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The effectiveness of interdisciplinary rehabilitation of patients with primary glioma during active anticancer treatment – a single-blinded randomized controlled clinical trial

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Introduction

This SAP will be used as a working description within a Ph.D. project investigating the effectiveness of interdisciplinary non-pharmacological rehabilitation of patients with glioma. The trial is registered at www.ClinicalTrial.gov under the identifier NCT02221986 and The Regional Ethics Committee of Southern Denmark approved the study under j. nr.: S-20140108.

Synopsis

Gliomas, also known as World Health Organization (WHO) grade I-IV brain tumours[1], are among the most devastating cancer diseases affecting humans. Poor prognosis, adverse effects from anticancer treatments and significant functional, emotional, and cognitive deficits affect the majority of patients, leaving them with impaired quality of life (QOL) and with a profound need for rehabilitation[2]. But according to a systematic literature review, rehabilitation in patients with brain tumours are rare[3]. This highlights the need to conduct research that investigates the effectiveness of non-pharmacological rehabilitation among patients affected by glioma in robust methodological designs.

Aim & study hypothesis

This randomized controlled clinical trial aims at investigating the effectiveness of standardized interdisciplinary non-pharmacological rehabilitation of patients with gliomas during anticancer treatments. The study tests the hypothesis that patients attending a rehabilitation intervention of physical therapy and occupational therapy during chemo-radiation will report improvement in 'overall QOL' superior to patients attending standard rehabilitation regimens.

A feasibility study and a protocol paper describing the design, methods, and outcomes have been published[4,5].

Study design

This study was designed as a parallel-arm randomized controlled clinical trial with patients allocated to an intervention-, or control group.

Study intervention

Patients allocated to the intervention received a rehabilitation intervention of six weeks physical therapy, and depending on needs, tailored occupational therapy. The intervention was initiated simultaneously with the establishment of chemo-radiation treatments, and all interventions occurred in continuance of the irradiation treatments at the Odense University Hospital (OUH), Denmark.

A case-report (under assessment) and a practice analysis[6] describing the rational of the intervention modalities have been published.

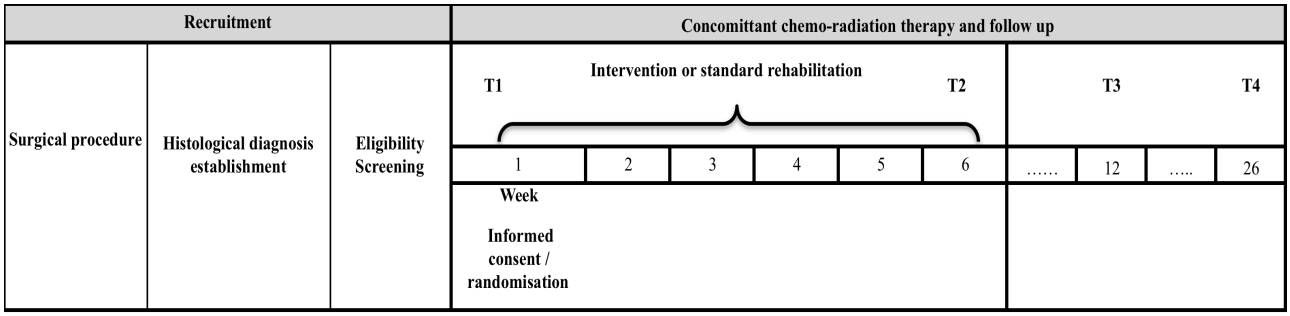
Controls

The control group received 'standard rehabilitation', which in this study is defined as the level of rehabilitation patients attend after discharge from Odense University Hospital (OUH). At discharge from the Neurosurgical department patients will have an evaluation of their need for rehabilitation, as per instruction from the Danish Health Authority[7]. This evaluation may advise: no rehabilitation acquired, rehabilitation established by the municipality, or as specialized neurorehabilitation at OUH.

Study objectives and outcomes

All outcomes were assessed at study entry (T1), at the completion of the intervention (T2), at a three-month follow-up (T3), and at a six-month follow-up (T4). This SAP deals with analyses that investigate the acute effects from T1 to T2 (Figure 1).

Figure 1 Study overview



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)

Purpose

The purpose was to compare changes from T1 to T2 between the intervention- and the control group in 'overall QOL'. The primary pre-specified outcome was the 'Global health Status/QOL' (GHS/QOL) scale from the European Organization for Research and Treatment of Cancer questionnaire (EORTC-QLQ-30). We hypothesize that patients attending the interdisciplinary rehabilitation (intervention) during chemo-radiation treatment will report improvements superior to patients having standard rehabilitation (control).

Primary Outcome

The GHS/QOL uses two unweighted responses to summarize a global score that measures 'overall QOL'. Patients' were asked to respond to the following questions: '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?' Each item is scored on a scale ranging from 1 [very poor] to 7 [excellent]. According to methods described in the 3rd edition of the EORTC-QLQ-C30 Scoring Manual, a linear transformation [GHS/QOL: S = ((RS −1) range)×100] was used to standardize raw scores to a numeric value ranging from 0 to 100, where a higher score represents a higher/better level of 'overall QOL'[8]. 'Overall QOL' was chosen as a relevant outcome as the intervention is expected to have little impact on a clinical outcome of survival time[9]. Global health rating scales are the simplest way to measure QOL and frequently used in clinical research. They are easy to understand, allow expression of the disparate values and preferences of individual patients[10], and they gives a concise way of summarizing the diverse components of health[11]. This study is the first to assess the effectiveness of non-pharmacologic rehabilitation in a randomized trial and we found no support in the literature to select a health-related quality of life (HRQOL) domain over another, in respect to where an effect from the rehabilitation would be evident.

Exploratory objectives and outcomes

The examination of exploratory secondary outcomes of HRQOL domains and symptoms, and functional performances allows for clinical indebt interpretation. They will only be supportive, explanatory and/or hypothesis generating which is why multiplicity is not considered a problem[12] (Table 1).

Table 1. Exploratory secondary outcomes

Patient reported outcomes	
EORTC-QLQ-30	All domains beside GHS/QOL, and all single items
EORTC-QLQ-BN20	All domains and single items
Functional performance measures	
The Åstrand / Rhyming ergometer test	Cardiovascular function
A 3-8 repetition maximum tests of main extremity muscle synergies (kg)	Dynamic muscle strength
10-meter walk test	Gait function
SWAY measurements of postural control performed (cm^2)	Postural sway

Sample size

This study is the first to investigate the effectiveness of standardized rehabilitation of patients with glioma in a randomized design. Therefore, information regarding SD and expected effect from previous studies is unavailable. The sample-size is consequently based on a pre-trial with a limited sample of 24 patients. According to a review of the literature, a minimal clinically important difference of 10 points in 'GHS/QOL' scale has been suggested[13]. The trial was designed as a superiority trial, in the sense that we expect patients allocated to the intervention arm to improve at least 10 points or more than patients allocated to the standard rehabilitation arm, in the primary outcome of GHS/QOL from baseline to follow-up. To detect a 10-point difference in GHS/QOL between arms, with SD based on results from a feasibility study (n=24), a one-tailed sample size was calculated. At an expected 'effect size' of 10 points (0.407) with SD ± 24.6 increase in 'GHS/QOL' with a statistical power of β 0.8 and α of 0.05, the study requires 76 participants in each arm. To meet an expected dropout rate of approximately 15%, we will try to include 88 participants in each group.

Settings, recruitment and study population

Odense University Hospital is one of four national hospitals to perform surgery and medical treatment of patients with glioma, and the only hospital within the Region of Southern Denmark. Approximately 90 patients with primary glioma undergo surgical resection annually. All patients in this trial are recruited from the Neurosurgical department whereas the interventions and assessments were conducted in specially designed facilities at the Rehabilitation- and Neurology department.

Recruitment

Patients eligible for entering the study had to comply with all inclusion criteria listed in table 2

Table 2. Eligibility criteria

Inclusion criteria	Exclusion criteria
Confirmed diagnosis of glioma (WHO I-IV) Age ≥18 Attending treatment at OUH Ability to communicate in Danish	Karnofsky Performance Status ≥70 Pregnancy Psychiatric diagnosis (such as uncontrolled schizophrenia, actively suicidal/self-harm or physically aggressive (based on clinical judgment)) Heart problems (New York Heart Association group III and IV) Severe impressive or expressive aphasia

Randomization and blinding

The randomization sequence was created using Statistical Package for the Social Sciences (SPSS) version 21 Windows, and stratified by tumour classification (WHO grade II) / (WHO grade III+IV) with a 1:1 allocation. Random blocks varying in size from 8-10 was prepared in continuous numbered, opaque and sealed envelopes by a staff-member otherwise uninvolved in the conduction of the study. Immediate after baseline assessments, the allocation was reviled to the patient but kept hidden for the outcome assessor. In contrast to pharmacological interventions, it was not possible to blind patients to whether they received the rehabilitation interventions or not.

Implementing the SAP

A statistician will supervise all analyses.

The following procedure will be used.

- A database for the purpose of this study is established in collaboration between Odense Patient data Explorative Network (OPEN) and the principal researcher. This model will be approved by the academic seniority.
- A data manager will code each treatment arm into a ´group treatment A´ and ´group treatment B´.
- Blinded data will be handed to the primary author and a statistician, which will conduct the analyses.
- Blinded results will be presented to the authors of the manuscript (as listed on the front page). Two consensus statements will be made prior to 'unblinding' the group allocation. One assuming that A is the intervention group, and one assuming that A is the control group.

Statistical analyses

We will use descriptive statistics to describe group characteristics.

Primary outcome

To test the study hypothesis that patients allocated to the intervention will experience effects in 'overall QOL' superior to patient in the standard rehabilitation group, and to predict an 'overall QOL score at follow-up', a multiple linear regression will be calculated based on group-allocation, gender, tumour grade and baseline values of GHS/QOL.

GHS/QOL residuals after regression on covariates (group allocation, gender, tumour grade, and baseline values of GHS/QOL) will be checked for normality by visual inspection using a Q-Q plot. Variance homogeneity will be inspected from plots of residuals against predicted outcome.

Superiority is investigated using 95% confidence interval (CI) of the mean change in GHS/QOL between the two arms. The intervention is considered superior to standard rehabilitation regimens when the lower of the 95% CI excludes the superiority margin.

All analyses are made by the complete case analyse principle, which should not produce any biases, as missing data are considered to be missing completely at random[14], as according to the EORTC-QLQ-30 scoring manual[8]. Further, as only few observations are expected to be missing only a minimal harm will be done[15].
For sensitivity, a baseline value comparison of completers and non-completers will be conducted.

For exploratory purposes, per-protocol (PP) analysis including patients only with high adherence and compliance will be conducted. This means that patients not fully committed to the criteria are excluded from the analysis.

Adherence is defined by the number of sessions attended at the physical therapist supervised intervention. Adherence was dichotomized and considered high if the patient attended 10 or more session (>60%), and low if the patient attended nine or fewer sessions (<60%).

Compliance is defined as the exercises performed by the patients at each physical therapist supervised session. Compliance was dichotomized and considered high if the patient completed six or more exercise from a possible seven exercises, as a mean, and low if the patient completed five or fewer exercises at the attended session.

Exploratory secondary outcomes

All secondary outcomes will be handled similar to the primary outcomes.

Major Protocol Deviations

In this SAP a corrected power calculation was conducted, due to application of wrong methods in the study protocol[4]. However, as we use the same data material to conduct the corrected calculation, and because the estimates are based on a limited sample, it is mealy to be considered as a rough estimate.
Due to experiences gained from active patient recruitment, minor protocol deviations were made in the recruiting of

patients. However, this should have no influence on the scientific conclusion of the study.

Originally we considered imputing missing values under consideration of generalized estimating equations or linear mixed models. However, we will follow instructions from a statistician and abstain from imputing data.

Table and figure legends and explanations

Table 1 Exploratory secondary outcome

Table 2 Eligibility criteria

Table 3 Baseline demographics for patients with primary glioma allocated to the intervention-, versus the standard rehabilitation group.

Table 4 GHS/QOL at T1 and T2 of the intervention-, versus control among patients primary glioma. Data are derived from multiple linear regressions and adjusted for group-allocation, gender, tumour grade, and baseline GHS/QOL scores. The table illustrates the results from the complete case population.

Table 5
Exploratory outcomes of EORTC-QLQ-30, BN-20, and functional performance measures.

Figure 1 Study overview

Figure 2 Flow of participants throughout the study

Table 1

Patient reported outcomes	
EORTC-QLQ-30	All domains beside GHS/QOL, and all single items
EORTC-QLQ-BN20	All domains and single items
Functional performance measures	
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A 3-8 repetition maximum tests of main extremity muscle synergies (kg)	Dynamic muscle strength
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Table 2:

Inclusion criteria	Exclusion criteria
Confirmed diagnosis of glioma (WHO I-IV) Age ≥18 Attending treatment at OUH Ability to communicate in Danish	Karnofsky Performance Status ≥70 Pregnancy Psychiatric diagnosis (such as uncontrolled schizophrenia, actively suicidal/self-harm or physically aggressive (based on clinical judgment)) Heart problems (New York Heart Association group III and IV) Severe impressive or expressive aphasia

Table 3

Variable	Intervention group (n=x)	Control group (n=x)
Age, years		
Median (range)		
Gender (male *(%))*		
Body Mass Index (kg/m2)		
Mean (SD)		
Married, cohabiting, or in a relationship (n= (%))		
Completed secondary school or higher (n= (%))		
Primary School		
Vocational education		
Secondary school		
Short-term 3rd level education		
Medium length 3rd level education		
Long-term 3rd level education		
Other		
Employment status (n= (%))		
Student		
Unemployed, working at part-time or full-time		
Early retirement or retired due to age		
Other		
Karnofsky performance status (n= (%))		
100		
90		
80		
70		
Time from surgery to study entry, days		
Median (range)		
WHO grade (n= (%))		
II		
III		
IV		
Hemisphere (n= (%))		

Right

Left

Both

Post resection residual tumour (n= (%))

Total removal[1]

Partial removal[2]

Decompression[3]

Eloquent tumour location (n= (%))

Yes (n= (%))

Medical treatment modalities

Surgery, radiation therapy and chemotherapy (n= (%))

Surgery and chemotherapy (n= (%))

Surgery and radiation therapy (n= (%))

Other (n= (%))

Corticosteroid therapy (n= (%))

Yes (n= (%))

Antiepileptic drug use (n= (%))

Yes (n= (%))

AMPS, Mean (SD)

Motor

Process

Rehabilitation at discharge from the hospital

No rehabilitation (n= (%))

Municipality services (n= (%))

Specialized neurorehabilitation at the hospital (n= (%))

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[1]All preoperatively imaged visually suspected tumour tissue is expected to be removed
[2]More than 50% of the original tumour volume is expected to be removed
[3]Less than 50% of the original tumour volume is expected to be removed

Table 4

Primary outcome	Intervention group predicted	Control group predicted	Coefficient	p-value (95%CI)	Adjusted R^2 *
GHS/QOL Scale (0-100)					

*Adjusted for gender, group-allocation, tumour-grade, and baseline GHS/QOL values.

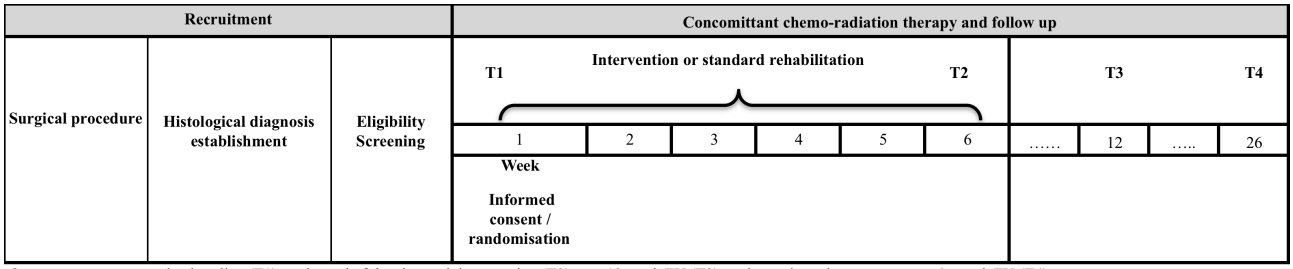
Table 5

Exploratory outcome	Intervention group predicted	Control group predicted	Coefficient	p-value	95% CI
EORTC-QLQ-30					
Physical functioning					
Role functioning					
Emotional functioning					
Cognitive functioning					
Social functioning					
Fatigue					
Nausea and vomiting					
Pain					
Dyspnoea					
Insomnia					
Appetite loss					
Constipation					
Diarrhoea					
Financial difficulties					
BN-20 (symptoms)					
Future uncertainty					
Visual disorder					
Motor dysfunction					
Communication deficit					
Headaches					
Seizures					
Drowsiness					
Itchy skin					
Hair loss					
Weakness of legs					
Bladder control					
Functional performance					
Aerobe power					
1RM Leg press					
1RM Knee extension					
1RM Knee flexion					
1RM Elbow extension					
1 RM Elbow flexion					
Ten meter walking test (m/s)					

Postural SWAY 95%(cm2)					

Adjusted for gender, group-allocation, tumour-grade, and baseline GHS/QOL values.

Figure 1 Study overview



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)

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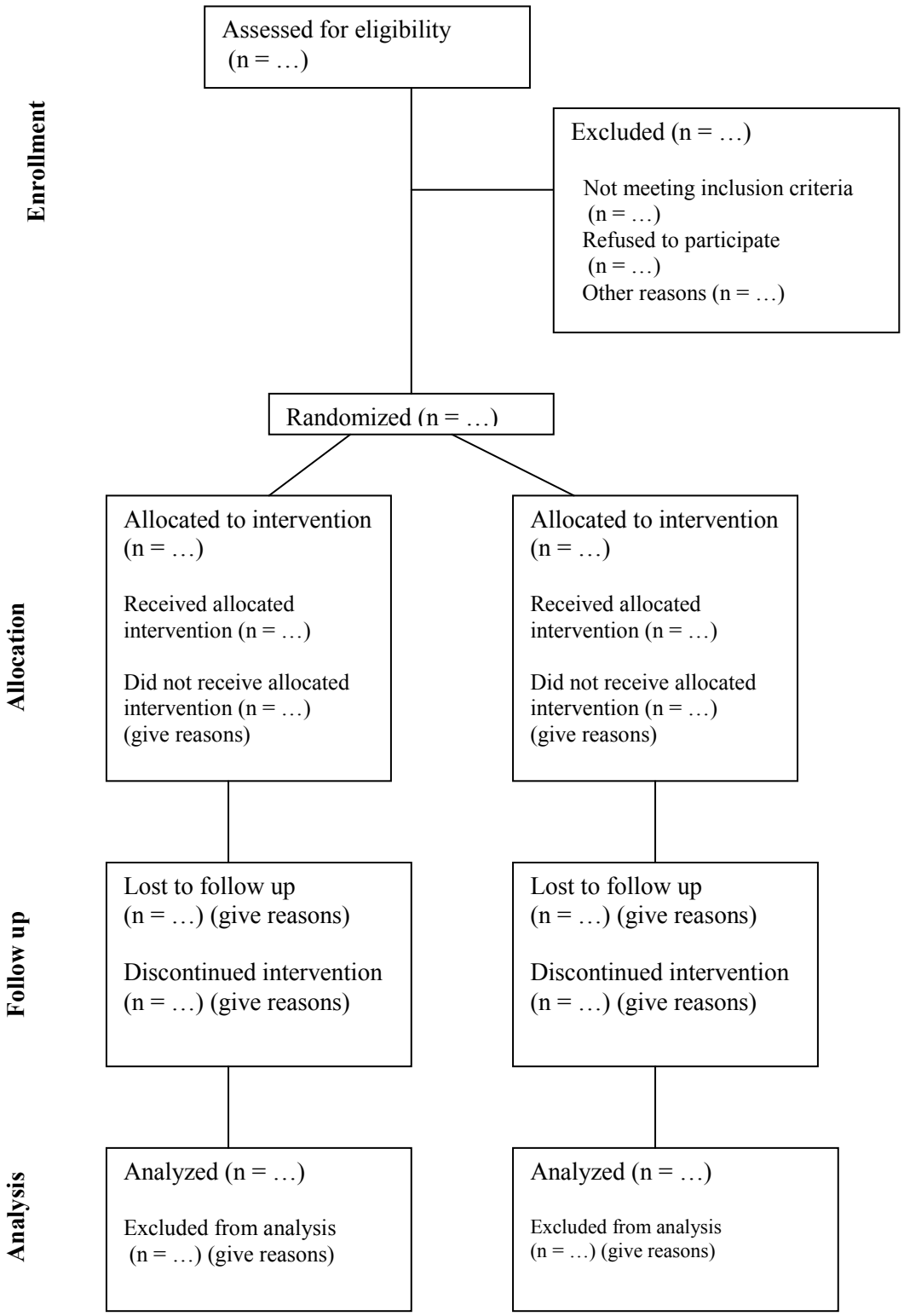
Figure 2 Flowchart



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