Interdisciplinary rehabilitation of patients with glioma during anti-cancer treatment

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Preface

The motivation for the current research originates from an intention to improve the clinical practice of rehabilitation in neurooncology settings by conducting research that contributes to strengthening clinical guidelines.

The scientific work presented in this dissertation was made at the Department of Sports Science and Clinical Biomechanics Faculty of Health Science at The University of Southern Denmark (SDU), Denmark, in collaboration with the Rehabilitation Department, the Neurosurgical-, and Neurological department at Odense University Hospital (OUH), Denmark.

The principal supervisor was Professor Karen Søgaard (SDU). The associate professor Lisbeth Kirstine Rosenbek Minet (SDU and OUH), and the physicians Jens Ole Jarden (Herlev University Hospital, University of Copenhagen, Denmark) and Dagmar Beier (OUH) acted as co-supervisors.

The project received financial support from the Region of Southern Denmark, Faculty of Health Science, SDU and the Rehabilitation Department, OUH.

List of Papers

I Hansen A, Søgaard K, Rosenbek Minet LK, Jarden JO. A 12-week interdisciplinary rehabilitation trial in patients with gliomas – a feasibility study, Disability and Rehabilitation 2017

II Hansen A, Rosenbek Minet LK, Søgaard K, Jarden JO. The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among patients with primary glioma: an RCT study protocol. BMJ Open 2014

III Hansen A, Rosenbek Minet LK, Pedersen CB, Beier D, Jarden JO, Søgaard K. The Influence of Hemispheric Lesions on Health-Related Quality of Life and Functional Performance of Patients with Glioma: An Exploratory Cross-sectional Study (In manuscript)

IV Hansen A, Pedersen CB, Jarden JO, Beier D, Minet Rosenbek LK, Søgaard K. The effectiveness of interdisciplinary rehabilitation of patients with primary glioma during active anticancer treatment – a sing-blinded randomized controlled trial (In manuscript)

Acknowledgement

First and foremost I would like to give my warmest appreciation to the persons who participated in this research. All those hours spend exercising and having fun talking has truly affected me in positive ways.

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Finally, my most profound admiration goes to my daughter Esther and my son Willy, who has shown me the meaning of unconditional love; this thesis is dedicated to you with the hope that you will walk light-hearted through life.

Anders Hansen, February 2018

Thesis at a glance

This dissertation comprises two clinical trials and a cross-sectional study. It includes patients diagnosed with primary glial-cell brain tumors.
The clinical trials include a feasibility study and a full-scale RCT. Based on data from these trials a cross-sectional study was created. A supplementary practice analysis (Hansen et al., 2017a) and a case report (Hansen et al., 2018) nested within this project have been published. Also, a qualitative study is under assessment.

Paper I

Aim
To evaluate the safety and feasibility of a 12-week interdisciplinary rehabilitation intervention of patients with primary glioma.

Participants
24 functional independent patients with glioma entered a two-part rehabilitation intervention. Part one included six weeks of supervised physical therapy and occupational therapy at the hospital. Part two involved self-administered training following a protocol.

Methods
A clinical feasibility study investigating predefined feasibility objectives of safety, consent-rate, dropout rates, adherence, the responsiveness of assessment tools, and patient satisfaction.

Conclusion
This study demonstrates that an interdisciplinary rehabilitation intervention of physical therapy and occupational therapy in the initial treatment phase of patients with gliomas and Karnofsky performance status ≥70 is safe and feasible, if relevant inclusion criteria are adhered to and precautionary screenings done. However, failure to reach predefined feasibility objectives at part two has led to a protocol revision for a randomized controlled trial.

Paper II

A protocol describing the rational and designing of an RCT.

Paper III

Aim

To investigate if patients with gliomas located in the left- or right hemisphere differ in health-related quality of life and functional performance outcomes at the beginning of medical anti-cancer treatments.

Participants

81 patients combined from the feasibility study (*paper I*) and the RCT (*paper IV*) attended the analysis.

Method

This exploratory, cross-sectional study stratifies patients into two groups based on an affected right or left hemisphere. Group differences were assessed of demographic, tumor, and medication variables as well as health-related quality of life and functional performance outcomes.

Conclusion

The main result implies that the location of a tumor in the right- or left hemisphere has no consequence for health-related quality of life and only little impact on symptoms and functional performance outcomes in the early disease state. Based on this study, no consideration of laterality has to be taken into account when designing a rehabilitation intervention intended to improve functional performance or health-related quality of life.

Paper IV

Aim

To investigate the effectiveness of an interdisciplinary rehabilitation intervention on overall QOL compared to standard rehabilitation.

Method

A randomized, controlled, single-blinded trial comparing interdisciplinary rehabilitation to standard rehabilitation of patients actively attending medical anti-cancer treatments.

Conclusion

Patients with glioma attending rehabilitation interventions of physical therapy and occupational therapy during active anti-cancer treatment insignificantly improve overall QOL compared to patients having the standard rehabilitation practice. They statistically significantly improved 'cognitive functioning', decrease a continuum of symptoms including fatigue, and improve functional performances

Abbreviations

ADL	Activity of daily living
BMI	Body Mass Index
BBS	Bergs Balance Score
CI	Confidence Interval
CNS	Central Nervous System
EORTC	European Organization for Research and Treatment of Cancer
GBM	Glioblastoma Multiforme
HGG	High-grade glioma
HRR	Heart rate reserve
HRQOL	Health-related quality of life
KPS	Karnofsky Performance Status
LGG	Low-grade glioma
OUH	Odense University Hospital
QOL	Quality of life
RCT	Randomized Controlled Trial
RM	Repetition Maximum
SD	Standard Deviation
WHO	World Health Organization

Definitions

Eloquent tumor location:
Refer to the combination of the sensory or motor cortex, language cortex, internal capsule, thalamus, corpus callosum, fornix, and/or hypothalamus.

Interdisciplinary team:
A group of health-care professionals from diverse fields who work in a coordinated fashion toward a common goal for the patient.

Patients:
Patients with a glioma disease included in the trials.

Primary investigator:
The author of this thesis.

Rehabilitation:
"Rehabilitation is a targeted, temporary process of cooperation between a citizen, relatives and professionals. The aim is that citizens, who have or are at risk of gaining substantial limitations in their physical, psychological and/or social functional capacity, attain an independent and meaningful life. Rehabilitation is based on the entire life situation of and decisions made by the citizen and consists of coordinated, coherent and knowledge-based efforts"(Marselisborgcentret, 2004).

Therapists:
Physical therapists or occupation therapists supervising the intervention

1 Introduction

1.1 Rehabilitation of patients with cancers

Cancer is a significant worldwide problem and among the leading causes of morbidity and mortality. With improved survival benefits from advanced therapies (Zeng et al., 2015) a corresponding focus on rehabilitation has naturally evolved, as many patients experienced impairments in everyday living (Gerber et al., 2017; Mishra et al., 2012b; Gamble et al., 2011; Back et al., 2014). But that was not always the case. Rehabilitation of patients with a cancer diagnosis was previously regarded as an oxymoron because of the poor related prognosis. As a direct consequence was rehabilitation for many years ignored in the scientific literature (Cheville, 2005; Gerber et al., 2017). But within recent decades a positive attitude toward rehabilitation has grown, both politically and amongst health-care professionals (Gamble et al., 2011; Gerber et al., 2017). Through research and comprehensive theoretical thinking, rehabilitation has progressed from simple supportive and palliative care to include complex interventions designed to re-establish body functions, restore or remediate functional losses, and to adapt the environment, which allows for participation in daily activities and life roles (Gilchrist et al., 2009).

One modality that recently has gained considerable attention regarding the rehabilitation of patients with cancers is physical exercise. It can attenuate or treat physiological and psychological challenges experienced by cancer survivors and improve various aspects of QOL (Mishra et al., 2012a; Mishra et al., 2012b). Historically, a safeguarding attitude toward these patients from physical activity was the norm. But over recent decades, extensive research into exercise after a cancer diagnosis has changed the discursive approach to the perception of exercise rehabilitation and cancer (Jones and Alfano, 2013). This evidence is produced primarily of patients with breast, colon, prostate, or hematologic cancers. Therefore, research to extend quality rehabilitation in rare cancer types such as brain cancer still needs to be conducted.

1.1.1 Cancer in Denmark and the start of a Neurooncology clinic

Cancer is a significant problem in Denmark as there in 2016 were 41.720 new cancer cases (Sundhedsstyrelsen, 2017). Historically, Denmark did not produce the same quality of cancer treatment as our fellow Nordic countries. This led to a national initiative in the year 2000 to improve treatment and survival outcomes. This current project was designed to follow after the third initiative from 2010 “national cancer plan III” (Sundhedsstyrelsen, 2010). The previous ‘cancer plan II’ (Sundhedsstyrelsen, 2005) emphasized that rehabilitation should be evidence-based and resulted in an improved follow-up of cancer patients. To adhere to the ‘cancer plans’ to improve quality, OUH established a Neurooncology center designed especially to manage patients with brain tumors. Its purpose was to help patients experience a holistic approach from a multidisciplinary neurooncology team to manage patients’ issues. The clinic offers a range of neurological medical assistance to alleviate unwanted effects of treatment as well as disease deterioration in assistance with neurosurgeons, oncologists, radiologists, pathologists and nuclear medicine professionals, but also offers specialized neurorehabilitation from physical therapists, occupational therapists, neuropsychologists and social counselors.

This research was developed as a co-work between the Neurooncology clinic and the Rehabilitation department at OUH. It includes patients with gliomas, a specific type of brain tumors, and aims to extend quality rehabilitation efforts. The following section gives an introduction to brain tumor fundamentals and an update on the current knowledge on rehabilitation.

1.2 Brain tumor definition

The human organism comprises a multitude of tissue, each specially adapted to their essential function. This tissue consists of many distinct entities of cells, which are named according to the task they have to perform. There are numerous differences in these cells, yet, essentially all are programmed to repair or reproduce themselves. If this repairing or reproducing is interrupted, the cells may multiply uncontrollably, which leads to tumor pathology. If the tumor can migrate to the surrounding tissue, it is characterized as malignant (aggressive), whereas, if it does not, it is per definition benign (non-aggressive).

Primary brain tumors originate from the brain, vessels, meninges, or in the intracranial space, whereas secondary tumors/metastases have traveled to the brain from primary tumors elsewhere in the organism. Brain tumors differ from other tumor types by various characteristics. 1) They are located inside the cranium, which may cause severe symptoms due to increased intracranial pressure. 2) They may invade healthy tissue, which makes radical surgical removal impossible. 3) They often locate at vital brain areas, which further impedes the possibility of surgical removal, and 4) benign tumors can degenerate to a malignant characteristic (Kolb and Whishaw, 2003; Armstrong et al., 2016; DNOG, 2016).

1.2.1 Glial-cell brain tumor definition

'Glioma' is a term that encompasses any tumor that derives from supportive tissue (glia-cells) of the brain. They represent a significant part of all brain tumors and include the most aggressive subtypes with poor outcomes related (Ostrom et al., 2016). Glioma subtypes can be distinguished from their origin of different glial cells: astrocytes, oligodendrocytes, oligoastocytes, or ependymocytes (Ostrom et al., 2014). In this thesis, they are classified following the WHO, which according to the latest revision from 2016 divides gliomas into four grades (I-IV). These are based on the malignant characteristics of the tumor (Louis et al., 2016). But when defining gliomas, the term 'benign' may seem deceptive, as the main difference between a 'benign' and a 'malignant' glioma concerns the growth rate. Hence, for this research 'low-grade glioma'

(LGG) refers to any grade I-II glioma (least malignant) whereas ‘high-grade glioma’ (HGG) refers to any grade III-IV glioma (highly malignant).

1.3 Deficits and impairments associated with a specific brain lesion

The brain is responsible for controlling the activity in all body parts and organs. It is roughly formed of three structures: the brainstem, the cerebellum, and the cerebrum. Of main focus in this research is the cerebrum, or cortex. It controls higher brain functions such as thoughts, speech, memory, problem solving, attention and emotions. It divides into left- and a right hemisphere, which each have distinct responsibilities (Drewes et al., 2016). Each hemisphere further divides into four sections/lobes: the frontal, the parietal, the temporal, and the occipital lobe. Patients with brain tumors may experience deficits or impairments, which correlate to the exact location of the tumor. Table 1 gives a summary of the primary deficits associated with brain tumors in each hemisphere and lobe, which may require rehabilitation.

Table 1 Deficits associated with a brain tumor at a specific hemisphere and lobe

Tumor location	**Left hemisphere**	**Right hemisphere**
Frontal lobe	Personality changes, apathy, impaired planning, expressive aphasia, contralateral motor weakness and motor seizure.	Personality changes, motor weakness, and seizure.
Temporal lobe	Loss of verbal memory, short-term memory loss, fluent aphasia, complex partial seizure and contralateral homonymous superior quadrantanopia.	Loss of visual spatial memory, complex partial seizure and contralateral homonymous superior quadrantanopia.
Parietal lobe	Contralateral sensory deficit, aphasia, syndromes, alexia, agraphy, contralateral homonymous inferior quadrantanopia and sensory seizure.	Contralateral sensory deficit, contralateral homonymous inferior quadrantanopia, sensory seizure, contralateral hemispatial neglect, visual neglect, constructional apraxia and sensory seizure.
Occipital lobe	Contralateral homonymous hemianopia and alexia.	Contralateral homonymous hemianopia.

Inspired by Flowers, 2000 (Flowers, 2000)

1.4 Patients with glioma have many deficits and a high symptom burden

The patient group is unique in the sense that not only does the damage to the brain result in neurological impairment. Also adverse effects from anti-cancer treatments produce substantial symptoms (Alentorn et al., 2016). Combined with the emotional distress of the underlying cancer disease, patients with gliomas face a significant symptom burden. Mukand and colleagues (2001) evaluated the extent of neurological deficits of 51 patients with primary brain tumors admitted to an inpatient rehabilitation facility. They found that 75% of the patients had three or more concurrent neurological deficits. Impaired cognition was present in 80% of patients, which was followed by weakness in 78% (Mukand et al., 2001). In 2007 Pace et al. found that the most frequent disability of 121 patients was hemiparesis (62%) and gait disturbances (57%) (Pace et al., 2007). A prospective study by Johnson from 2012 assessing cognitive function of 80 patients with Glioblastoma Multiforme (grade IV) immediately after surgery confirmed deficits of memory in 60% and of executive functions in 53% of patients (Johnson et al., 2012). In a study of 96 patients, 56% reported pain and 42% reported headaches (Khan and Amatya, 2013). Although the various study-populations were selected and the studies used different outcome assessment tools, it emphasizes that patients with brain tumors, including gliomas, have a significant symptom burden with multiple symptoms presenting simultaneously throughout the entire disease. These deficits make patients at risk of having reduced physical, psychological, and social functions, which may impair their ability to live an independent and meaningful life and influence HRQOL (Jones et al., 2010a).

1.5 Factors to influence health-related quality of life of patients with glioma

Patients with primary glial-cell tumors are characterized by low health-related quality of life (HRQOL), not only compared to healthy adults (Taphoorn and Bottomley, 2005; Taphoorn et al., 2007; Lucchiari et al., 2015), but also to other significant cancer populations (Taphoorn et al., 1994; Klein et al., 2001). Age, gender, WHO classification, physical- and cognitive impairments, emotional distress, fatigue, and depression are factors best described to influence QOL (Cheng et al., 2009; Liu et al., 2009; Giovagnoli et al., 2005; Osoba et al., 2000; Pelletier et al., 2002; Armstrong et al., 2016).

1.6 Epidemiology and prognosis

Gliomas are relatively rare cancers. They constitute the 17th most common cancer type and roughly represent 2% of all cancers (Chandana et al., 2008; Walsh et al., 2016). Typically, malignancy increases with age

(Ohgaki and Kleihues, 2005). Therefore does LGG predominantly affect the younger population, whereas HGG primarily affects older adults (Walsh et al., 2016; Wick et al., 2018). According to the national Danish Cancer Registry, 1.820 patients had a CNS tumor in 2016 (Sundhedsstyrelsen, 2017), with more than half of these being glioma types (DNOR, 2017).

Regardless of state-of-the-art treatments, patients with gliomas, and in particular HGG, hold poor prognosis. Survival studies in American and European countries state that about 50% of patients with WHO III gliomas are alive after one year and 25% lives after five years, whereas 37% of Glioblastoma Multiforme patients (WHO grade IV astrocytoma) live more than a year with less than 10% lives after five years (Visser et al., 2015; Ostrom et al., 2013; Thakkar et al., 2014; Stupp et al., 2005). As a consequence of the relatively slow growth, patients with LGG present with a superior survival-outcome (Sanai et al., 2011; van Coevorden-van Loon et al., 2017) compared to HGG. In general, the survival heavily depends on prognostic factors. Table 2 gives a summary of the best-defined factors with relevance for this research.

Table 2 Selected known factors associated with god or bad prognosis of patient with gliomas

Factors	**Good prognosis**	**Poor prognosis**
Age	< 40	>70
KPS[1]	80-100	<60
Size	<3 cm	>6 cm
Site	Non-dominant hemisphere, cortical/frontal	Dominant hemisphere, bilateral, deep-seated
WHO grade	I-III	IV
Type	Oligodendroglioma	Astrocytoma
Surgery	Complete resection	Biopsy only
Comorbidity	Nil	Several/serious

(KPS[1]) Karnofsky Performance Status. Inspired by Day (2016) (Day et al., 2016a)

1.7 Standard triple-modality-treatment to reduce tumor growth

Standard anti-cancer treatments of patients with HGG involve craniotomy to remove tumor cells to the extent that is safely feasible. In deep brain or critically (eloquent) located tumors where partial or macro-radical resections are limited, a biopsy for a histological establishment is taken (Watts and Sanai, 2016). Post-surgical medical treatments include The Stupp regimen of concomitant radiation and chemotherapy (Stupp et al., 2009). In patients with GBM the standard radiation schedule is given for 33 consecutive weekdays

(Weller et al., 2017). The current standard for chemotherapy is given concomitant to radiotherapy and followed by adjuvant maintenance chemotherapy (Weller et al., 2017). Alternative strategies may be applied depending on tumor subtypes, individual biomarkers, or performance status.

1.8 Rehabilitation of patients with glioma

A glioma disease is among the most significant challenges within neurological-, and oncology rehabilitation settings (Vargo, 2011; Jones et al., 2010a). The 'healthiest' patients (LGG with high KPS) face a chronic illness with follow-up assessments needed for their entire life, whereas the most affected patients (HGG with low KPS) have a short life expectancy and may be unable to care for themselves. Optimizing rehabilitation is therefore of primary clinical importance within this population.

Historically, rehabilitation needs were described in 80% of the patients with CNS malignancies, which makes the patient group among the highest demanding cancer types for rehabilitation (Lehmann et al., 1978). But despite the significant need for rehabilitation, patients with gliomas are rarely referred to rehabilitation services (Kirshblum et al., 2001; Tang et al., 2008; Geler-Kulcu et al., 2009; Formica et al., 2011; Khan et al., 2014; Khan et al., 2013; Pace et al., 2016). Though the reason is likely multi-faceted, authors have argued that it may reflect a short admission time at the neurosurgical department. It is also suggested that medical professionals treating patients are unaware of the rehabilitation services available, or have doubts regarding their potential (Kirshblum et al., 2001; Formica et al., 2011; Day et al., 2016a). But, evidence establishing the effectiveness of rehabilitation is slowly emerging (Khan et al., 2014; Formica et al., 2011; Zucchella et al., 2013; McCarty et al., 2017). It has for some time been clear that patients with brain tumors attending inpatient rehabilitation acquire functional effects (Fu et al., 2010; Gehring et al., 2009; Roberts et al., 2014; O'Dell et al., 1998; Marciniak et al., 2001) parallel to patient with stroke and traumatic brain injuries that present with matching impairments of functioning (Geler-Kulcu et al., 2009; Huang et al., 2000; Greenberg et al., 2006; Han et al., 2015), which creates a robust argument to also incorporate systematic rehabilitation of patients with glioma.

There is some existing literature to support that patients' benefit from outpatient rehabilitation. Sherer and colleagues in 1997 gave the first indication of favorable outcomes from post-acute rehabilitation as 50% of the patients improved after rehabilitation (community independence and employment) (Sherer et al., 1997). Pace et al. (2007) found statistically significant functional gains in the Barthel Index, KPS and of improved QOL after home-based rehabilitation (Pace et al., 2007). In a study by Cheville et al. from 2010, a subgroup of 12 patients with glioma reported improvements in physical wellbeing following a multidisciplinary outpatient rehabilitation intervention during radiation therapy (Cheville et al., 2010). In a clinical trial by Khan et al. (2014) HGG survivors with a median of two years after the initial diagnosis improve sphincter control, communication, and cognition from multidisciplinary rehabilitation, and maintained the gains for up to six months (Khan et al., 2014). In a recent study (2017), 49 patients with malignant brain tumors had stable HRQOL at the conclusion of an interdisciplinary outpatient rehabilitation program, and at one and three-month follow-ups (McCarty, 2017). Furthermore, studies of inferior methodology or of limited data material have found improvements from outpatient rehabilitation, including exercise (Cormie et al., 2015; Levin et al., 2016; Capozzi et al., 2016; Nicole Culos-Reed et al., 2017; Gehring et al., 2017; Gill-Body et al., 1997; Hansen et al., 2017a; Hansen et al., 2018; McCarty et al., 2017). In conclusion, outpatient rehabilitation as a non-pharmacological intervention may lead to potential improvements in daily life, functional outcome, and in HRQOL. But the academic literature still lacks studies investigating the effectiveness of outpatient rehabilitation in robust methodological designs, as a Cochrane review from 2013 identified no studies with sufficient quality for inclusion in the review (Khan et al., 2013).

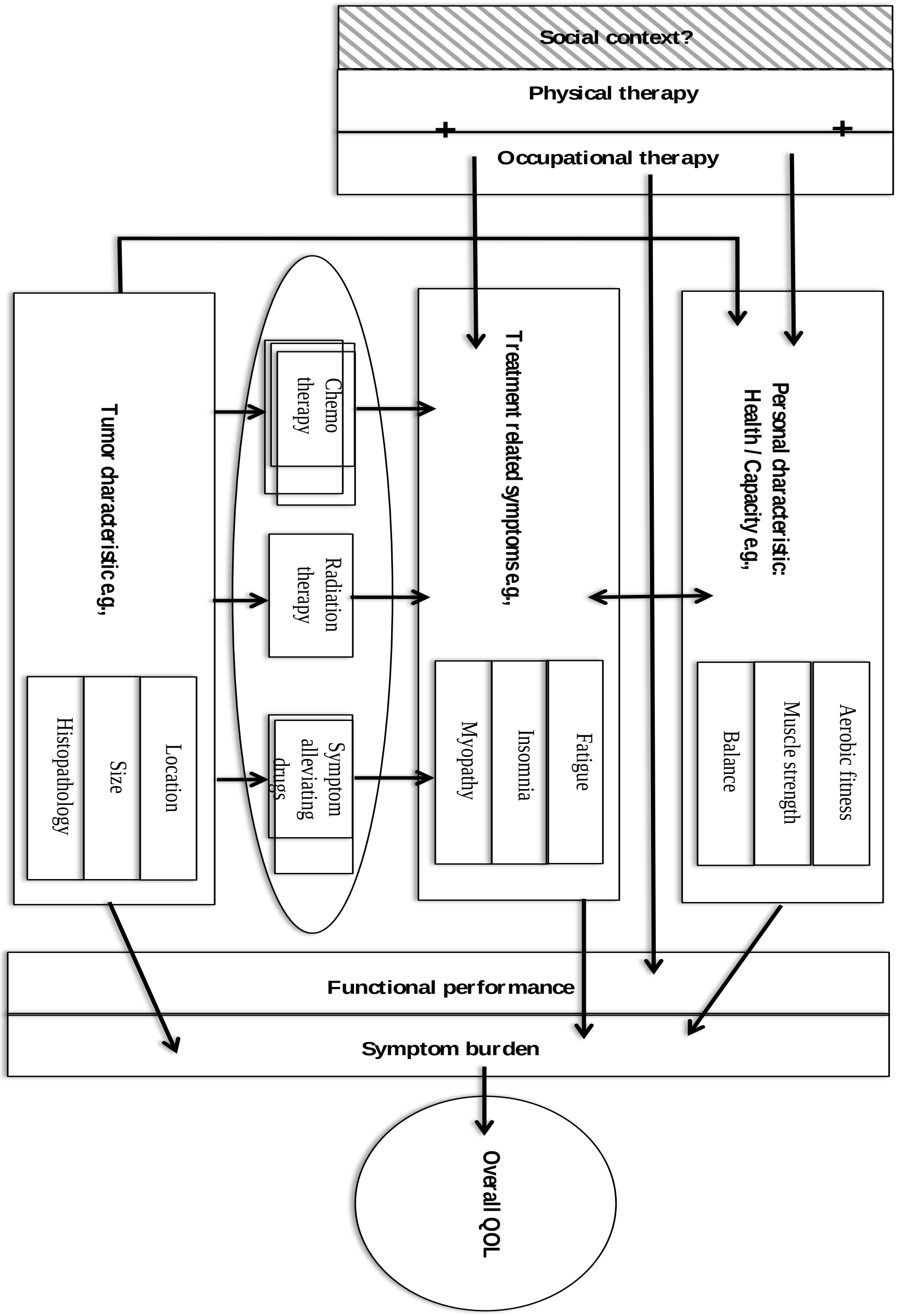
1.9 Rational and theoretical considerations

During the first year of the diagnosis patients' activity levels decrease (Piil et al., 2018). A sedentary behavior combined with cancer treatments impair cardiorespiratory function and produce muscle wasting, which is associated with poor prognosis, morbidity, and mortality of patients with cancer (Cormie et al., 2015; Strasser et al., 2013; Steins Bisschop et al., 2012). Further, the symptoms, functional impairments, and decreased functional performance, which often follow the disease limits patients' ability to perform simple daily activities (Piil et al., 2018), which affects psychological outcomes as autonomy, depression, loss of hope and aspiration and significantly influence QOL (Jones et al., 2010b). As proposed by Jones and Alfano (Jones and Alfano, 2013) a possible solution for reversing this negative cascade is to attend rehabilitation, with a strong emphasis on exercise. Exercise, as a part of rehabilitation, improves oxygen uptake and muscle strength (Gehring et al., 2017; McNeely et al., 2006; De Backer et al., 2009). Improved functional performance and physical capacity significantly reduces symptoms, including fatigue (Adamsen et al., 2009), and helps patients develop their everyday living. Improved functioning promotes positive psychological effects of independence, confidence and hope in patients with brain tumors (Hackman, 2011; Cormie et al., 2015).

Based on a model of Liu and colleagues, 2009 (Liu et al., 2009) overall QOL of patients with glioma is constructed and affected by multiple factors. These include 1) 'Patient factors' as characteristics affect patients' perception and symptom experiences. 2) 'Tumor factors' as the location, laterality, and size of the tumor may impose specific neurological symptoms, and 3) 'Treatment factors' as surgery, radiation, chemotherapy and concomitant medication positively or negatively impact symptoms.

Based on these assumptions it seems theoretically plausible that interdisciplinary rehabilitation can influence patients with glioma' 'overall QOL, as physical therapy with a strong emphasis on exercise and occupational therapy potentially improves functional performance and reduces symptoms related to 'patient', 'tumor' and 'treatment' factors (Liu et al., 2009; Vargo et al., 2016; Gillison et al., 2009; Khan et al., 2014) (figure 1).

Figure 1 Model to describe how physical therapy with a strong emphasis on exercise and occupational therapy potentially improves overall QOL through improved functional performance and reduced symptoms related to 'patient', 'tumor' and 'treatment' factors



Aim

This thesis aims to develop an interdisciplinary rehabilitation program with a strong emphasis on physical training, which is safe for patients with primary glioma, and superior to the current practice in terms of having an effect on overall QOL.

2.1 Specific aims and hypothesis of the scientific papers

Paper I

To assess the safety and feasibility of an interdisciplinary rehabilitation intervention of patients with primary glioma during active anti-cancer treatment.

Paper II

To describe the rationale and designing of an RCT protocol.

Paper III

To explore if patients with gliomas located at the right- or left-hemisphere differ regarding HRQOL and functional performance outcomes.

Paper IV

To investigate the effectiveness of a six-week interdisciplinary rehabilitation intervention compared to standard rehabilitation on 'overall QOL' of patients attending active anticancer treatment.

- It is hypothesized that the intervention will result in a superior increase of 'overall QOL' by improving functional performance and reduced symptomatology compared to the standard rehabilitation at the six-week follow up assessment.

3 Method

Paper I was presented to The Regional Scientific Ethical Committees for Southern Denmark under Project-ID: S-20130003. They notified that according to Danish law, no ethics approval was required for this type of study. Informed consent was obtained from all participating individuals. The Regional Ethics Committee of Southern Denmark approved the RCT (*paper IV*) under j. No: S-20140108 and the study conformed to the Declaration of Helsinki (World Medical, 2013) by fulfilling all general ethical recommendations. The study was registered at www.ClinicalTrias.gov under the identifier NCT02221986.

3.1 Study designs

This thesis includes two clinical trials. These include an initial preparatory feasibility study (*paper I*) and a full-scale RCT (*paper IV*). In between a study protocol (*paper II*) describing the development and rationale of the RCT were made public. It also includes an exploratory cross-sectional study of baseline data from the two clinical trials (*paper III*).

The following information applies both clinical trials and the related cross-sectional study unless otherwise stated (*paper I, III* and *IV*).

3.2 Settings

OUH is one of four national hospitals, and the only hospital within the Region of Southern Denmark to perform surgery and manage chemo-radiation treatments of patients with glioma. Approximately 90 patients are treated annually. All assessments and intervention took place at the Rehabilitation, and the Neurology department, OUH.

3.3 Study population

Patients eligible for study entry had to comply with all criteria as listed in table 3.

Table 3 Criteria for in- and exclusion

Inclusion	Exclusion
▪ Histologically confirmed diagnosis of glioma (WHO grade I-IV) ▪ Age ≥18 ▪ Treatment at OUH ▪ Ability to communicate in Danish	▪ Ependymomas (as they are extremely rare) ▪ Karnofsky Performance Status <70 ▪ Pregnancy ▪ Psychiatric diagnosis (schizophrenia, actively suicidal/self-harm, or physically aggressive) ▪ Heart problems (New York Heart Association group III or IV) ▪ Severe impressive or expressive aphasia

The reason for excluding patients presenting with KPS <70 was to ensure inclusion of patients that were able to conduct the interventions at an active and independent level, having cognitive ability to complete questionnaires, and be socially competent to interact with other patients in the research. Other reports investigating physical functioning support this criterion, and ensure comparability (Ruden et al., 2011; Jones et al., 2010a).

3.4 Recruitment

Recruiting of patients in the feasibility study (*paper I*) was made by the consulting physician at the Neurooncology center, OUH. This procedure restricted participation to include patients residing at Funen (local island), which created geographical limitations.

Recruitment of patients in the RCT (*paper IV*) was informed on the feasibility study (*paper I*), and followed standardized procedures in cooperation with a specialist nurse. She approached all eligible patients and asked permission for the primary investigator to make contact when the histological diagnosis of glioma was confirmed. The study included patients from the entire Region of Southern Denmark.

3.5 Trial intervention

Patients that entered (*paper I*), or were allocated to study interventions (*paper IV*) received interdisciplinary rehabilitation of physical therapy and occupational therapy. The intervention was initiated simultaneously with the establishment of the chemo-radiation treatment and ran for the full six weeks of the standard radiation regime. All interventions were completed in immediate continuation of the irradiation treatment, as the patients already attended the hospital. Follow-up assessment was aligned with the conclusion of the radiation treatments.

3.5.1 Physical therapy interventions

The supervised physical therapy intervention included three sessions per week (Monday, Wednesday, Friday) and was conducted in groups with up to four patients attending simultaneously. The intervention included a fixed exercise protocol, but had time allocated to perform individual physical therapy related to patients' specific deficits or impairments. Intensities and loads of the exercises were individually calculated based on results from the baseline assessment. A detailed rationale for developing the intervention is described in a case report (Hansen et al., 2018). Table 4 describes the content of the physical therapy supervised interventions. Balance enhancing exercises were performed by the Nintendo Wii balance board (playing Wii Fit Plus) or by therapist-guided exercises. Table 5 describes the content of the balance training.

Table 4 An example of the exercise protocol template

Week 1	Exercise #	Exercise name	Time / Sets* Reps	Intensities /Load	Watt/ pulse/ km Weight (kg)	Comments, NRS
Warm-up 5 min.						
Date: **Session# x**	1	Cycle /treadmill	20 min	65-75% HRR	xxx	
	2	Leg press	3 x12	12RM*	Xxx	
BP: xx/xx	3	Elbow extension	3 x12	12RM*	Xxx	
Resting pulse: xxx	4	Elbow flexion	3 x12	12RM*	Xxx	
	5	Knee extension	3 x12	12RM*	Xxx	
	6	Knee flexion	3 x12	12RM*	Xxx	
	7	Balance PT guided / Nintendo Wii	Describe:			

*Progressed to 10 RM at the sixth session. Equipment: Cycle [SCIFIT ISO1000], Treadmill [SCIFIT AC5000] Resistance training machines [Tuffstuff 804, 806, 830]. HRR Heart-rate reserve, NRS Numeric rating scale 0 (best) 10 (worst).

Table 5 A description of the balance exercises performed

Nintendo Wii balance games from Wii Fit Plus	
Tilt Table	Players try to direct a marble (or several depending on level) into a hole(s) by tilting the body left and right, or leaning forward and backward. Players have 30 seconds to complete the game to enter the next level. The game focuses on weight shifting in mediolateral and anteroposterior directions, quick motor response ability and improvement of attention and coordination by visual feedback
Ski slalom	Players try to ski down a slalom slope trying to navigate through gates by leaning left and right, and leaning forward and backward to control the pace. The game focuses on shifting weight in anteroposterior and mediolateral directions, changing and maintaining the position of the center of gravity and improvement of attention and coordination by visual feedback
Ski jump	Players try to jump as far as possible from a steep slope, standing in a position of flexed hips, knees and angles and rapidly extending at a precise moment holding the upraised position. The game focuses on quick motor response ability and improvement of attention and coordination by visual feedback
Physical therapist guided 'core stability' exercises on a therapist ball in a sitting position	
Static sitting balance	· Maintain correct lumbar posture and balance while seated on the therapist ball · Sit with eyes closed · Spread your arms and alternately rotate the head to each side
Trunk Flexion	· Flex and extend the trunk without moving forward or backward · Flex and extend the lumbar part of the spine · Trunk Flexion Flex and extend the hips (with similar trunk movement) by leaning forward and backward · Laterally flex the trunk · Rotate the trunk
Weight shift	· Shift weight from one side to the other and lean forward and backward with small controlled rolling movements · Weight shift Reach destined objects by forward- and laterally flexing the trunk (rotating components was also included) · The physical therapist gave perturbations in all directions

Precautionary screenings were made before each session (Hansen et al., 2014). Intensities and loads were adjusted according to the daily status of patients.

3.5.2 Occupational therapy interventions

The occupational therapeutic intervention included two sessions per week (Tuesday, Thursday).

Initially, an interview identifying resources and limitations of everyday life occupations and occupational performances was performed by the Canadian Occupational Performance Measure (COPM) (Law et al., 2015). If a patient, based on the COPM interview, confirmed no impairments of occupational performances, the therapy was not applied. To enable the therapist and patient to create goals for the intervention the Assessment of Motor and Process Skills (AMPS) was performed (Fisher, 2010). The intervention was concluded before the full duration of the intervention course if the patient and therapist, in collaboration, decided that the set goals were attained. A thorough rationale for designing the occupational therapy intervention has been published (Hansen et al., 2017a).

3.6 Adherence and compliance

- Adherence was defined as the number of physical therapy sessions attended by a patient. Adherence was dichotomized and considered high if the patient attended 10 or more sessions, and low if attending nine or fewer sessions.

- Compliance was defined as exercises performed at each physical therapy session. Compliance was dichotomized and considered high if the patient completed six or more exercises from a possible seven, and low if five or fewer were completed at each session.

Adherence and compliance of occupational therapy were assessed in the feasibility study (*paper I*) for exploratory reasons.

3.7 Patient characteristics

At the baseline assessment patient characteristics were self-reported (age, gender, living status, educational degree, and employment status). Anthropometric variables of weight and height were measured to calculate body mass index (BMI: kg/m2). In the cross-sectional study (*paper III*) and the RCT (*paper IV*) specific tumor and treatment variables were retrospectively extracted from pre- and post-resection MRI definitions (tumor location at left- or right-hemisphere, lobe, if the tumor created displacement of midline structures, residual tumor after surgery, and hematoma or infarct in the cavity) by an experienced Neurosurgeon, and from medical records (histopathology, radiation, chemotherapy steroid, and antiepileptic drug use). Performance status (KPS) was evaluated at the assessment.

3.8 Outcome measures

A statistical analysis plan that was made public before data was analyzed describes outcome measures and analyses intended for reporting in the RCT (Hansen, 2018). Some outcome measures are not presented in this thesis, as they do not inform on the specific aim. Table 6 presents a summary of the outcome measures used.

Table 6 A schematic view of the outcome measures used

Paper	I	III	IV	Not reported in this thesis
Patient-reported outcome measures				
• EORTC-QLQ-30	✓	✓	✓	–
• EORTC-BN-20	✓	✓	✓	–
• The Physical Activity Scale	–	–	–	✓
• Impact on Participation and Autonomy Questionnaire	–	–	–	✓
• Physical activity at leisure time (Saltin & Grimby)	–	–	–	✓
• EuroQol (Eq5-D)	–	–	–	✓
Functional performance outcomes measures				
• The Watt-Max cycle test	✓	✓	–	–
• The Åstrand / Rhyming ergometer test	–	✓	✓	–
• 3-8 repetition maximum tests of main extremity synergies (legpress, knee flexion & extension, elbow flexion & extension)	✓	✓	✓	–
• 10 Meter walking test	✓	✓	✓	–
• Bergs Balance Scale	✓	–	–	–
• Postural SWAY measures	–	–	✓	–
• Assessment of Motor and Process Skills	✓	✓	–	–

EORTC: European Organization for Research and Treatment of Cancer.

3.8.1 Patient-reported outcomes to measure health-related quality of life

HRQOL was measured by the European Organization for Research and Treatment of Cancer questionnaire (EORTC-QLQ-30) (Aaronson et al., 1993) and the specific brain cancer module QLQ-BN20 (Taphoorn et al., 2010). Both questionnaires have been comprehensively tested for psychometrics (Osoba et al., 1994; Taphoorn et al., 2010). The EORTC-QLQ-C30 consists of multi-item scales and single-item measures, which creates a Global Health Status/QOL scale (GHS/QOL), five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), three symptom scales (fatigue, nausea and vomiting, and pain), and six single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). According to methods described in the 3rd edition of the EORTC-QLQ-C30 Scoring Manual, all measures are linearly transformed to a numeric value ranging from 0 to 100. High values for the GHS/QOL and functional scales represent high QOL and high levels of functioning, whereas high values for symptom scales/items represents a high symptom burden (Fayers PM, 2001).

The QLQ-BN20 consists of four multi-item symptom scales (future uncertainty, visual disorder, motor dysfunction and communication deficit), and seven single symptom items (headaches, seizures, drowsiness, itchy skin, hair loss, weakness of legs, and bladder control). All measures were linearly transformed to a 0–100 value, with higher values representing higher levels of symptoms (Taphoorn et al., 2010).

3.8.2 Measures used to assess functional performance

As the study includes a population with significant variations in functional impairments and age, a continuum of functional performance tests was applied to ensure that vital aspects of functioning were measured.

Functional performance was defined by quantitative measures of (I) aerobic power, (II) dynamic muscle strength (knee extension, knee flexion, elbow flexion, elbow extension and leg press), (III) balance, and (IV) walking ability.

3.8.3 Maximum oxygen uptake

***Paper* I**

The Watt-max cycle test was used to assess maximum oxygen uptake by a formula developed by Andersen et al. (Andersen, 1995). The test started with a familiarization and warm-up period at a submaximal load of 100 Watt for men and 70 Watt for women, with a pedal frequency at 70 rounds per minute (rpm). The load was increased by 35 Watt every two minutes until the patient reached exhaustion.

***Paper* IV**

The Aastrand-Rhyming cycle ergometer test was used to assess maximum oxygen uptake (Astrand and Ryhming, 1954). The endpoint builds on a linear relationship between maximum oxygen uptake and heart rate. The workload pulse was supervised using a wireless heart rate transmitter (Polar FT40). During the first minutes, resistance (Watt) was increased to produce a steady-state heart rate between 110 and 170 beats/min. at 60 rpm. If the heart rate after six minutes was >110 and <170beats/min. without fluctuating more than five beats/min. for one minute, the test was complete.

Both tests predict patients' maximal oxygen uptake, which was divided by body weight to estimate aerobic power ($mlO^2.kg^{-1}.min^{-1}$).

3.8.4 Muscle strength

Dynamic muscle strength was assessed by the repetition maximum principle, where one repetition maximum (RM) for a given exercise is the maximum load that can be handled in a single execution. Patients performed a 3-8RM test. 1RM loads were predicted by Brzycki's equation (Brzycki, 1993).

3.8.5 Walking ability

Walking ability was assessed by a 10-meter walking test. Three trials of 10-meter walking at habitual speed initiated from a standing position were conducted. Time was registered with a stopwatch able to record 1/100 seconds. The average time was used to estimate gait velocity by dividing to a m/sec (Watson, 2002).

3.8.6 Balance

Paper I

Balance evaluations were made using the Berg Balance Scale (Berg et al., 1992) (BBS), which is a valid and reliable tool for assessing balance (Blum and Korner-Bitensky, 2008). It comprises a set of 14 simple balance related tasks, ranging from 'standing up from a sitting position' to 'standing on one leg'. The degree of success at each task is given a score from zero (unable) to four (independent). The final measure is the sum of all tasks.

Paper IV

A Nintendo Wii Balance Board using a custom-written software in Matlab assessed static balance. Three trials of 30-second, double-limb standing test with feet together, and hands placed on contralateral shoulders, and eyes open was performed. Between trials, 30 seconds of rest was given. Measures of the center of pressure consisting of anterior/posterior and medio/lateral displacements were calculated. A 95% confidence ellipse area (CEA) was calculated for the center of pressure as the reported outcome (Prieto et al., 1996)

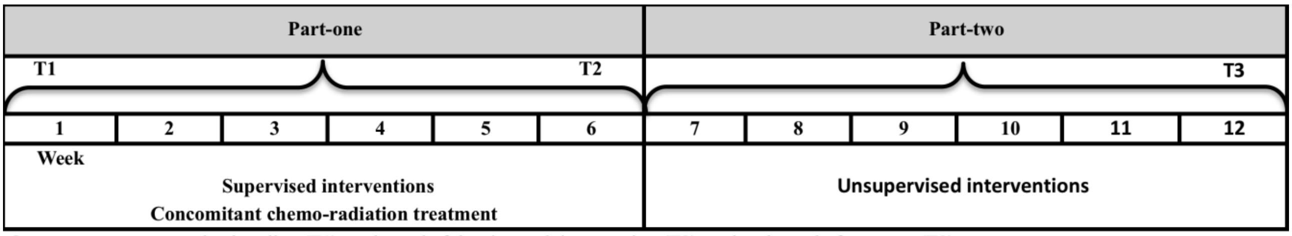
3.9 Procedure

3.9.1 Paper I

The feasibility study investigated the safety and feasibility of a two-part interdisciplinary rehabilitation intervention lasting for 12 weeks in total (figure 2). Each part included six weeks of physical therapy and occupational therapy if needed. Part one was conducted during the period of the chemo-radiation therapy at OUH with interventions as previously described. Part two was conducted in immediate continuation of part one. It included a six-week membership at a local gym. Patients followed instructions from an exercise protocol and extended the exercise intervention at part one. If the patient attended occupational therapy at part one, a weekly telephone-guided intervention was given by the treating occupational therapist. At follow-up, patients were asked to elaborate on their experience of participating the intervention for an evaluation questionnaire customized to the trial.

Outcomes were assessed at study entry (T1), at the conclusion of part one (T2), and at the end of part two (T3).

Figure 2 A schematic view of the study course



Outcomes were assessed at baseline (T1), at the end of the six-week intervention (T2), and at the end of part-two (T3)

Safety and feasibility were monitored and assessed using the following predefined criteria:

- A high level of clinical safety, defined as absence of injuries related to the intervention
- 80% consent from patients invited
- 20% drop-out
- 80% mean adherence to the physical therapy and occupational therapy
- Potential effects in HRQOL, symptoms and functional performance
- Assessment tools were feasible and responsive to changes within the patient group
- 80% of patients rated that they were satisfied with the overall intervention at part one and two respectively

3.9.2 Paper III

An exploratory cross-sectional study of patients from the two clinical trials was carried out. It was designed to evaluate baseline data of patients with primary glioma at the beginning of the chemo-radiation treatment. Patients were for exploratory reasons stratified into two groups by a tumor location at the left- or right-hemisphere from MRI definitions. The intention was to investigate if patients differ regarding HRQOL and functional performance. Patients with a WHO grade I tumor or with a tumor affecting both hemispheres were excluded from the analysis to isolate pure hemispheric tumors. Also patients with a tumor located in the brainstem were excluded the analyses, as the side of the brainstem lesion is of no consequence for HRQOL and functional performance.

3.9.3 Paper IV

This assessor-blinded RCT with assessments at baseline (T1), at follow-up at six weeks (T2), at 12-week follow-up (T3), and at six-month follow-up (T4) was designed to investigate the effectiveness of an interdisciplinary rehabilitation intervention of patients with primary glioma, compared to patients attending standard rehabilitation. Results presented in this thesis are limited to the acute effects from T1 and T2 (figure 3) as T3, and T4 follow-up data are incomplete. The study intervention was as previously described.

Figure 3 A schematic view of the study course

<table>
<tr><th colspan="3">Recruitment</th><th colspan="10">Concomittant chemo-radiation therapy and follow up</th></tr>
<tr><td rowspan="3">Surgical procedure</td><td rowspan="3">Histological diagnosis establishment</td><td rowspan="3">Eligibility Screening</td><td>T1</td><td colspan="4">Intervention or standard rehabilitation</td><td>T2</td><td colspan="2">T3</td><td colspan="2">T4</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>……</td><td>12</td><td>…..</td><td>26</td></tr>
<tr><td>Week
Informed consent / randomisation</td><td colspan="5"></td><td colspan="4"></td></tr>
</table>

Outcomes were assessed at baseline (T1), at the end of the six-week intervention (T2), at a 12 week FU (T3), and questionnaires were sent at 6 month FU (T4)

3.9.3.1 Controls

The control group received standard rehabilitation, which corresponded to the level of rehabilitation a patient would attend after hospital discharge. Before leaving the Neurosurgical department at OUH, patients will have an evaluation of their need for rehabilitation, per instruction from the Danish Health Authority (Sundhedsstyrelsen, 2015). This evaluation may advise: no rehabilitation, rehabilitation established by the municipality, or as specialized outpatient rehabilitation established at the hospital.

3.9.3.2 Randomization and blinding

The randomization sequence was created using Statistical Package for the Social Sciences (SPSS) version 21 for Windows, and stratified patients by tumor classification LGG / HGG with an even allocation. Blocks randomly varying in sizes from 8-10 were prepared in continuously numbered, opaque and sealed envelopes by a staff-member otherwise uninvolved in the conduction of the study. Immediate after baseline assessments, the allocation was revealed to the patient but kept hidden from outcome assessors.

3.9.3.3 Primary objective and outcome

The primary outcome was to compare changes from T1 to T2 between groups in the GHS/QOL domain (q 29 +30) from EORTC-QLQ-30 questionnaire (Osoba et al., 1998).

Patients were asked: “How would you rate your overall health during the past week?” and ”How would you rate your overall quality of life during the past week?” The overall summarized score of GHS/QOL reflect a patients’ ‘overall QOL’.

3.9.3.4 Secondary outcomes

The secondary outcomes were to compare changes from T1 to T2 between the groups in measures of HRQOL domains, symptoms, and functional performance.

3.10 Sample size

Paper I

When the feasibility study was designed, no study had investigated the feasibility of an interdisciplinary rehabilitation effort of patients with gliomas in the initial treatment phase. As such, no previous data were available for the sample size estimations. However, according to the literature, a sample size between 24 and 50 is sufficient to obtain viable feasibility objectives (Lancaster et al., 2004; Browne, 1995; Sim and Lewis, 2012; Julious, 2005).

Paper IV

This study is the first to investigate the effectiveness of interdisciplinary rehabilitation of patients with glioma using a randomized design; therefore information regarding SD and effect size from this sort of intervention from previous studies was unavailable. The sample size was consequently calculated based on results from the feasibility study *(paper I)*. At the expected ‘effect size’ of 10 points (0.407) with SD ± 24.6 in ‘overall QOL’ with a statistical power of $\beta = 0.8$ and $\alpha = 0.05$, the study required 76 participants in each group. To meet an expected dropout rate of approximately 15% a total of 88 participants in each group were planned.

3.11 Statistical evaluation

Patient demographics and characteristics in all three papers are reported from descriptive statistics using number and mean, or median and range. Statistical analyses were performed in SPSS for paper I, and in Stata 15 (StataCorp, College Station TX, USA) for the cross-sectional study (*paper III*) and the RCT (*paper IV*).

3.11.1 Paper I

Descriptive statistics were used to evaluate feasibility and safety objectives. Based on the complete case principle paired sample t-tests were used to compare outcome measures from T1 to T2, and T2 to T3 of EORTC-QLQ-30, BN-20, and functional performance outcomes.

3.11.2 Paper III

Summary statistics describe group characteristics, and independent t-tests or Chi^2 tested group differences. Statistical significance of outcome measures of EORTC-QLQ-30, BN-20, and functional performance was assessed using independent t-tests. To investigate any confounding effects, which may be caused by the subset of different WHO grades, a subgroup was constructed. It included patients with grade IV tumors only (Glioblastoma Multiforme) by excluding patients with grade II and III tumors. All analyses conducted on the complete cohort (including the grade II and III cohort) were repeated on the Glioblastoma Multiforme subgroups.

3.11.3 Paper IV

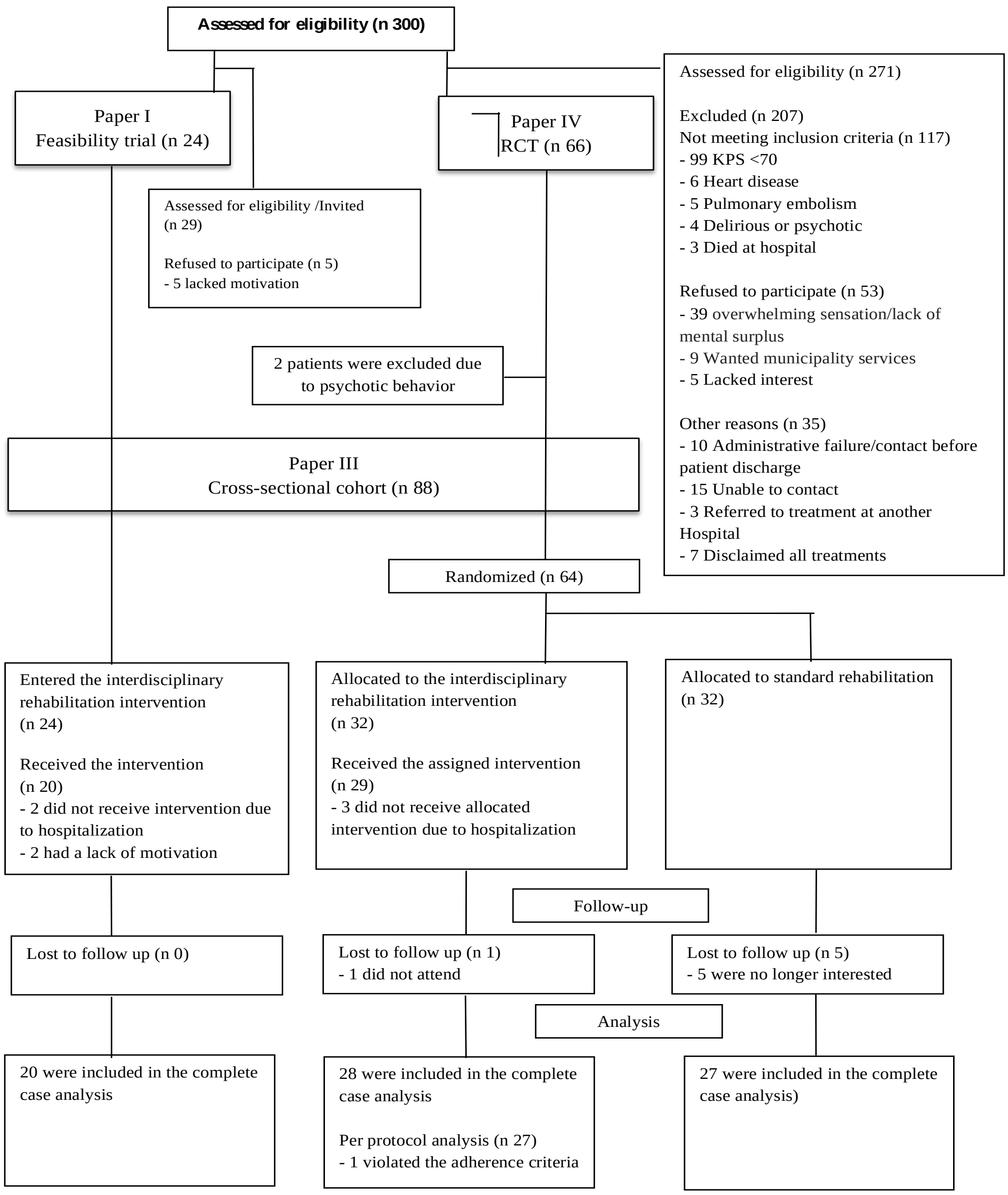
The analysis was based on a complete case principle. To test the effectiveness of the intervention on the primary outcome, a multiple regressions model was created with overall QOL at follow-up adjusted for group-allocation, gender, tumor grade (II / III-IV) and overall QOL baseline values. Overall QOL residuals after regression on covariates were checked for normality by visual inspection using a Q-Q plot, and variance homogeneity were inspected from plots of residuals against the predicted outcome. All secondary outcomes were handled similarly to the primary outcome. For sensitivity, per-protocol analysis including only patients with high adherence and compliance were conducted, and a baseline value comparison of completers and non-completers was performed.

4 Results

In total, 88 patients with primary glioma (mean age 55.4, SD 13.5) have contributed to the findings of the thesis. Figure 4 illustrates the flow of patients in the respective studies. During the period of active patient intake, 300 patients with confirmed primary glioma diagnosis were assessed for eligibility. Inspite considerable efforts, one cannot be sure whether some patients may have slipped by unnoticed, but assuming 90 patients are diagnosed each year, the vast majority of patients have been assessed for eligibility.

4.1 Patient flow

Figure 4 Flow chart for the entire study population; enrolment, follow-up, and analysis.



Schematic study design. On the left-hand side, the feasibility study (*paper I*) is outlined. On the right-hand side the RCT (*paper IV*) is outlined. These studies pass through the cross-sectional study (*paper III*). Interdisciplinary rehabilitation: six weeks of rehabilitation during anti-cancer treatments. Standard rehabilitation: the usual rehabilitation regimen during anti-cancer treatments.

4.2 Paper I

The feasibility study evaluated the safety and feasibility of an interdisciplinary rehabilitation intervention of patients with glioma attending anticancer treatments, to provide a foundation for designing an RCT protocol.

4.2.1 Safety and feasibility objectives

Between April 2014 and March 2015, 24 of 29 invited patients consented the feasibility study (83%) (median age 62, range 20-77, male 14, HGG 20).
No patients got injured, fell or displayed signs of discomfort, spontaneous or unexpected reactions, or had adverse effects related to the intervention. 15 patients (63%) attended occupational therapy at part one. In total, four patients (17%) were lost to follow-up during part one. Two of these were hospitalized, and two lacked motivation. After the conclusion of part one and before initiating part two, eight patients (45%) were excluded as the therapists evaluated that it was not safe for them to participate in the self-administered intervention because of physical, cognitive, or visual deficits. These patients were referred to municipality rehabilitation services. During part two, one patient was forced to pull out because of exercise restrictions from eye surgery. This resulted in nine of 20 of the remaining patients were lost to follow (45%). Post hoc analysis found no differences in baseline variables between complete-cases and those who were lost to follow-up. Two patients had occupational therapy during the second part.

Adherence to the physical therapy and occupational therapy at part one was high (89% and 83%), whereas it was low at part two (53% and 100%) (table 7).

Table 7 Conclusions of predefined safety and feasibility objectives in a schematic view based on descriptive statistics.

Feasibility objectives	Part one (%)	Part two (%)
• A high level of clinical safety	Yes	Yes
• 80% consent from patients invited	Yes (83%)	–
• 20% drop-out	Yes (17%)	No (45%)
• 80% mean adherence to the PT and OT sessions	Yes (89%, 83%)	No (53%, 100%)
• Potential effects in HRQOL, symptoms and functional performance	Yes	No
• Assessment tools were feasible and responsive to changes within the patient group	No	–
• 80% of patients rated satisfaction with the overall intervention at part one and two respectively	Yes (95%)	No (63%)

Yes=met predefined safety and feasibility objectives, No= did not meet predefined safety and feasibility objectives.
PT, physical therapy OT, occupational therapy. The table is from *paper I*

4.2.2 HRQOL, symptoms and functional performance

Based on the EORTC-30 questionnaire from T1 to T2, patients statistically significant increased 'emotional functioning' (p=0.02) and decreased 'fatigue' (p=0.01) (table 8). Results from the BN-20 showed that patients decreased symptoms of 'future uncertainty' (p=0.01), but were also more affected by 'hair loss' (p<0.01) (table 9). Functional performance was improved by muscular strength: Leg press (p<0.01), knee extension (p<0.01), knee flexion (p<0.01), elbow extension (p<0.01), elbow flexion (p<0.01), and in aerobic power (p=0.05). Patients also reduced step frequency of walking 10 meters (p<0.01) (table 10).

Data from T2 to T3 showed no statistically significant changes in clinically relevant scales or items in EORTC-QLQ-30, EORTC-BN-20 or functional performance related to this study.

Table 8 Health-related quality of life outcome variables and p-values

Outcome Variable	**Mean (SD)**		**Mean difference (95% CI)**	***p*-value**
n=20	T1	T2		
Global health status / QoL				
Global health status	65.8 (24.6)	71.7 (21.2)	-05.8 (-19.8 to 8.2)	0.40
Functional Scales				
Physical function	83.7 (20.6)	87.3 (14.0)	-03.7 (-10.9 to 3.5)	0.30
Role function	65.8 (37.3)	70.8 (27.0)	-05.0 (-18.2 to 8.2)	0.44
Emotional function	74.2 (24.6)	84.2 (21.8)	-10.0 (-18.4 to -1.6)	**0.02**
Cognitive function	64.2 (31.2)	72.5 (21.8)	-08.3 (-19.5 to 2.8)	0.14
Social function	75.8 (23.9)	81.7 (26.4)	-05.8 (-19.3 to 7.6)	0.38
Symptom scales / items				
Fatigue	41.1 (26.8)	27.2 (20.9)	13.9 (04.2 to 23.6)	**0.01**
Nausea and vomiting	08.3 (14.8)	05.0 (07.8)	03.3 (-03.2 to 09.8)	0.30
Pain	04.2 (09.2)	09.2 (17.5)	-05.0 (-13.0 to 03.0)	0.21
Dyspnoea	06.7 (13.7)	05.0 (12.2)	01.7 (-04.5 to 07.8)	0.58
Insomnia	25.0 (30.3)	16.7 (29.6)	08.3 (-07.6 to 24.2)	0.29
Appetite loss	05.0 (12.2)	03.3 (10.3)	01.7 (-04.5 to 07.8)	0.58
Constipation	15.0 (22.9)	13.3 (27.4)	01.7 (-12.2 to 15.5)	0.80
Diarrhoea	05.0 (16.3)	06.7 (17.4)	-01.7 (-11.1 to 07.8)	0.72
Financial difficulties	10.0 (24.4)	05.0 (12.5)	05.0 (-08.7 to 18.7)	0.45

Paired sample *t*-test

CI Confidence Intervals. T1 Baseline, T2 six week follow up.

High scores equal high levels of QOL and functioning from the Global health status /QOL and functioning scale, whereas high levels of symptom scales/ items represents a high symptom burden. The table is from paper *I*

Table 9 Symptom variable variables and p-values

Outcome Variable	Mean (SD)		Mean difference (95% CI)	*p* value
n=20	T1	T2		
Future uncertainty	33.3 (28.7)	15.0 (18.1)	18.3 (07.3 to 29.3)	**0.01**
Visual disorder	07.8 (11.5)	06.7 (11.6)	01.1 (-01.8 to 04.0)	0.43
Motor dysfunction	12.2 (22.8)	09.4 (17.0)	02.8 (-02.2 to 07.8)	0.26
Communication deficit	15.6 (25.1)	11.7 (19.2)	03.9 (-01.5 to 09.3)	0.15
Headaches	10.0 (15.7)	06.7 (13.7)	03.3 (-05.3 to 12.0)	0.43
Seizures*	01.7 (07.5)	01.7 (07.5)	-	-
Drowsiness	58.3 (28.4)	43.3 (32.6)	15.0 (-02.1 to 32.1)	0.08
Itchy skin	06.7 (13.7)	13.3 (19.9)	-06.7 (-17.5 to 04.2)	0.21
Hair loss	03.3 (14.9)	36.7 (28.4)	-33.3 (-48.5 to -18.1)	**0.01**
Weakness of legs	15.0 (22.9)	08.3 (18.3)	06.7 (-01.5 to 14.8	0.10
Bladder control	15 .0 (29.6)	11.7 (24.8)	03.3 (-01.5 to 08.1)	0.16

Paired sample *t*-test
*The correlation and t cannot be computed because the standard error of the difference is 0.
CI Confidence Intervals. CI Confidence Intervals. T1 Baseline, T2 six week follow up.
High levels of symptom scales/ items represent a high symptom burden. The table is from paper *I*.

Table 10 Physical function outcome variables and p-values

Outcome Variable	Mean (SD) T1	Mean (SD) T2	Mean difference (95% CI)	*p* value
Muscle strength (kg) (n=19)				
Leg press	118.1 (33.5)	156.3 (36.0)	-38.2 (-54.8 to -21.6)	**0.01**
Knee extension	051.5 (16.6)	066.0 (19.7)	-14.5 (-19.7 to -09.2)	**0.01**
Knee flexion	044.8 (16.8)	052.3 (15.2)	-07.5 (-11.5 to -03.5)	**0.01**
Arm flexion	028.5 (12.6)	032.7 (13.1)	-04.2 (-06.4 to -02.0)	**0.01**
Arm extension	018.1 (05.3)	022.6 (06.0)	-04.5 (-50.8 to -03.0)	**0.01**
Gait function (n=19)				
Gait velocity (sec.)	07.6 (02.4)	07.2 (01.7)	00.4 (-00.1 to 00.9)	0.14
Step frequency	13.7 (03.0)	12.6 (02.0)	01.1 (00.4 to 01.8)	**0.01**
Balance (n=19)				
Bergs Balance scale	53.8 (03.6)	54.8 (02.0)	-01.1 (-03.0 to 00.9)	0.26
Cardiovascular fitness (n=17)				
Aerobic power	22.6 (10.1)	26.7 (16.1)	-04.1 (-08.1 to 00.0)	**0.05**
Activity and Performance status (n=10)				
Motor	02.1 (01.4)	02.2 (01.2)	-00.1 (-00.4 to 00.2)	0.39
Process	01.7 (00.5)	01.5 (00.5)	00.1 (-00.2 to 00.5)	0.43

Paired samples t-test
CI Confidence Intervals .The table is from paper *I*. CI Confidence Intervals. T1 Baseline, T2 six week follow up.

4.2.3 Assessment tools

Though the Watt-Max cycle test was responsive to chances, it was not considered feasible within the patient group. Some patients were forced to conclude the test before valid measures could be assessed as their ability to reach maximum cardiovascular function was compromised by fatigue or weakness of the legs. Likewise, the Bergs Balance Scale showed limitations regarding ceiling-effects in detecting impaired balance and thus was not responsive to changes.

4.2.4 Patient satisfaction with the intervention course

Based on responses from the evaluation questionnaire patients, in general, were satisfied with the content at part one, but displeased with part two (table 11). The following significant quotes are used to illustrate important aspects of patients taking part in a rehabilitation intervention.

'*Keep the exercise training at the hospital for all 12 weeks. I need help with my training, and I do not get that in a gym. Generally, I have been extremely pleased with the program at the University Hospital, and I think that the therapists have shown great empathy and insight toward my needs'*. (Female, 43 y, WHO grade II)

'*It is hard for me to assess the effect of the physical training, but I have not doubt that the physical contact and the shared physical constraint on the team have been of the utmost importance for my energy and my belief in the continued treatment. So, physical training in a social "team-frame" under therapeutic guidance is undoubtedly relevant and valuable*'. (Male, 67 y, WHO grade IV)

Table 11 Patients evaluation on the feasibility study

Part one	*n*	**Strongly or partly agree** (%)	**Neutral** (%)	**Strongly or partly disagree** (%)
The amount and intensity of interventions was acceptable	20	90	0	10
Time consumption at assessment trials was acceptable	20	75	20	5
I was overall satisfied with the content of part one	20	95	0	5
Part two				
The gym training was satisfying	8	50	0	50
The telephone-guided OT intervention was satisfying	2	100	0	0
Time consumption at assessment trials was acceptable	8	25	12.5	62.5
I was satisfied overall with the content of part two	8	62.5	0	37.5

Table is from *paper I*

4.3 Paper III

This exploratory cross-sectional study evaluates baseline data of patients at the beginning of their chemo or radiation therapy. It investigates if patients with tumors located at the left- or right hemisphere differ in HRQOL, symptoms, and functional performance outcomes, which might suggest differentiated rehabilitation approaches.

In total, 90 patients were assessed between April 2014 and December 2017. Two patients were excluded at assessments due to psychotic behavior and was referred to evaluations elsewhere. Due to the purpose of this study, seven patients have been excluded from the analysis due to either bilateral hemispheric tumors (*n*=4), tumor location in the brain stem (*n*=2) or from having a WHO grade I tumor (*n*=1). This resulted in a cohort of 81 patients available for analysis. The mean time from the craniotomy to assessments was 40 days in both groups. 45 patients (56%) had a tumor in the right hemisphere, and 36 patients (44%) had a tumor in the left hemisphere. 70 patients (86%) had an HGG, and 11 patients (14%) had an LGG. No statistically significant differences in anthropometric, socio-demographic variables or KPS were found. Except significantly more patients with tumors in the left hemisphere had their tumor located in a critical (eloquent) brain area ($p<0.01$) the remaining details of tumor variables, surgical and medical variables were similar among the groups.

4.3.1 HRQOL, symptoms, and functional performance

Patients with gliomas located at the right- or left hemisphere present with similar HRQOL (table 12). The only present group differences were found in the QLQ-BN-20 item 'communication deficits (p=0.01)', which were more frequent in the left side, and in the item 'headache (p=0.02)', which were more frequent in the right side gliomas (table 13).

Table 12 Health-related quality of life of patients with left and right hemispheric glioma assessed by the EORTC-QLQ-30

Variable	**Right hemisphere (n=45)**	**Left hemisphere (n=36)**	**p-value**
	Mean (SD)	Mean (SD)	
Global health status/QOL	66.1 (20.4)	64.1 (23.9)	0.69
Physical functioning	80.8 (20.0)	85.1 (18.0)	0.32
Role functioning	57.5 (35.7)	64.8 (35.0)	0.38
Emotional functioning	73.6 (22.7)	76.4 (22.1)	0.59
Cognitive functioning	63.3 (31.5)	66.7 (27.0)	0.62
Social functioning	76.7 (30.3)	76.9 (24.6)	0.98
Fatigue	43.9 (27.3)	33.6 (24.3)	0.08
Nausea and vomiting	14.4 (20.0)	14.4 (24.9)	0.99
Pain	14.4 (18.5)	09.7 (18.0)	0.26
Dyspnea	11.4 (21.5)	09.3 (18.9)	0.65
Insomnia	20.0 (27.0)	29.6 (30.6)	0.14
Appetite loss	15.6 (28.1)	14.8 (25.8)	0.90
Constipation	13.3 (22.9)	06.5 (13.8)	0.12
Diarrhea	08.9 (19.3)	06.5 (15.6)	0.55
Financial difficulties	13.6 (25.2)	12.0 (27.8)	0.79

High scores equal high levels of QOL and functioning from the Global health status /QOL and functioning scale, whereas high levels of symptom scales/ items represents a high symptom burden. Table is from *paper III*.

Table 13 The symptom burden of patients with left and right hemispheric glioma assessed by the BN-20

Variable	**Right hemisphere (n 45)**	**Left hemisphere (n 36)**	**p-value**
	Mean (SD)	Mean (SD)	
Future uncertainty	31.4 (25.2)	27.3 (22.7)	0.45
Visual disorder	15.4 (18.6)	14.2 (20.2)	0.78
Motor dysfunction	13.4 (19.5)	13.3 (20.5)	0.97
Communication deficit	08.6 (13.5)	19.4 (24.1)	**0.01**
Headaches	25.9 (30.9)	12.0 (21.3)	**0.02**
Seizures	04.4 (16.8)	08.3 (23.1)	0.38
Drowsiness	41.5 (34.9)	38.0 (29.0)	0.63
Itchy skin	20.7 (26.9)	16.7 (21.8)	0.46
Hair loss	11.9 (28.6)	08.3 (18.5)	0.52
Weakness of legs	09.6 (23.2)	06.5 (15.6)	0.49
Bladder control	12.6 (25.9)	07.44 (19.7)	0.32

High levels of symptom scales/ items represents a high symptom burden. The table is from paper *III*.

Patients with tumors in the right-hemisphere had greater difficulties with process-skills when performing ADL-tasks, than patients with left-hemispheric tumors ($p<0.01$). Otherwise, the groups presented with similar functional performance outcomes (table 14).

Table 14 Functional performance of patients with left and right hemispheric glioma

Variable	**Right hemisphere (n=45)**	**Left hemisphere (n=36)**	**p-value**
	Mean (SD)	Mean	
Walking ability (m/s)	0.78 (00.1)	0.76 (0.1)	0.55
Leg press (kg)	128.8 (40.8)	133.0 (44.0)	0.66
Aerobic fitness ($ml.O^{2}$-^{1}.kg-^{1})	13.8 (5.3)	13.6 (3.5)	0.84
$AMPS^{motor}$	2.2 (0.6)	2.4 (0.7)	0.24
$AMPS^{process}$	1.4 (0.4)	1.7 (0.4)	**<0.01**

Assessment of motor and process skills (AMPS)

The table is from paper *III*.

Within the Glioblastoma Multiforme sub-group analysis, there were respectively 34 and 26 patients with a tumor in the right and in the left hemisphere. All results from the complete cohort analysis (including grade II and III) were confirmed in the Glioblastoma multiforme subgroup, except patients with right-hemispheric tumors were statistically significant more affected by fatigue (p=0.05)

4.4 Paper IV

This randomized, controlled trial investigates the effectiveness of a six-week interdisciplinary rehabilitation intervention on overall QOL compared to standard rehabilitation.

Between December 2015 and December 2017, 64 patients underwent randomization with 32 patients allocated to each group. 28 of 32 patients (87%) in the intervention group and 27 of 32 patients (84%) in the control group attended follow-up assessment. Therefore, 55 patients were included in the complete case analysis (86%). One patient violated the adherence criteria, resulting in 54 patients contributing to the per-protocol analysis (84%). 15 patients (47%) in the intervention group attended occupational therapy. There were no differences in demographic characteristics or baseline outcomes of completers and non-completers. Baseline characteristics were well matched in the two study groups despite an uneven distribution of gender (p=0.03). Adherence and compliance were equally high (96%) within the intervention group, as per a priori adherence and compliance definition.

4.4.1 HRQOL, symptoms and functional performance

In the complete case analysis, the intervention group had a statistically non-significant greater improvement of overall QOL compared to the control group with an adjusted mean difference of 9% (95CI, -3.88 to 21.91). Within the control group the adjusted numerical difference from baseline to follow-up was -6.1% (95%CI, -15.1 to 2.89) and in the intervention group 2.9% (95%CI, -5.91 to 11.74). As compared with the control group, the intervention group had statistically significant greater improvement in the HRQOL domain 'cognitive functioning' (p<0.01), decreased symptoms of 'fatigue' (p=0.03) (table 1), 'visual disorder' (p=0.02), 'communications deficits' (p<0.01), 'drowsiness' (p=0.04), 'itchy skin' (p=0.02) (table 16), and improved functional performance of 'aerobic power' (p<0.01), 'leg press' (p=0.01), and 'elbow extension' (p=01) (table 17). The per protocol analysis also showed a statistically non-significant improvement of overall QOL in the intervention group. Of the secondary outcomes, the analysis yielded results similar to those of the complete case analysis, except that there were statistically significant between-group differences on the HRQOL domain 'social functioning' (p=0.03) (table 15) and in symptoms of 'pain' (p=0.02) and 'motor dysfunction' (p=0.04) in favor of the intervention group (table 16).

Table 15 Multiple linear regressions on EORTC-QLQ-30 outcomes at follow-up. All regressions are adjusted for group allocation, gender, tumor-type and baseline values. The table illustrates results between the groups in the complete case and the per protocol population

	Complete Case						Per Protocol			
				95% CI				95% CI		
Variable	Control mean	Intervention mean	*β*-coefficient	Upper	Lower	*p*	*β*-coefficient	Upper	Lower	*p*
GHS/QOL	59.0	68.0	09.0	-03.87	21.91	0.17	09.9	-03.88	23.19	0.14
Physical functioning	80.8	87.6	06.7	-00.52	14.01	0.07	07.2	-00.43	14.74	0.06
Role functioning	58.7	70.4	11.7	-03.17	26.57	0.12	13.7	-01.49	28.99	0.08
Emotional functioning	75.9	80.2	04.3	-07.67	16.28	0.47	06.8	-04.33	17.92	0.23
Cognitive functioning	61.3	77.8	16.5	05.43	27.56	**<0.01**	17.2	05.72	28.63	**<0.01**
Social functioning	71.0	81.5	10.5	-01.90	22.93	0.09	13.1	01.20	24.93	**0.03**
Fatigue	45.9	33.6	-12.3	-23.52	-01.01	**0.03**	-13.4	-24.87	-01.93	**0.02**
Nausea and vomiting	11.6	11.8	00.2	-09.68	10.10	0.97	00.6	-09.55	10.83	0.90
Pain	17.9	08.0	-09.9	-20.64	00.75	0.07	-12.2	-22.34	-01.98	**0.02**
Dyspnea	13.3	09.7	-03.6	-14.98	07.78	0.53	-02.1	-13.94	09.64	0.72
Insomnia	27.7	17.3	-10.4	-26.90	06.10	0.21	-11.8	-28.83	05.23	0.17
Appetite loss	18.6	15.5	-03.1	-17.58	11.26	0.66	-05.5	-20.02	09.01	0.45
Constipation	09.1	06.7	-02.4	-14.19	09.36	0.68	-02.0	-14.20	10.22	0.75
Diarrhea	14.9	05.9	-09.0	-18.58	00.60	0.07	-08.1	-17.96	01.67	0.10
Financial difficulties	20.4	14.9	-05.5	-14.46	03.38	0.22	-05.2	-14.42	04.02	0.26

CI Confidence Intervals
β Average group mean difference
High scores equal high levels of QOL and functioning from the Global health status /QOL and functioning scale, whereas high levels of symptom scales/ items represents a high symptom burden. The table is from *paper IV*

Table 16 Multiple linear regressions on EORTC-BN-20 outcomes at follow-up. All regressions are adjusted for group allocation, gender, tumor-type and baseline values. The table illustrates results between the groups in the complete case and the per protocol population

	Complete Case						**Per Protocol**			
				95% CI				95% CI		
Variable	Control mean	Intervention mean	*β*-coefficient	Upper	Lower	*p*	*β*-coefficient	Upper	Lower	*p*
Future uncertainty	29.6	20.3	-09.3	-21.93	03.31	0.15	-10.6	-23.35	02.24	0.10
Visual disorder	14.0	07.1	-06.9	-12.71	-01.05	**0.02**	-06.9	-12.96	-00.88	**0.03**
Motor dysfunction	17.1	09.3	-07.8	-16.96	01.27	0.09	-09.3	-18.26	-00.38	**0.04**
Communication deficit	20.5	04.1	-16.4	-24.53	-08.30	**<0.01**	-16.6	-25.11	-08.19	**<0.01**
Headaches	21.2	08.7	-12.5	-24.11	-00.80	**0.04**	-12.5	-24.41	-00.67	**0.04**
Seizures	06.5	05.6	-00.9	-09.94	08.07	0.84	-00.9	-10.29	08.41	0.84
Drowsiness	41.3	29.2	-12.1	-23.45	-00.65	**0.04**	-13.5	-24.71	-02.20	**0.02**
Itchy skin	19.9	05.8	-14.1	-25.81	-02.49	**0.02**	-13.9	-25.96	-01.84	**0.03**
Hair loss	42.2	26.0	-16.2	-33.36	01.03	0.07	-16.2	-34.09	01.64	0.07
Weakness of legs	12.4	04.7	-07.6	-18.02	02.76	0.15	-07.4	-18.20	03.36	0.17
Bladder control	09.8	02.4	-07.4	-17.75	02.90	0.16	-07.3	-18.00	03.44	0.18

CI Confidence Intervals
β Average group mean difference
High levels of symptom scales/ items represent a high symptom burden. The table is from paper *IV*.

Table 17 Multiple linear regressions on functional performance outcomes at follow-up. All regressions are adjusted for group allocation, gender, tumor-type and baseline values. The table illustrates results between the groups in the complete case and the per protocol population

	Complete Case						**Per Protocol**			
				95% CI				95% CI		
Variable	Control mean	Intervention mean	*β*-coefficient	Upper	Lower	*p*	*β*-coefficient	Upper	Lower	*p*
Aerobic power	13.30	16.20	02.9	00.93	04.95	**<0.01**	03.2	01.07	05.23	**<0.01**
1RM Leg press	136.5	158.4	22.0	05.42	38.50	**0.01**	24.9	08.79	41.07	**<0.01**
1RM Knee extension	58.60	66.20	07.5	-00.92	15.98	0.08	08.1	-00.55	16.82	0.07
1RM Knee flexion	51.30	53.10	01.8	-04.77	08.43	0.58	02.7	-03.76	09.15	0.40
1RM Elbow extension	21.10	25.00	03.8	00.83	06.79	**0.01**	04.0	01.16	07.01	**<0.01**
1 RM Elbow flexion	32.50	38.80	06.3	02.61	10.01	**<0.01**	60.3	02.55	10.07	**<0.01**
Walking ability (m/s)	00.76	00.80	00.0	-00.08	00.09	0.10	00.0	-00.01	00.09	0.08
Balance 95% CEA (cm^2)	08.00	06.40	-01.6	-04.31	01.11	0.24	-01.7	-04.47	01.17	0.22

CI Confidence Intervals
CEA Confidence ellipse area
β Average group mean difference

5 Discussion

5.1 General findings

This research aimed to develop an interdisciplinary rehabilitation intervention with a strong emphasis on physical training, which is safe for patients with primary glioma, and superior to the current practice regarding effects on HRQOL, functional performance and symptomology. Results from the feasibility study (*paper I*) indicate that the intervention of supervised physical and occupational therapy during active medical anti-cancer treatment is safe and feasible, improves outcomes of some HRQOL domains, improves functional performance, reduces symptoms, and importantly, is valued by patients. The cross-sectional study (*paper III*) found that no differences in HRQOL exist between patients with gliomas located in the right or left hemisphere in the early disease period (40 days after resection). Only a few differences of symptomatology and functional performance were found. The RCT (*paper IV*) indicate that patients attending rehabilitation interventions of physical therapy and occupational therapy during active anti-cancer treatment insignificantly improve overall QOL compared to patients having the standard rehabilitation practice. They statistically significantly improved 'cognitive functioning', decrease a continuum of symptoms including fatigue, and improve functional performances.

5.2 Feasibility, safety, and supervision of the rehabilitation intervention

When the feasibility study (*paper I)* was designed, no previous trials had investigated the feasibility of outpatient rehabilitation of patients attending medical treatments. One previous investigation related to the patient group had established that quantitative functional assessments were safe and feasible (Jones et al., 2010b). In a retrospective survey of 106 matching patients, just 45% declared that they were interested in taking part in a physical activity program during adjuvant treatment and less than half (47%) felt that they were able to exercise during active treatment. Also, the majority of the responders preferred to exercise at home as opposed to a hospital or community-based fitness center (Jones et al., 2007). The findings suggest that patients find it hard to commit to concomitant intervention during medical procedures. Therefore, the feasibility study was ambitiously designed to evaluate the feasibility of rehabilitation in a hospital setting, as well as self-administered interventions in a gym. In contrast to the reported findings from the retrospective survey, our study found that the intervention at the hospital was feasible and positively rated by the patients (table 11). Several papers within this patient group have since confirmed that supervised interventions are safe and feasible (Milbury et al., 2017; Cormie et al., 2015; Nicole Culos-Reed et al., 2017; Capozzi et al., 2016). It was further concluded that the self-administered intervention (part two) was not feasible (table 7) due to low adherence and because it only suited specific patients with superior performance status. In contrast to this finding, a recent trial of home-based exercise intervention was found feasible in a subset of patients with stable WHO grade II or III gliomas years after diagnosis (Gehring et al., 2017). Most likely the different results are caused by the apparent differences of the inclusion criteria.

A consensus exists that exercise is safe for patients with cancer (Schmitz et al., 2010). During the feasibility study (*paper I*) and the subsequent RCT (*paper IV),* the general opinion was supported as no incidences related to the exercise intervention were registered. But specifically among patients with brain tumors, the consensus seems not to be publicly accepted. Based on empirical observations from this research a substantial discourse against exercise as dangerous was noticed. Although purely speculative, as the hypothesis was not tested, it is supported by one study that advises patients with brain tumors against vigorous exercise, as it may promote seizures (Adamsen et al., 2009). When recruiting for patients, many caregivers advised their loved ones against participation, as they felt it would add an unnecessary burden on the patient, in an already stressful treatment period. Also, some patients were reluctant to participate and only consented as a neurooncologist and a nurse were close by. On the contrary, the precaution screening before the exercise intervention combined with the daily observations from therapists and other patients, in general, ensured a high level of safety. One of the two patients that were hospitalized during part one of the feasibility study was directly founded on the therapists' observations. The patient gradually changed his behavior and became increasingly manic, which likely was an adverse effect from aggressive steroid use. Also, one patient from the control group in the RCT was referred for a cardiologic evaluation based on the therapists' observation. Although clearing the precaution screening before assessment, the patient developed cardiac arrhythmia during the aerobic fitness assessment. The chemotherapy was later found to be the cause. Besides, no adverse effects from the physical exercise occurred, these incidences supports that the additional meetings with therapists improve the general safety of patients during medical treatments.

Patients experience significant fluctuation in their daily physical, mental and emotional condition, particularly during periods of active treatment. This contributes to an inconsistency of functioning, which may hamper exercise retention and intervention adherence when not supervised. At part one of the feasibility study (*paper I*), a majority of patients in the daily sessions expressed a direct concern about performing vigorous exercise unsupervised. It has previously been reported that breast cancer survivors feel that the supervision of exercise interventions is crucial to reduce the fear of overexertion, injury and worsening of symptoms (Hayes et al., 2009). It seems plausible that patients with gliomas have similar concerns. Within this patient group, with the specific barriers of disease-related motor deficits, the supervision may have been a substantial contributing factor to the high adherence and study results. In both clinical trials the adherence was high (89%, 96%) considering the vulnerability of the patient group, and higher than what is reported in exercise studies of other cancer populations (Bourke et al., 2014). The high adherence may also be contributed to the design of the intervention just after radiation treatment, as patients did not have to travel to get interventions. It implies that the time-period of active chemo and radiation treatment at the hospital could be an optimal setting for patients to engage in physical an occupational rehabilitation interventions, especially as the intervention was able to reduce the treatment-related symptoms.

5.3 The impact on health-related quality of life from the interdisciplinary rehabilitation

Clinical drug trials of patients with glioma have traditionally focused on improving the overall and progression-free survival. Presently, QOL is considered to be of equal or even greater importance, as QOL outcomes may reveal issues that are more important to the patient than survival time (Taphoorn and Bottomley, 2005; Efficace and Taphoorn, 2012; Polin et al., 2005; Dirven et al., 2014; Walker et al., 2003), which justify the use of overall QOL as a primary outcome in this trial.

In the exploratory cross-sectional study (*paper III*) it was found that a tumor location at the right- or left-hemisphere respectively had no consequence for patients' perception of HRQOL in the early disease stage (table 12). This finding is a useful supplement to the sparse information on a possible specific impact of an affected right- or left hemisphere that could lead to a specific demand for rehabilitation. The result validates that no consideration of laterality has to be accounted for when designing a rehabilitation intervention intended to improve HRQOL at this disease state. Though previous studies reports differences of whether patients with left- or right-hemispheric gliomas perceive worse HRQOL (Palese et al., 2008; Cheng et al., 2009; Hahn et al., 2003; Giovagnoli et al., 1996; Salo et al., 2002) this result support most recent findings (Drewes et al., 2016; Cheng et al., 2010; Flechl et al., 2017). However, the studies use different methods and instruments, which hampers direct comparisons and a clear interpretation.

Results from the feasibility study (*paper I*) indicated that the intervention positively improves overall QOL (5.8%, p=0.4). Also, the domain "emotional functioning" (p=0.02) statistically significantly improved from baseline to follow-up (table 8). A recent report suggests that an improved emotional functioning could reflect patients being pro-active in their treatment by taking control of their life (Piil et al., 2018). In this study, patients commenced a healthy lifestyle through exercise, which may have led to the improved emotional functioning.

Results from the RCT (*paper* IV) further strengthen the view that interdisciplinary rehabilitation intervention improves patients HRQOL more than standard rehabilitation as all functioning domains (table 15), as all but one symptom item improved in favor of the intervention group (table 15, 16). Although the primary outcome of a 10% difference in overall QOL between groups was not found, it was close (9%). The control group had an adjusted numerically mean decrease in 'overall QOL' of -6.1%, which is within the proposed minimal clinically important difference ±5-10% range (Maringwa et al., 2011). It may reflect the natural course of declined QOL patients with glioma eventually experience (Henriksson et al., 2011). The intervention group, however, improved by 2.9%. A similar result was found in a subgroup analysis of 12 patients with brain cancer, from a study including multiple cancer populations (Cheville et al., 2010). The findings suggest that an interdisciplinary rehabilitation intervention, with a strong emphasis on exercise, can maintain, or even prevent declines of overall QOL of patients attending anticancer treatments, which is a significant finding. It strengthens the clinical argument to implement systematic rehabilitation within this patient group. Despite the promising result, the statistically non-significance of the finding is supported by other rehabilitation studies (Khan et al., 2014; McCarty et al., 2017). It is likely that the six weeks of intervention was not enough time for the physical progress of the exercise to affect overall QOL. Furthermore, a clear definition of QOL has yet to be defined. The concept of QOL is hard to grasp since QOL means different things to different people and in different situations (Fayers PM, 2015). This implies that QOL constructs from multiple factors and that the outcomes of symptomatology and functional performance investigated in this study are just a few factors that may impact overall QOL. This makes 'overall QOL' difficult to impact through a single intervention. It could also reflect a low sample size or a large variation in the data. Some patients scored maximum 'overall QOL' at follow-up (100%), which intuitively appears unusual given patients' significant disease, disabilities, and impairments. This may, however, to some extent be explained by patients neglecting the importance of their disease as a coping mechanism to maintaining aspiration and hope (Cavers et al., 2013; Andrewes et al., 2013). This also makes it difficult for new interventions to impact overall QOL.

In *paper IV*, patients in the intervention group increased cognitive functioning more than the control group ($p<0.01$) (table 15). An improved cognitive functioning from outpatient rehabilitation is also found in another study within this patient group (Khan et al., 2014). These findings are concluded from self-reported instruments, which may be useful from a cognitive symptom perspective, but do not provide the full extent of cognitive functioning (Vargo, 2017). One RCT investigating the effectiveness of a cognitive rehabilitation program on cognitive function, which was assessed from objective neuropsychologists tests, found positive short- and long-term effects on cognitive performance (Gehring et al., 2009). Although promising, comprehensive neuropsychologist testing seems unrealistic for patients in many clinical situations because of a low KPS or severely fatigue, but are also challenging to implement for institutions (Vargo, 2017).
It has been suggested that improvements in aerobic power and physical capacity may be associated with increases of cognitive function, both in patients with brain tumors and in general cancer populations (Smith et al., 2010; Cormie et al., 2015; Back et al., 2014). One study also correlates decreased fatigue with reduced cognitive disabilities and concentration problems (Goedendorp et al., 2014). Furthermore, occupational therapy is also found to improve cognitive functioning of cancer patients by impacting specific functional limitations including communication deficits, comprehension, task completion, work performance, quality of life, and role expectations (Player et al., 2014). Although causality in this trial cannot be confirmed, it is possible that the improved cognitive functioning correlates with the enhanced functional performance, decreased fatigue, the occupational therapy intervention, or as a combination between these.

5.4 Symptoms

From the exploratory cross-sectional study (*paper III)* it was found that patients with tumors located at the right and left hemisphere predominantly had matching symptom burdens (table 12), except patients with left hemispheric tumors had greater communication deficits (p=0.01) (table 13). This result is to be expected, as the left hemisphere is the supposed central site for critical functions, including speech (Drewes et al., 2016). Patients with right-hemispheric gliomas were more affected by headaches than their left-hemisphere comparisons (p=0.02) (table 13). Though the observational design of this cross-sectional study does not permit interpretations regarding causality, it confirms findings from a recent cross-sectional study including 527 patients (Russo et al., 2017).

The feasibility study (p*aper I*) provided some evidence to support that interdisciplinary rehabilitation decreases patients' 'future uncertainty' (p=0.01) (table 9). One study has suggested that the remission of functional performance in the first months after resection may attribute to patients realizing that they are functioning relatively well after surgery and radiotherapy (Bosma et al., 2009). Therefore it is likely that the intervention, which was able to improve functional performance, may have impacted 'future uncertainty'. *Paper IV* supports this finding as patients from the intervention group had a more considerable decrease in the symptom 'future uncertainty' compared to the controls (p=0.15) (table 16) although it was not statistically significant.

Patients from baseline to follow-up also had a statistically significant higher symptom burden of 'hair loss' (p=0.01) (table 15), which most likely was caused by the concomitant chemo and radiation treatment.

Fatigue is a primary disabling symptom, which impacts HRQOL and affects most patients (Armstrong and Gilbert, 2012; Vargo, 2017). It has profound consequences for patients as it leads to avoidance of social and physical activities to reduce discomfort. This may reinforce conditions of sedentary behavior and reduced activity that further leads to decrements of aerobic power, muscle wasting, and QOL. Results from the cross-sectional study *(paper III)* suggests that fatigue is the most burdensome symptom experienced by patients at the beginning of radiation treatment and imply that patients with a tumor in the right hemisphere are more affected by fatigue (p=0.08) (table 12). Though causality cannot be confirmed, it may correlate to the inferior process skills, which was also found of patients with right-sided lesions (p<0.01) (table 14), as these patients have to apply considerably more focus to process skills when performing everyday life tasks. It may be an important finding, which could be implemented into the designing of rehabilitation interventions.

The feasibility study *(paper I)* indicated that patients statistically significant reduce fatigue from attending the intervention (p<0.01) (table 8). It was confirmed by the RCT (*paper IV*), which showed that patients attending the intervention reduced fatigue compared to the control group (p=0.03) (table15). This is interesting, as patients are increasingly affected by fatigue during the second part of irradiation treatment (Hickok et al., 2005; Armstrong and Gilbert, 2012; Vargo et al., 2016). The finding confirms that a rehabilitation intervention, with a strong emphasis on exercise, significantly reduces fatigue, as found in robust methodological studies of various cancer populations (Cramp and Byron-Daniel, 2012; Mitchell et al., 2014). It is, however, the first to provide the evidence of patients with glioma (Day et al., 2016b).

Other symptoms of 'visual disorder' ($p=0.02$), 'communication deficits' ($p<0.01$), ' headaches' ($p=0.04$), 'drowsiness' ($p=0.04$), and 'itchy skin' ($p=0.02$) (table 16) were also found to decrease more in patients attending the intervention. Though these are important findings, the designing of the intervention with its interdisciplinary nature cannot confirm causality.

In general, the reduced symptom burden of patients attending the interdisciplinary rehabilitation may have significant importance, as a study of patients with HGG found that depression, fatigue, sleep disturbance, and cognitive impairment made a symptom cluster that could explain almost a third of the variance in QOL (Fox et al., 2007). The reduced cognitive functioning and fatigue found in this trial emphasize the belief that the early rehabilitation of physical therapy and occupational therapy can improve patients overall QOL.

5.5 Functional performance

The cross-sectional study (*paper III*) found matching functional performance, except the fact that patients with right-hemispheric gliomas had inferior process-skills when performing ADL-tasks ($p<0.01$) as ironing, cooking, or vacuuming (table 14). The association between inferior process-skills and patients with right-sided lesions correlates well with established neuroanatomy, as the right-hemisphere associates with the spatial processing of information and stimuli (Stone et al., 1992). Therefore, it is likely that patients with tumors in the right cortical hemisphere find it more difficult to plan and process everyday life tasks. Neurorehabilitation professionals focusing on improving executive functions, mainly occupational therapists and neuropsychologist, are encouraged to take the hemisphere into account when designing rehabilitation interventions.

An interesting finding in this study was that patients in general presented with an average aerobic power of 13.7 (table 14). Although extremely low, this result validates findings from Jones and colleagues from 2010, where an incremental cardiorespiratory gas exchange test assessed the aerobic fitness of 35 patients with matching performance status (Jones et al., 2010a). It may be of significant importance within the patient group as exercise behavior has shown to be an independent predictor of survival in patients with malignant recurrent glioma (Ruden et al., 2011).

The feasibility study (*paper I*) clearly suggested that patients improved muscle strength of leg press ($p<0.01$), knee extension ($p<0.01$), knee flexion ($p<0.01$), elbow extension ($p<0.01$), elbow flexion ($p<0.01$), reduced step frequency of walking 10 meters ($p=0.01$), and improved aerobic power ($p=0.05$) from the intervention (table 10). Within the RCT (*paper IV*) the majority of these findings were confirmed as patients attending the rehabilitation intervention statistically significant improved muscle strength of leg press ($p=0.01$), elbow extension ($p=0.01$), elbow flexion ($p<0.01$), and aerobic fitness ($p<0.01$) compared to controls (table 17). Patients from the intervention group also improved the HRQOL domain 'physical functioning' compared to the control group ($p<0.07$) (table 12). Though it was statistically non-significant, it supports that the intervention may counteract the natural course of declined physical function that patients with glioma experience during chemo-radiation (Keilani et al., 2012). Combined with the improved aerobic power, and muscle strength, the result may be of paramount importance as patients with brain tumors who improve their physical status through rehabilitation promote coping strategies, feelings of independence, confidence and hope (Hackman, 2011), which strongly influence overall QOL.

Summarized: Positive findings of improved functional performance and decreased symptoms support the theoretical rationale that interdisciplinary rehabilitation of patients attending active anticancer treatments may improve overall QOL through improved functional performance and reduced symptoms. Although the intervention was not superior regarding enhancing overall QOL compared to standard rehabilitation, it may have been, had the number of patients reached the estimated sample size. However, the statistically significant improvements of some HRQOL domains, functional performance, and reduced symptoms in the intervention group creates a robust clinical argument to implement systematic rehabilitation interventions of patients with glioma during treatments of radiation and chemotherapy, and that the hospital could be an optimal setting to do so.

5.6 Methodological considerations

The methodological strength of this research is the strict pathway from a feasibility study to an RCT (including a nested qualitative study, a practice analysis (Hansen et al., 2017a), and a case report (Hansen et al., 2018)), with a protocol (Hansen et al., 2014) and an exploratory cross-sectional study informing on the content included. The papers are based on different study designs representing different levels of the evidence hierarchy (Hoppe et al., 2009). *Paper I* was designed as an exploratory clinical feasibility study, with all possible considerations for methodological issues taken into account. It provided a sound foundation for developing a protocol with a maximum likelihood of a successful outcome. *Paper II* described the protocol created by the SPIRIT Statement: Defining Standard Protocol Items for Clinical Trials (Chan et al., 2013), which enhances the transparency for conducting the RCT. *Paper III* was a cross-sectional study, which was based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, which improve the quality of reporting observational studies (von Elm et al., 2007). Although it included just one data point, which limits the possibility to prove causal effects, it is valuable in finding associations and creating hypotheses. It validated that the intervention in the RCT was not affected the hemispheric tumor location. *Paper IV* was designed to meet the criteria of an RCT, which is considered to reflect strong evidence of intervention study designs. It was conducted to be as methodologically rigorous as possible by committing to the CONSORT statement for reporting RCTs (Moher et al., 2012).

5.6.1 Interdisciplinary rehabilitation

Patient with glioma often presents with multiple and complex physical, cognitive, or psychosocial impairments. No single profession within healthcare disciplines is experts in all these areas. To effectively obtain successful rehabilitation outcomes a holistic, interdisciplinary team approach was used. Due to the vast variety of dysfunctions experienced by this patients group, the intervention was designed to include two health care professions of physical therapy and occupational therapy, as these professions help patients to improve functioning and everyday life participation.

Within the occupational therapy profession, the assumption is that the autonomy of having choices and ability to engage in everyday life occupations influences health and wellbeing (Townsend and Polatajko, 2007). To successfully achieve this, a patient-centered approach is often used (Sumsion and Law, 2006). It develops a partnership between the patient and therapist that are founded on respect for the patient's values and choices, and where the patient is encouraged to engage in functional performance and to commit to involvement in a variety of environments. Strictly adhering to this patient-centered approach may have led to some patients resigned from occupational therapy, as they described no restrictions on occupational performance using the COPM as a guide to the initial interview. This could imply that some patients may have missed out on the occupational therapy although a need for occupational therapy may have been present, as rated by the professional. Some patients tend to overrate the ability to function to maintain hope and aspiration (Cavers et al., 2013; Andrewes et al., 2013). Therefore, the COPM seems not an ideal instrument to assess patient with potential cognitive deficits for impairments of occupational performance.

Despite the randomization and significant efforts to control all known factors, the pragmatic nature of this clinical design may have created confounding effects. On a regular basis, neurooncology nurses observed the physical therapeutic interventions. They answered questions and informed patients, which may have impacted the results by entering the interdisciplinary team.

5.6.2 Internal validity

The rigid RCT design, with the blinding and randomization procedure used to investigate the primary outcome, is strength of the study design. The designing of the intervention at the establishment of chemo-radiation treatment further created a strong foundation for group comparisons by leveling out any potential effects from the medical treatments. Also, a high adherence and only a few dropouts are strong features. All testing was conducted at the same location, with the same equipment, and using the same therapists, who were all experienced and highly dedicated to rigorous testing procedures. The functional performance outcome measures used were feasible and responsive to changes (Hansen et al., 2017b; Hansen et al., 2018), and in general, the consistency with previous results strengthens the validity of the findings.

Despite the methodological advantage of the design used, there are also non-ignorable limitations, which have to be considered. The sample size calculation relied in our case on experiences from the feasibility study (*paper I*), which only included 24 patients. Regardless of great efforts in recruiting patients in the RCT (*paper IV*), the predestined sample size aimed for was not obtained. Though the inclusion process spanning three years, the recruiting from a single hospital and the necessary exclusion criteria led to a lower than expected number of patients. The final sample included merely 38% of the calculated sample size. However, difficulties in recruiting patient with cancer in exercise trials are a renowned problem, and this is the first study attempting to investigate the effectiveness of interdisciplinary rehabilitation of patients with glioma using a randomized design. The present RCT study involved 64 patients, and although the effect on the primary outcome of overall QOL was too small to be detected, the sample provided consistent statistically significant beneficial effects on essential scales such as ‘cognitive functioning’ and ‘fatigue’. In general, it is difficult to design a study including various outcome variables whose demands in study size differs considerably. We found positive trends in all but one outcome variable (Nausea and vomiting $p=0.97$), which is impressive considering the many outcome variables included. Therefore, despite the non-significant result of the primary outcome, the trial with its strict design contributes to the current knowledge and can be used in reviews and meta-analyses.

5.6.3 External validity

The RCT was conducted with as high external validity as possible. Only the exclusion criteria considered necessary, due to the physical content of the intervention was implied. The exclusion criteria of KPS <70 was a major contributing factor to the sample size as 47% of the patients screened were ineligible for participation. The generalizability is further hindered due to the homogeneity of the sample, as patients in the present study were all involved in clinical trials with a strong emphasis on exercise. This prevents our findings from being generalized to a more diverse glioma population. Our observations on HRQOL, functional performance and symptomatology must, therefore, be applied only to functional independent patients and interpreted with caution.

5.6.4 Standard rehabilitation as controls

The standard rehabilitation used in the control group also contributed to problems in recruiting patients. Some patients were reluctant to engage in the trial, as there was a risk of entering a non-rehabilitation control group. Also, it was not possible to specify the amount and type of rehabilitation that the 'controls' have had. The advantage, however, was that the intervention compares to true 'usual care' controls, which reduces the risk of rehabilitation bias, given that patients in the control group initiate rehabilitation in other settings, which would diminish the actual effect of the intervention (Jones and Alfano, 2013)

6 Conclusions

This thesis has established that it is safe and feasible for patients with glioma to attend an interdisciplinary rehabilitation intervention of physical therapy and occupational therapy during medical treatments. It also suggests that self-administered exercise is only feasible for a small and select subgroup of patients with superior performance status (*paper I*). Furthermore, it suggests that no consideration of laterality needs to be taken into account when designing a rehabilitation intervention, in the early disease state, with the purpose of improving HRQOL (*paper III*). Lastly, the research indicates that patients attending rehabilitation interventions of physical therapy and occupational therapy during active anti-cancer treatment insignificantly improve overall QOL compared to patients having the standard rehabilitation practice. They statistically significantly improved 'cognitive functioning', decrease a continuum of symptoms including fatigue, and improve functional performances (*paper IV*).

7 Clinical perspective and recommendations

This research provides evidence that patients with glioma can improve HRQOL domains, improve functional performance, and decrease symptoms related to their disease and concomitant medical treatments. It cements the rationale that rehabilitation is important for these patients in the early treatment phase. The statistically significant improved 'cognitive function' and the decreased symptom of 'fatigue' are vital factors for patients' everyday living and correlate with overall QOL. The research further suggests that the hospital may be an optimal setting for rehabilitation as patients already attend medical treatment. The geographical location secured that patients did not have to travel for rehabilitation, which may lower the adherence due to fatigue. The location at the hospital guaranteed a high adherence and optimized safety, as patients were under the close supervision of a multidisciplinary team including physical therapists, occupational therapists, nurses, and a neurooncologist. With the clinical importance of these findings, it must be considered if rehabilitation should be offered to all patients. Based on empirical experiences gained from this research the following structure to improve early rehabilitation of patients with glioma is recommended.

Approximately one week before initiating radiation treatment, or one month after resection, the patient consults a radiologist and a nurse at the hospital. This is an ideal time to assess the patient's need for rehabilitation, as the patient has lived in his/her own home and encountered impairment of or difficulties with everyday life situations. If the nurse or oncologist through a screening process (questions or instruments) assess that the patient has needs for rehabilitation, the patient should be referred to the rehabilitation department for thorough assessments. Administrative planning of time of radiation treatment and rehabilitation could fairly easily be coordinated, as shown in this research. This method guarantees all patients with rehabilitation needs will initiate timely rehabilitation, in accordance with 'the national cancer plans'.

8 Future research

The rehabilitation research area of patients with brain cancers is still in its infancy. This research investigated the acute effects of a rehabilitation intervention. For these results to have significant weight, they need to be verified by other trials. Future studies are also warranted to investigate the long-term effects of rehabilitation conducted during chemo and radiation treatments.
This research included a heterogenetic sample of patients with glioma, as they ranged from WHO grade I-IV. It makes the results more impressive as the vast majority had Glioblastoma Multiforme (grade IV). It is likely that patients with LGG may have even greater benefits than HGG, due to the different disease trajectory. Therefore, rehabilitation interventions designed especially for LGG and HGG are warranted.

9 English Summary

Introduction

Glioma, also known as World Health Organization (WHO) grade I-IV brain tumors, is among the most devastating cancer diseases affecting humans. Poor prognosis, adverse effects from anticancer treatments with significant functional, emotional, and cognitive deficits affect the majority and leaves patients with impaired health-related quality of life (HRQOL), and a profound need for rehabilitation. But according to the academic literature, only a minority of patients is referred to rehabilitation. This highlights the need for research that investigates the effectiveness of rehabilitation among this patient group in robust designs. This thesis aims to develop an interdisciplinary rehabilitation program with a strong emphasis on physical training, which is safe for patients with primary glioma, and superior to the current practice regarding an effect on overall QOL. The research includes a clinical trial evaluating the safety and feasibility of a rehabilitation intervention during anticancer treatments and a randomized, controlled single-blinded trial (RCT) that investigates the effectiveness of a six-week interdisciplinary rehabilitation intervention during chemo- and radiotherapy. By pooling patients from the two clinical trials, an exploratory cross-sectional cohort was made. The purpose was to explore if patients with tumors affecting the left- or right-hemispheric significantly differ in HRQOL and functional performance in the early disease stage.

Methods

24 patients included the feasibility study. It comprised two parts of rehabilitation. In part one, patients attended six weeks of supervised physical therapy and occupational therapy during their concomitant chemo-radiation treatments. In part two, patients self-administered training for six weeks at a local gym, following a training protocol. Predefined feasibility criteria of safety, consent rate, dropout, adherence, and patient satisfaction determined whether the intervention was feasible for implementation in an RCT design.

64 functional independent patients (Karnofsky Performance Status ≥70) with a confirmed diagnosis of glioma attending chemo-radiation treatment were involved in the RCT. They were randomly allocated into two groups. 32 patients had interdisciplinary rehabilitation interventions, and 32 patients, acting as controls, followed standard rehabilitation regimens. The intervention included supervised physical therapeutic group-based exercises with modalities of cardiovascular-, resistance-, and balance training, and depending on needs, individually goal-based occupational therapy. The control group followed the rehabilitation services they were referred to at discharge from the Neurosurgical Department (i.e., no rehabilitation, or municipality based rehabilitation). Assessments were made at study entry (baseline) and the end of the intervention after six weeks. Health-related quality of life (HRQOL) was assessed from the generic ‘European Organization for Research and Treatment of Cancer questionnaire’ (EORTC-QLQ-30). The Global Health Status/QOL

domain (items 29 +30) was the primary outcome. Functional performance measures included a continuum of tests assessing walking ability, dynamic muscle strength, cardiovascular function, and standing balance.

In a nested cross-sectional study, baseline data of HRQOL and functional performance were pooled from the two clinical trials. After exclusions, 81 patients have included the analysis. To investigate if patients with tumors located in the left or right-hemisphere differ in HRQOL and functional performance in the early disease state, patients were stratified by 'tumor laterality'.

Results

Predefined feasibility objectives of safety (100%), consent rate (>80%), drop out (<20%), adherence (>80%), and patient satisfaction (>80%) was achieved during the supervised part one of the feasibility study. However, failure to meet predefined feasibility objectives during the unsupervised part two led to a protocol revision of the RCT.

In the exploratory cross-sectional study, it was found, that the tumor location at the right- or left-hemisphere had no consequence for HRQOL, and only little impact on symptoms and functional performance outcomes (communication deficits $p<0.01$, headache $p=0.04$, and process skills $p<0.01$) in the early disease period (40 days after resection).

In the RCT, patients attending the intervention non-significantly improved overall QOL more than the control group (adjusted mean difference, 9% [95% confidence interval, -3.8 to 22.9]). The intervention was superior to the standard rehabilitation to improve 'cognitive functioning $p<0.01$', functional performance outcomes of 'aerobic power $p<0.01$', muscle strength of 'leg press $p=0.01$', 'elbow flexion, and elbow extension $p=0.01$' as well as reduce symptoms of 'fatigue $p<0.01$', 'visual disorder $p<0.01$', 'communication deficits $p<0.01$', 'headache $p<0.01$', drowsiness $p<0.01$', and 'itchy skin $p<0.01$'.

Implication

Results of the feasibility study indicate that interdisciplinary rehabilitation of physical therapy and occupational therapy during active anti-cancer treatments are safe and feasible if supervised by healthcare professionals. The cross-sectional study validated that no considerations of laterality have to be taken into account when designing a rehabilitation intervention aiming to improve HRQOL. Results from the RCT impose that patients with glioma having interdisciplinary rehabilitation during medical treatment enhance health-related quality of life, reduce symptoms, and improve functional performance after six weeks more than patients having standard rehabilitation procedure.

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10 Dansk Resúme

Introduktion

Gliomer, defineret af Verdenssundhedsorganisationen (WHO) som grad I-IV hjernetumorer, er blandt de mest destruktive kræftsygdomme, som kan ramme mennesker. Usikker prognose og bivirkninger fra kræftbehandlinger med betydelige funktionelle, følelsesmæssige og kognitive funktionsnedsættelser til følge påvirker flertallet, og efterlader patienterne med nedsat helbredsrelateret livskvalitet (HRQOL) samt et stort behov for rehabilitering. Men ifølge den akademiske litteratur henvises kun et mindretal af patienter til rehabilitering. Dette fremhæver behovet for forskning, der undersøger effektiviteten af rehabilitering blandt patienter, der er ramt af gliomer i robuste metodologiske design. Formålet med dette Ph.d. projekt er at udvikle et tværfagligt rehabiliteringsprogram med vægt på fysisk træning, som er sikker for patienterne, og bedre end den nuværende praksis til at øge patienternes samlede livskvalitet. Forskningen indeholdt en klinisk forundersøgelse, der evaluerede sikkerheden og gennemførligheden ved at deltage i en rehabiliteringsindsats for patienter under antikræft behandling, 2) og et lodtrækningsforsøg (RCT), der undersøgte effektiviteten af en seks ugers tværfaglig rehabiliteringsintervention af patienter som modtager kemo- og strålebehandling. Ved at samle patienter fra de to kliniske forsøg blev der konstrueret en tværsnitskohorte. Formålet var at undersøge, om patienter med tumorer i henholdsvis højre og venstre hjernehalvdel, væsentligt adskiller sig fra hinanden med henblik på HRQOL og funktionelle præstationer i det tidlige sygdomsstadium.

Metoder

24 patienter indgik i forundersøgelsen, som var opdelt i to rehabiliteringsdele. I del et deltog patienterne i et seks ugers rehabiliteringsforløb, som var superviseret af fysioterapeuter og ergoterapeuter. Det forgik på OUH, mens patienterne samtidig modtog kemo- og stråleterapi. Del to indeholdt seks ugers intervention i et lokalt fitnesscenter, hvor patienterne trænede efter en skræddersyet træningsprotokol. Forudbestemte gennemførlighedskriterier for patientsikkerhed, samtykkefrekvens, frafald, fremmøde, og patienttilfredshed bestemte om interventionen var gennemførlig og brugbar i det videre lodtrækningsforsøg.

64 patienter, som modtog medicinsk behandling deltog i lodtrækningsstudiet. De blev ligeligt fordelt i to grupper. 32 patienter modtog tværfaglig rehabilitering, mens 32 patienter, der fungerede som kontroller modtog vanlig rehabilitering. Patienter med en verificeret gliøs-tumor og et højt funktionsniveau (Karnofsky Performance Status $\geq$70) indgik i studiet. Interventionen omfattede superviseret fysioterapeutiske træning på hold og indeholdt konditions-, styrke og balance-træning og individuel fysioterapi samt ergoterapi efter behov. Kontrolgruppen fulgte det rehabiliteringstilbud, de blev henvist til ved udskrivning fra den Neurokirurgiske afdeling (sv.t. ingen rehabilitering eller kommunal rehabilitering). Målinger af patienterne blev foretaget ved studiets start (basisline) og ved afslutningen af rehabiliteringsindsatsen (seks ugers opfølgning). Helbredsrelateret livskvalitet (HRQOL) blev vurderet ud fra det generiske "European Organization for Research and Treatment of Cancer spørgeskema" (EORTC-QLQ-30). Studiets primære mål

var at under søge overordnet livskvalitet. Funktionelle præstationer blev målt via en samling af test, som indbefattede en vurdering af patienternes gangfunktion, muskelstyrke, kondition, og stående balance.

I den indlejrede tværsnitsundersøgelse blev baseline data for HRQOL og funktionelle præstation vurderet fra alle patienter i de to kliniske forsøg. Efter udelukkelse af patienter, som ikke var egnede til undersøgelsen, blev 81 patienter inkluderet i analysen. For at undersøge, om patienter med tumorer placeret i venstre eller højre hjernehalvdel adskiller sig med HRQOL og funktionelle præstationer, blev patienterne inddelt i to grupper ud fra tumorens placering.

Resultater

Forudbestemte gennemførlighedskriterier for sikkerhed (100%), samtykkefrekvens (>80%), frafald (<20%), fremmøde (<80%) og patienttilfredshed (>80%) blev opnået i del et, mens der var manglende opfyldelse af gennemførlighedskriterierne for selvtræningsdelen i del to. Det førte til en revision af protokollen for lodtrækningsstudiet.

Tværsnitsundersøgelse fandt, at tumors placeringen i henholdsvis højre eller venstre hjernehalvdel ikke havde indvirkning på patienterne HRQOL, og kun få påvirkninger af symptomer og funktionelle præstationsresultater (kommunikationsbesvær p<0,01, hovedpine p=0,04 , og proces færdigheder p<0,01).

I lodtrækningsstudiet forbedrede patienter, som deltog i interventionen deres generelle livskvalitet mere end patienterne i kontrolgruppen (justeret middelværdi for forskel, 9% [95% sikkerhedsinterval, -3,8 til 22,9]). Interventionsgruppen forbedrede signifikant deres 'kognitive funktion p<0,01' og funktionelle præstationer i form af 'kondition p<0,01' ', muskelstyrken ved ’ben pres p=0,01’, albuebøj og albuestræk p=0,01 ' og reducere symptomer af 'træthed p<0,01', 'synsforstyrrelser p<0,01', 'kommunikationsbesvær p <0,01', 'hovedpine p<0,01', døsighed p <0,01 'og' kløende hud p<0,01 'mere end patienter, som modtog vanlige rehabilitering.

Implikationer

Resultaterne af gennemførlighedsundersøgelsen demonstrerede, at tværfaglig rehabilitering af patienter, som modtog aktiv kræftbehandling er sikker og gennemførlige, såfremt det superviseres af terapeuter. Tværsnitsundersøgelsen fandt, at der ved tilrettelæggelsen af rehabiliteringsinterventioner ikke skal tages hensyn til, om patienterne har tumorer i højre eller venstre hjerne halvdel, såfremt målet med rehabiliteringen er at forbedre patienterne generelle HRQOL. Resultater fra lodtrækningsstudiet antyder, at patienter med gliomer, som modtager tværfaglig rehabilitering under medicinsk behandling forbedrer domæner indenfor helbredsrelaterede livskvalitet, reducerer symptomer og forbedrer funktionelle præstationer efter seks uger, mere end patienter, der modtager vanlig rehabiliteringsindsatser.

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11 References

Adamsen L, Quist M, Andersen C, et al. (2009) Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *BMJ* 339: b3410.

Alentorn A, Hoang-Xuan K and Mikkelsen T. (2016) Presenting signs and symptoms in brain tumors. *Handb Clin Neurol* 134: 19-26.

Andersen LB. (1995) A maximal cycle exercise protocol to predict maximal oxygen uptake. *Scand J Med Sci Sports* 5: 143-146.

Andrewes HE, Drummond KJ, Rosenthal M, et al. (2013) Awareness of psychological and relationship problems amongst brain tumour patients and its association with carer distress. *Psychooncology* 22: 2200-2205.

Armstrong TS, Bishof AM, Brown PD, et al. (2016) Determining priority signs and symptoms for use as clinical outcomes assessments in trials including patients with malignant gliomas: Panel 1 Report. *Neuro Oncol* 18 Suppl 2: ii1-ii12.

Armstrong TS and Gilbert MR. (2012) Practical strategies for management of fatigue and sleep disorders in people with brain tumors. *Neuro Oncol* 14 Suppl 4: iv65-72.

Astrand PO and Ryhming I. (1954) A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *J Appl Physiol* 7: 218-221.

Back M, Back E, Kastelan M, et al. (2014) Cognitive Deficits in Primary Brain Tumours: A Framework for Management and Rehabilitation. *Journal of Cancer Therapy* 5: 74-81.

Berg KO, Wood-Dauphinee SL, Williams JI, et al. (1992) Measuring balance in the elderly: validation of an instrument. *Can J Public Health* 83 Suppl 2: S7-11.

Blum L and Korner-Bitensky N. (2008) Usefulness of the Berg Balance Scale in stroke rehabilitation: a systematic review. *Phys Ther* 88: 559-566.

Bosma I, Reijneveld JC, Douw L, et al. (2009) Health-related quality of life of long-term high-grade glioma survivors. *Neuro Oncol* 11: 51-58.

Bourke L, Homer KE, Thaha MA, et al. (2014) Interventions to improve exercise behaviour in sedentary people living with and beyond cancer: a systematic review. *Br J Cancer* 110: 831-841.

Browne RH. (1995) On the use of a pilot sample for sample size determination. *Stat Med* 14: 1933-1940.

Brzycki M. (1993) Strength testing: predicting a one-rep max from repetitions to fatigue. *Journal of Physical Education, Recreation and Dance* 64(1):88-90.

Capozzi LC, Boldt KR, Easaw J, et al. (2016) Evaluating a 12-week exercise program for brain cancer patients. *Psychooncology* 25: 354-358.

Cavers D, Hacking B, Erridge SC, et al. (2013) Adjustment and support needs of glioma patients and their relatives: serial interviews. *Psychooncology* 22: 1299-1305.

Chan AW, Tetzlaff JM, Altman DG, et al. (2013) SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 158: 200-207.

Chandana SR, Movva S, Arora M, et al. (2008) Primary brain tumors in adults. *Am Fam Physician* 77: 1423-1430.

Cheng JX, Liu BL, Zhang X, et al. (2010) Health-related quality of life in glioma patients in China. *BMC Cancer* 10: 305.

Cheng JX, Zhang X and Liu BL. (2009) Health-related quality of life in patients with high-grade glioma. *Neuro Oncol* 11: 41-50.

Cheville AL. (2005) Cancer rehabilitation. *Semin Oncol* 32: 219-224.

Cheville AL, Girardi J, Clark MM, et al. (2010) Therapeutic exercise during outpatient radiation therapy for advanced cancer: Feasibility and impact on physical well-being. *Am J Phys Med Rehabil* 89: 611-619.

Cormie P, Nowak AK, Chambers SK, et al. (2015) The potential role of exercise in neuro-oncology. *Front Oncol* 5: 85. doi: 10.3389/fonc.2015.00085

Cramp F and Byron-Daniel J. (2012) Exercise for the management of cancer-related fatigue in adults. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD006145. DOI: 10.1002/14651858.CD006145.pub3.

Day J, Gillespie DC, Rooney AG, et al. (2016a) Neurocognitive Deficits and Neurocognitive Rehabilitation in Adult Brain Tumors. *Curr Treat Options Neurol* 18: 22.

Day J, Yust-Katz S, Cachia D, et al. (2016b) Interventions for the management of fatigue in adults with a primary brain tumour. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.:CD011376. DOI: 10.1002/14651858.CD011376.pub2

De Backer IC, Schep G, Backx FJ, et al. (2009) Resistance training in cancer survivors: a systematic review. *Int J Sports Med* 30: 703-712.

Dirven L, Aaronson NK, Heimans JJ, et al. (2014) Health-related quality of life in high-grade glioma patients. *Chin J Cancer* 33: 40-45.

DNOG. (2016) **[in danish]** Guidelines for treating intracranial gliomas in adults. http://www.dnog.dk/assets/files/Retningslinier PDF/DNOG 2016 Gliom retningslinje final.pdf. Dansk Neuro Onkologisk Gruppe.

DNOR. (2017) [in danish] Annual Report 2016. https://www.sundhed.dk/content/cms/84/4684_dnor-årsrapport-2016-endelig-offentlig.pdf. Dansk Neuro Onkologisk Register.

Drewes C, Sagberg LM, Jakola AS, et al. (2016) Quality of life in patients with intracranial tumors: does tumor laterality matter? *J Neurosurg* 125: 1400-1407.

Efficace F and Taphoorn M. (2012) Methodological issues in designing and reporting health-related quality of life in cancer clinical trials: the challenge of brain cancer studies. *J Neurooncol* 108: 221-226.

Fayers PM AN, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. (2001) The EORTC QLQ-C30 Scoring Manual (3rd Edition). *Published by: European Organisation for Research and Treatment of Cancer, Brussels.*

Fayers PM MD. (2015) Introduction. *Quality of Life.* John Wiley & Sons, Ltd, 1-33.

Fisher AG, Bray Jones, K (2010) *Assessment of Motor and Process Skills. Vol. 1: Development, standardization, and administration manual*: (7th ed.) Fort Collins, CO: Three Star Press.

Flechl B, Sax C, Ackerl M, et al. (2017) The course of quality of life and neurocognition in newly diagnosed patients with glioblastoma. *Radiother Oncol* 125: 228-233.

Flowers A. (2000) Brain tumors in the older person. *Cancer Control* 7: 523-538.

Formica V, Del Monte G, Giacchetti I, et al. (2011) Rehabilitation in neuro-oncology: a meta-analysis of published data and a mono-institutional experience. *Integr Cancer Ther* 10: 119-126.

Fox SW, Lyon D and Farace E. (2007) Symptom clusters in patients with high-grade glioma. *J Nurs Scholarsh* 39: 61-67.

Fu JB, Parsons HA, Shin KY, et al. (2010) Comparison of functional outcomes in low- and high-grade astrocytoma rehabilitation inpatients. *Am J Phys Med Rehabil* 89: 205-212.

Gamble GL, Gerber LH, Spill GR, et al. (2011) The future of cancer rehabilitation: emerging subspecialty. *Am J Phys Med Rehabil* 90: S76-87.

Gehring K, Kloek CJ, Aaronson NK, et al. (2017) Feasibility of a home-based exercise intervention with remote guidance for patients with stable grade II and III gliomas: a pilot randomized controlled trial. *Clin Rehabil*: Epub ahead of print doi. 269215517728326.

Gehring K, Sitskoorn MM, Gundy CM, et al. (2009) Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol* 27: 3712-3722.

Geler-Kulcu D, Gulsen G, Buyukbaba E, et al. (2009) Functional recovery of patients with brain tumor or acute stroke after rehabilitation: a comparative study. *J Clin Neurosci* 16: 74-78.

Gerber LH, Hodsdon B, Comis LE, et al. (2017) A Brief Historical Perspective of Cancer Rehabilitation and Contributions From the National Institutes of Health. *PM R* 9: S297-S304.

Gilchrist LS, Galantino ML, Wampler M, et al. (2009) A framework for assessment in oncology rehabilitation. *Phys Ther* 89: 286-306.

Gill-Body KM, Popat RA, Parker SW, et al. (1997) Rehabilitation of balance in two patients with cerebellar dysfunction. *Phys Ther* 77: 534-552.

Gillison FB, Skevington SM, Sato A, et al. (2009) The effects of exercise interventions on quality of life in clinical and healthy populations; a meta-analysis. *Soc Sci Med* 68: 1700-1710.

Giovagnoli AR, Silvani A, Colombo E, et al. (2005) Facets and determinants of quality of life in patients with recurrent high grade glioma. *J Neurol Neurosurg Psychiatry* 76: 562-568.

Giovagnoli AR, Tamburini M and Boiardi A. (1996) Quality of life in brain tumor patients. *J Neurooncol* 30: 71-80.

Goedendorp MM, Knoop H, Gielissen MF, et al. (2014) The effects of cognitive behavioral therapy for postcancer fatigue on perceived cognitive disabilities and neuropsychological test performance. *J Pain Symptom Manage* 47: 35-44.

Greenberg E, Treger I and Ring H. (2006) Rehabilitation outcomes in patients with brain tumors and acute stroke: comparative study of inpatient rehabilitation. *Am J Phys Med Rehabil* 85: 568-573.

Hackman D. (2011) "What's the point?" exploring rehabilitation for people with 1 degrees CNS tumours using ethnography: patients' perspectives. *Physiother Res Int* 16: 201-217.

Hahn CA, Dunn RH, Logue PE, et al. (2003) Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. *Int J Radiat Oncol Biol Phys* 55: 992-999.

Han EY, Chun MH, Kim BR, et al. (2015) Functional Improvement After 4-Week Rehabilitation Therapy and Effects of Attention Deficit in Brain Tumor Patients: Comparison With Subacute Stroke Patients. *Ann Rehabil Med* 39: 560-569.

Hansen A, Boll M, Minet L, et al. (2017a) Novel occupational therapy intervention in the early rehabilitation of patients with brain tumours. *British Journal of Occupational Therapy* 80: 603-607.

Hansen A, Pedersen, Christian Bonde; Jarden, Jens Ole; Beier, Dagmar; Rosenbek Minet, Lisbeth Kirstine ; Søgaard, Karen. (2018) Statistical Analysis Plan: The effectiveness of interdisciplinary rehabilitation of patients with primary glioma during active anticancer treatment – a single-blinded randomized controlled clinical trial. University of Southern Denmark.

Hansen A, Rosenbek Minet LK, Sogaard K, et al. (2014) The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among patients with primary glioma: an RCT study protocol. *BMJ Open* 4: e005490.

Hansen A, Sogaard K and Minet LR. (2018) Development of an exercise intervention as part of rehabilitation in a glioblastoma multiforme survivor during irradiation treatment: a case report. *Disability and Rehabilitation* Epub ahead of print: doi 10.1080/09638288.2018.1432707

Hansen A, Sogaard K, Minet LR, et al. (2017b) A 12-week interdisciplinary rehabilitation trial in patients with gliomas - a feasibility study. *Disabil Rehabil* Epub ahead of print: doi.10.1080/09638288.2017.1295472

Hayes SC, Reul-Hirche H and Turner J. (2009) Exercise and secondary lymphedema: safety, potential benefits, and research issues. *Med Sci Sports Exerc* 41: 483-489.

Henriksson R, Asklund T and Poulsen HS. (2011) Impact of therapy on quality of life, neurocognitive function and their correlates in glioblastoma multiforme: a review. *J Neurooncol* 104: 639-646.

Hickok JT, Morrow GR, Roscoe JA, et al. (2005) Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. *J Pain Symptom Manage* 30: 433-442.

Hoppe DJ, Schemitsch EH, Morshed S, et al. (2009) Hierarchy of evidence: where observational studies fit in and why we need them. *J Bone Joint Surg Am* 91 Suppl 3: 2-9.

Huang ME, Cifu DX and Keyser-Marcus L. (2000) Functional outcomes in patients with brain tumor after inpatient rehabilitation: comparison with traumatic brain injury. *Am J Phys Med Rehabil* 79: 327-335.

Johnson DR, Sawyer AM, Meyers CA, et al. (2012) Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. *Neuro-Oncology* 14: 808-816.

Jones LW and Alfano CM. (2013) Exercise-oncology research: past, present, and future. *Acta Oncol* 52: 195-215.

Jones LW, Friedman AH, West MJ, et al. (2010a) Quantitative assessment of cardiorespiratory fitness, skeletal muscle function, and body composition in adults with primary malignant glioma. *Cancer* 116: 695-704.

Jones LW, Guill B, Keir ST, et al. (2007) Exercise interest and preferences among patients diagnosed with primary brain cancer. *Support Care Cancer* 15: 47-55.

Jones LW, Mourtzakis M, Peters KB, et al. (2010b) Changes in functional performance measures in adults undergoing chemoradiation for primary malignant glioma: a feasibility study. *Oncologist* 15: 636-647.

Julious SA. (2005) Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics* 4: 287-291.

Keilani M, Krall C, Marosi C, et al. (2012) Strength of skeletal muscle and self-reported physical performance in Austrian glioblastoma-patients. *Wien Klin Wochenschr* 124: 377-383.

Khan F and Amatya B. (2013) Use of the International Classification of Functioning, Disability and Health (ICF) to describe patient-reported disability in primary brain tumour in an Australian community cohort. *J Rehabil Med* 45: 434-445.

Khan F, Amatya B, Drummond K, et al. (2014) Effectiveness of integrated multidisciplinary rehabilitation in primary brain cancer survivors in an Australian community cohort: a controlled clinical trial. *J Rehabil Med* 46: 754-760.

Khan F, Amatya B, Ng L, et al. (2013) Multidisciplinary rehabilitation after primary brain tumour treatment. Cochrane Database of Systematic Reviews 1: Art. No.: CD009509.
DOI: 10.1002/14651858.CD009509.pub3

Kirshblum S, O'Dell MW, Ho C, et al. (2001) Rehabilitation of persons with central nervous system tumors. *Cancer* 92: 1029-1038.

Klein M, Taphoorn MJ, Heimans JJ, et al. (2001) Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. *J Clin Oncol* 19: 4037-4047.

Kolb B and Whishaw IQ. (2003) *Fundamentals of Human Neuropsychology*: Worth Publishers.

Lancaster GA, Dodd S and Williamson PR. (2004) Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 10: 307-312.

Law MC, Baptiste S, Carswell A, et al. (2015) *Canadian occupational performance measure*: 5th ed. Ottawa, Canada: CAOT Publications ACE; 2014.

Lehmann JF, DeLisa JA, Warren CG, et al. (1978) Cancer rehabilitation: assessment of need, development, and evaluation of a model of care. *Arch Phys Med Rehabil* 59: 410-419.

Levin GT, Greenwood KM, Singh F, et al. (2016) Exercise Improves Physical Function and Mental Health of Brain Cancer Survivors: Two Exploratory Case Studies. *Integr Cancer Ther* 15: 190-196.

Liu R, Page M, Solheim K, et al. (2009) Quality of life in adults with brain tumors: current knowledge and future directions. *Neuro Oncol* 11: 330-339.

Louis DN, Perry A, Reifenberger G, et al. (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 131: 803-820.

Lucchiari C, Botturi A, Silvani A, et al. (2015) Cognitive strategies and quality of life of patients with high-grade glioma. *Support Care Cancer* 23: 3427-3435.

Marciniak CM, Sliwa JA, Heinemann AW, et al. (2001) Functional outcomes of persons with brain tumors after inpatient rehabilitation. *Arch Phys Med Rehabil* 82: 457-463.

Maringwa J, Quinten C, King M, et al. (2011) Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. *Ann Oncol* 22: 2107-2112.

Marselisborgcentret. (2004) [in Danish] Rehabilitation in Denmark: A White Paper about the concept of rehabilitation: Aarhus.

McCarty S, Eickmeyer SM, Kocherginsky M, et al. (2017) Health-Related Quality of Life and Cancer-Related Symptoms During Interdisciplinary Outpatient Rehabilitation for Malignant Brain Tumor. *Am J Phys Med Rehabil* 96: 852-860.

McNeely ML, Campbell KL, Rowe BH, et al. (2006) Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ* 175: 34-41.

Milbury K, Mallaiah S, Mahajan A, et al. (2017) Yoga Program for High-Grade Glioma Patients Undergoing Radiotherapy and Their Family Caregivers. *Integr Cancer Ther*: Epub ahead of print doi 1534735417689882.

Mishra SI, Scherer RW, Geigle PM, et al. (2012a) Exercise interventions on health-related quality of life for cancer survivors. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD007566. DOI: 10.1002/14651858.CD007566.pub2.

Mishra SI, Scherer RW, Snyder C, et al. (2012b) Exercise interventions on health-related quality of life for people with cancer during active treatment. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD008465.DOI: 10.1002/14651858.CD008465.pub2.

Mitchell SA, Hoffman AJ, Clark JC, et al. (2014) Putting evidence into practice: an update of evidence-based interventions for cancer-related fatigue during and following treatment. *Clin J Oncol Nurs* 18 Suppl: 38-58.

Moher D, Hopewell S, Schulz KF, et al. (2012) CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 10: 28-55.

Mukand JA, Blackinton DD, Crincoli MG, et al. (2001) Incidence of neurologic deficits and rehabilitation of patients with brain tumors. *Am J Phys Med Rehabil* 80: 346-350.

Nicole Culos-Reed S, Leach HJ, Capozzi LC, et al. (2017) Exercise preferences and associations between fitness parameters, physical activity, and quality of life in high-grade glioma patients. *Support Care Cancer* 25: 1237-1246.

O'Dell MW, Barr K, Spanier D, et al. (1998) Functional outcome of inpatient rehabilitation in persons with brain tumors. *Arch Phys Med Rehabil* 79: 1530-1534.

Ohgaki H and Kleihues P. (2005) Epidemiology and etiology of gliomas. *Acta Neuropathol* 109: 93-108.

Osoba D, Brada M, Yung WK, et al. (2000) Health-related quality of life in patients with anaplastic astrocytoma during treatment with temozolomide. *Eur J Cancer* 36: 1788-1795.

Osoba D, Rodrigues G, Myles J, et al. (1998) Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 16: 139-144.

Osoba D, Zee B, Pater J, et al. (1994) Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. *Qual Life Res* 3: 353-364.

Ostrom QT, Bauchet L, Davis FG, et al. (2014) The epidemiology of glioma in adults: a "state of the science" review. *Neuro Oncol* 16: 896-913.

Ostrom QT, Gittleman H, Farah P, et al. (2013) CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol* 15 Suppl 2: ii1-56.

Ostrom QT, Gittleman H, Xu J, et al. (2016) CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. *Neuro Oncol* 18: v1-v75.

Pace A, Parisi C, Di Lelio M, et al. (2007) Home rehabilitation for brain tumor patients. *J Exp Clin Cancer Res* 26: 297-300.

Pace A, Villani V, Parisi C, et al. (2016) Rehabilitation pathways in adult brain tumor patients in the first 12 months of disease. A retrospective analysis of services utilization in 719 patients. *Support Care Cancer* 24: 4801-4806.

Palese A, Lamanna F, Di Monte C, et al. (2008) Quality of life in patients with right- or left-sided brain tumours: literature review. *J Clin Nurs* 17: 1403-1410.

Pelletier G, Verhoef MJ, Khatri N, et al. (2002) Quality of life in brain tumor patients: the relative contributions of depression, fatigue, emotional distress, and existential issues. *J Neurooncol* 57: 41-49.

Piil K, Jakobsen J, Christensen KB, et al. (2018) Needs and preferences among patients with high-grade glioma and their caregivers - A longitudinal mixed methods study. *Eur J Cancer Care (Engl)* Epub ahead of print. doi: 10.111/ecc.12806

Player L, Mackenzie L, Willis K, et al. (2014) Women's experiences of cognitive changes or 'chemobrain' following treatment for breast cancer: a role for occupational therapy? *Aust Occup Ther J* 61: 230-240.

Polin RS, Marko NF, Ammerman MD, et al. (2005) Functional outcomes and survival in patients with high-grade gliomas in dominant and nondominant hemispheres. *J Neurosurg* 102: 276-283.

Prieto TE, Myklebust JB, Hoffmann RG, et al. (1996) Measures of postural steadiness: differences between healthy young and elderly adults. *IEEE Trans Biomed Eng* 43: 956-966.

Roberts PS, Nuno M, Sherman D, et al. (2014) The impact of inpatient rehabilitation on function and survival of newly diagnosed patients with glioblastoma. *PM R* 6: 514-521.

Ruden E, Reardon DA, Coan AD, et al. (2011) Exercise behavior, functional capacity, and survival in adults with malignant recurrent glioma. *J Clin Oncol* 29: 2918-2923.

Russo M, Villani V, Taga A, et al. (2017) Headache as a presenting symptom of glioma: A cross-sectional study. *Cephalalgia*: Epub ahead of print doi: 333102417710020.

Salo J, Niemela A, Joukamaa M, et al. (2002) Effect of brain tumour laterality on patients' perceived quality of life. *J Neurol Neurosurg Psychiatry* 72: 373-377.

Sanai N, Chang S and Berger MS. (2011) Low-grade gliomas in adults. *J Neurosurg* 115: 948-965.

Schmitz KH, Courneya KS, Matthews C, et al. (2010) American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc* 42: 1409-1426.

Sherer M, Meyers CA and Bergloff P. (1997) Efficacy of postacute brain injury rehabilitation for patients with primary malignant brain tumors. *Cancer* 80: 250-257.

Sim J and Lewis M. (2012) The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol* 65: 301-308.

Smith PJ, Blumenthal JA, Hoffman BM, et al. (2010) Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med* 72: 239-252.

Steins Bisschop CN, Velthuis MJ, Wittink H, et al. (2012) Cardiopulmonary exercise testing in cancer rehabilitation: a systematic review. *Sports Med* 42: 367-379.

Stone SP, Patel P, Greenwood RJ, et al. (1992) Measuring visual neglect in acute stroke and predicting its recovery: the visual neglect recovery index. *J Neurol Neurosurg Psychiatry* 55: 431-436.

Strasser B, Steindorf K, Wiskemann J, et al. (2013) Impact of resistance training in cancer survivors: a meta-analysis. *Med Sci Sports Exerc* 45: 2080-2090.

Stupp R, Hegi ME, Mason WP, et al. (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 10: 459-466.

Stupp R, Mason WP, van den Bent MJ, et al. (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 352: 987-996.

Sundhedsstyrelsen. (2005) [in danish] The National Cancer Plan II: Recommendations from the National Board of Health regarding improvements of the efforts in cancer care. Copenhagen.The National Board of Health http://www.sst.dk/~/media/336FBD856C854982956A7EC2EF2236D1.ashx.

Sundhedsstyrelsen. (2010) [in danish] Cancer Plan III: Strenghened focus on cancer Copenhagen: The National Board of Health; https://www.sst.dk/da/sygdom-og-behandling/kraeft/nationale-planer/~/media/F0DC5A3CCA8B4F88AEA1AB61677F8E58.ashx.

Sundhedsstyrelsen. (2015) [in danish] Follow-up program for brain cancer. Copenhagen. Danish Health Authority https://www.sst.dk/da/udgivelser/2015/~/media/8278993EA6F84AEEBDA136649AFF4B55.ashx.

Sundhedsstyrelsen. (2017) The Cancer Registry: New Cancer Cases in 2016. Copenhagen. Danish Health Authority www.sundhedsdatastyrelsen.dk.

Tang V, Rathbone M, Park Dorsay J, et al. (2008) Rehabilitation in primary and metastatic brain tumours: impact of functional outcomes on survival. *J Neurol* 255: 820-827.

Taphoorn MJ and Bottomley A. (2005) Health-related quality of life and symptom research in glioblastoma multiforme patients. *Expert Rev Pharmacoecon Outcomes Res* 5: 763-774.

Taphoorn MJ, Claassens L, Aaronson NK, et al. (2010) An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer* 46: 1033-1040.

Taphoorn MJ, Schiphorst AK, Snoek FJ, et al. (1994) Cognitive functions and quality of life in patients with low-grade gliomas: the impact of radiotherapy. *Ann Neurol* 36: 48-54.

Taphoorn MJ, van den Bent MJ, Mauer ME, et al. (2007) Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: results of a European Organisation for Research and Treatment of Cancer randomized clinical trial. *J Clin Oncol* 25: 5723-5730.

Thakkar JP, Dolecek TA, Horbinski C, et al. (2014) Epidemiologic and molecular prognostic review of glioblastoma. *Cancer Epidemiol Biomarkers Prev* 23: 1985-1996.

Townsend EA and Polatajko HJ. (2007) *Enabling Occupation II: Advancing an Occupational Therapy Vision for Health, Well-being, & Justice Through Occupation*: Canadian Association of Occupational Therapists.

van Coevorden-van Loon EMP, Coomans MB, Heijenbrok-Kal MH, et al. (2017) Fatigue in patients with low grade glioma: systematic evaluation of assessment and prevalence. *J Neurooncol* 133: 237-246.

Vargo M. (2011) Brain tumor rehabilitation. *Am J Phys Med Rehabil* 90: S50-62.

Vargo M, Henriksson R and Salander P. (2016) Rehabilitation of patients with glioma. *Handb Clin Neurol* 134: 287-304.

Vargo M. (2017) Brain Tumors and Metastases. *Phys Med Rehabil Clin N Am* 28: 115-141.

Visser O, Ardanaz E, Botta L, et al. (2015) Survival of adults with primary malignant brain tumours in Europe; Results of the EUROCARE-5 study. *Eur J Cancer* 51: 2231-2241.

von Elm E, Altman DG, Egger M, et al. (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 370: 1453-1457.

Walker M, Brown J, Brown K, et al. (2003) Practical problems with the collection and interpretation of serial quality of life assessments in patients with malignant glioma. *J Neurooncol* 63: 179-186.

Walsh KM, Ohgaki H and Wrensch MR. (2016) Chapter 1 - Epidemiology. In: Mitchel SB and Michael W (eds) *Handbook of Clinical Neurology.* Elsevier, 3-18.

Watson MJ. (2002) Refining the Ten-metre Walking Test for Use with Neurologically Impaired People. *Physiotherapy* 88: 386-397.

Watts C and Sanai N. (2016) Chapter 4 - Surgical approaches for the gliomas. In: Mitchel SB and Michael W (eds) *Handbook of Clinical Neurology.* Elsevier, 51-69.

Weller M, van den Bent M, Tonn JC, et al. (2017) European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. *Lancet Oncol* 18: e315-e329.

Wick A, Kessler T, Elia AEH, et al. (2018) Glioblastoma in elderly patients: solid conclusions built on shifting sand? *Neuro Oncol* 20: 174-183.

World Medical A. (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 310: 2191-2194.

Zucchella C, Capone A, Codella V, et al. (2013) Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumor: a randomized, controlled trial. *J Neurooncol* 114: 93-100.

Aaronson NK, Ahmedzai S, Bergman B, et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 85: 365-376.

12 Appendices