive problems in this patient group is of great importance. Yet, it is necessary to consider these results in the larger context of existing research on the topic, and to consider the limitations of this pilot study.

General Discussion

The first hypothesis predicted overall deficits in neurocognitive functioning for all domains in the treatment group compared to a healthy control group. Comparisons between these groups confirm this hypothesis, except for performance in two domains. For the trail making task combined score (BA) and the Rey Auditory Verbal Learning Task (RAVLT) recognition trial the treatment group did not do significantly worse than the healthy controls. This would indicate that mental flexibility and recognition memory is not significantly impaired in the LGG patients. One reason for a better performance on recognition trials is that it requires a lower threshold of certainty as even familiarity with a word is likely to give a correct recognition. Additionally, the TMT combined score (BA) has a limited range, which could give reduced power for analysis.

There were significant deficits in neurocognitive performance for the SDMT, TMT A, TMT B, RAVLT immediate and delayed recall, Rey CFT, letter (phonetic) fluency, and the Woordopnoemen (sematic fluency) tasks, which indicates that LGG patients experienced overall neurocognitive impairments. The cognitive domains that seem to be affected in this patient group are attention and processing speed, immediate and delayed recall, visuoconstructive abilities, phonetic and semantic fluency. However, it is not possible to separate whether this is due to toxicity from radiotherapy or other treatment modalities, from the tumor itself, epilepsy, or other factors. A larger sample that allows for multivariate analysis and repeated assessments over time is therefore needed to further investigate this. However, the differences observed between the treatment and control groups are in line with existing literature which suggests that neurocognitive deficits are present in LGG patient groups. The probable existence of such deficits is important to keep in mind when caring for this patient group to provide care that is best adapted to possible neurocognitive impairments.

Clinical Target Volume (CTV)

With regards to the clinical target volume, the initial hypothesis stated that larger volumes would correlate negatively with performance on processing speed tasks due to possible overall cortical atrophy or white matter lesions. However, tests that measure processing speed, such as the Trail Making Task part A (TMT A) and the Symbol Digit Modalities Test (SDMT) did not reveal any significant correlations with CTV. Instead, performance on the Rey Complex Figure Test (CFT) was significantly negatively correlated with increasing CTV. This would indicate that patients with larger CTV had worse visuoconstructive abilities. This result was unexcepted, and could be explained by other treatment or tumor factors that might correlate with an increased clinical target volume. It could also be in part due to limitations of the Rey CFT as it is a relatively easy test that might show evidence of a ceiling effect. Thus, the use of other assessments of visuospatial abilities in LGG patients could be useful in future

investigations, in particular with analysis including CTV volume. Additionally, it is interesting to note that the patient with the largest CTV volume (471.01cc) performed relatively well on the Rey CFT. This could indicate that other contributing factors may help explain this trend.

Interval Radiotherapy and Neuropsychological Assessment

For the interval between the end of radiotherapy and the time of neuropsychological assessment it was originally hypothesized that increased intervals would negatively correlate with performance of measures of processing speed such as the TMT part A and the SDMT. However, the correlations between interval and these assessments were not significant. Instead, phonetic fluency scores measured by the letter fluency test were significantly negatively correlated with an increasing interval. This would suggest that those who were tested longer periods after their radiotherapy treatment showed signs of decline in measures of fluency and executive function.

These observed impairments in phonetic fluency in patients with longer intervals since treatment could be due to delayed onset of deficits, as often seen in LGG patient groups, either from radiation-induced brain damage or effects from other treatment modalities. However, significant differences were not seen in other assessments, indicating that phonetic fluency in particular could be influenced by factors that vary with longer time intervals. Previous research into deficits in executive functioning in LGG patients have found that increased age and radiological evidence of RT-induced brain atrophy correlated with deficits in executive functioning (Ek, Kristoffersen Wilberg & Vestberg, 2017). It could therefore be that patients with a longer interval since RT were older, or that the decline was due to neurophysiological changes, such as decreased white matter volume, that had progressed over time. Since the patients in the study were stable at the time of participation it is unlikely that deficits are due to tumor progression. Integrating radiological findings such as white matter volume and cortical atrophy into the analysis would help understand these results in detail.

Tumor Location

For tumor location, the hypothesis was that left-sided tumors would perform worse on verbal memory and semantic fluency tasks compared to right-sided tumors as the left hemisphere is often dominant for language functions. Since all patients in this study were right-handed, it is highly likely that the left hemisphere was dominant for language in this group. The results confirm the hypothesis of tumor lateralization to some extent, as left-sided tumors performed significantly worse on the RAVLT immediate recall trial and on the semantic fluency measure (Woordopnoemen) for both the animal and occupation categories. This would suggest that radiation to the left-side of the brain contributes to reduced performance in tasks related to verbal memory. However, significant differences were not found in the RAVLT delayed recall trial, perhaps suggesting that other functional areas, such as the hippocampus, are more involved in later recall.

Further, the outlier seen in the analysis of tumor location and immediate recall in the 15 word test could be due to the young age of the patient. At the time of neuropsychological assessment the patient was 28 years old, which is the youngest age of all participants in the treatment group (M = 47.7).

Fatigue

A description of the Dutch Multifactor Fatigue Scale (DMFS) results indicated that the majority (62.5%) of patients had significant mental fatigue complaints that impacted their lives. This is in line with previous literature on fatigue in long-term assessments of LGG patients, where up to 40% of patients were found to experience severe fatigue 8 years post-treatment (Struik et al., 2009). The exact cause of this persistent fatigue in LGG patients is hard to pinpoint, but could be due to treatment, neurocognitive dysfunction, co-morbid disorders such as anxiety and depression, or the use of AEDs. Though this study supports the claim that fatigue is a common and important complaint to recognize in LGG patients, it was not possible to analyze which factors contribute to fatigue. However, it is interesting to note that this study used a fatigue measurement that separated mental and physical fatigue, which has not been commonly done in previous studies. The presence of severe mental fatigue and large absence of severe physical fatigue should be used as a guide to further investigate fatigue complaints. Moreover, the link between fatigue complains and health-related quality of life (HRQOL) is important to investigate further, as the results from the DMFS indicate that most patients cope relatively well with their fatigue. Thus, whether or not fatigue significantly impacts HRQOL in this patient group would be a worthwhile question to investigate to better support LGG patients.

Clinical Implications

Some possible clinical implications of these results could be prioritization of neurocognitive measures as a part of the treatment process for LGG patients. Neuropsychological assessment at diagnosis, or as a follow-up post-treatment, is not currently standard of care in LGG patients. This exploratory study indicates that neurocognitive deficits are present in this patient group, and that there might be correlations with treatment and tumor characteristics that could offer clinical value if monitored. Previous research on neurocognitive outcomes in LGG patients supports the view that these outcomes are important in patient quality of life later on. Further, assessment of neuropsychological functioning do not require too much time and could therefore be relatively easily implemented into the treatment process.

One valuable application of this research could be the monitoring of neurocognitive deficits, which may be used to develop an individualized neuropsychological rehabilitation program for the patient. With increased follow-up, it may be possible to improve some functions or, if irreversible, the patient may be given tools to cope with specific deficits. This could also help patients distinguish between complaints related to brain damage from the tumor itself or the treatment process, and other non-clinical factors such as environmental stress, mood disorders, or fatigue. With this distinction, patients may be able to get better treatment for neuropsychological complaints that are not directly related to the tumor or treatment process. It also might reduce stress and worry in patients by providing a more concrete overview of neuropsychological functioning.

Limitations

One of the main limitations of this pilot study is it's small sample size, which makes multivariate analysis and generalizable results unattainable. Further, this thesis chose to only handle a few variables in tumor and treatment characteristics for correlational analysis. This limited scope meant that the majority of radiological data and dose volume specifics was excluded from analysis, which could, if included, contribute to a more in-depth investigation.

The analysis only made a crude distinction between left and right hemisphere tumors to look for differences specific to function in the left-temporal lobe. A more detailed investigation into different tumor locations, such as frontal and temporal tumors, would give a more comprehensive account of functional neuroanatomical differences that might be important to neurocognitive outcomes. Further, a more extensive follow-up with neuropsychological testing at the time of diagnosis and later at different intervals after treatment could give a better overview of the development of neurocognitive deficits. Since only one neuropsychological assessment post-treatment was available in this study it is impossible to track the trajectory of cognitive functioning.

Future Recommendations

Future studies aiming to look at long-term neurocognitive functioning in LGG patients should consider using neuropsychological assessments such as the semantic fluency measure, the RAVLT, and the letter fluency test as easy-to-administer and quick assessments of verbal memory and fluency. Moreover, the SDMT and TMT part A and B are good measures of attention, mental processing speed and mental flexibility. Lastly, the incorporation of DMFS or other measures of both mental and physical fatigue could be good supplements to assess patient experience and better support patient needs.

There are also several areas of investigation that open up from the analysis in this thesis. One area of interest is the role of radiological data in neurocognitive deficits, and whether decreases in white matter volume or other neurophysiological measures are possible predictors for neurocognitive decline in certain domains. In particular, the role of general connectivity in the brain and executive functioning and processing speed is something that should be researched more closely. A more extensive study on the effects found in left-hemisphere tumors on semantic fluency and immediate recall is also needed to distinguish whether tumor location has a significant general impact on these language functions. Radiological data on doses given to certain regions, such as the hippocampus, would be valuable additions to this investigation. It would also be interesting to investigate whether deficits in some areas, such as executive functioning, memory, or language have a particularly strong effect on fatigue and health-related quality of life in the patient.

Another interesting area of future research is the interval between surgery and radiotherapy onset, which remains a point of controversy in the management of LGG patients. In particular, it would be worthwhile to see whether the interval between surgery and radiotherapy correlates with post-treatment NCF in any specific domain or with HRQOL measures.

Conclusion

This thesis has outlined one part of an exploratory study on the long-term neurocognitive outcomes in low-grade glioma (LGG) patients who have undergone radiotherapy treatment. Based on a review of existing background literature on the topic of neurocognitive function in LGG patients and specifically in post-radiotherapy patients, several factors of interest have been examined. Firstly, a general comparison was performed, using a healthy control group, to see whether the LGG patient group performed generally worse on neuropsychological testing. Secondly, using correlational analysis of existing patient data from a small sample of LGG patients, three factors relating to tumor and treatment characteristics were explored: Clinical target volume, tumor location, and the interval between radiotherapy treatment and neuropsychological assessment. Analysis revealed significant results for all treatment factors on at least one area of neurocognitive functioning. These results, though only explorative, indicate that this is an area of research that needs further attention in the future.

Due to the limited sample size used in this study, and the exclusion of the majority of the radiological data collected, there are several questions about the data that remain unanswered. Therefore, re-testing on a larger population and the inclusion of multivariate analysis is needed to fully understand the implications of this study. However, the results do indicate that there are relationships between treatment and tumor factors and neurocognitive outcomes.

The consideration of neurocognitive outcomes, both as long-term measures and as a part of the clinical management of low-grade glioma patients is still not common. However, this thesis has shown that increasing bodies of knowledge indicate that neurocognitive outcome is not only a measurement of the neuropsychological effects of the tumor and treatment modalities, but is also increasingly significant for long-term patient outcome and quality of life. Quality of life and the neuropsychological functioning of the patient should be considered together with other clinical measures such as progression-free survival, especially in relatively young patient groups with longer survival rates, such as in LGG patients.

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