ARTICLE DETAILS

TITLE (PROVISIONAL)  The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among primary glioma patients – an RTC study protocol

AUTHORS  Hansen, Anders; Rosenbek Minet, Lisbeth; Søgaard, Karen; Jarden, Jens

GENERAL COMMENTS

This paper has highlighted a significant gap in the literature around RCTs conducted for glioma patients and rehabilitation programs. The challenge is conducting this research with such a vulnerable population and the additional burden placed on them, especially for those who receive standard treatment.

The ethically issue about conducting the RCTs for this group has not been adequately addressed and I believe that even the phase 1 program should have ethics approval.

It concerns me that under ethical considerations this protocol states 'this study poses no serious ethical issues in general'. I am also concerned that the glioma patient will be approached on Day 1 post-operatively.

I believe there needs to be clearer guidelines in place to assess if the patient is not longer able to participate due to disease progression or burden/impact of research on their well-being. Also there needs to be stipulated a clear referral system to counselling etc if required.

Besides the intervention it is important to identify the committment of time for the assessment tools for both groups and importantly what possible follow-up and gain the control group may receive from this research.

Due to the nature of this intervention I think an additional qualitative component is required to elaborate on the psycho-social aspect of this intervention.

I believe the anticipated sample size anticipated for this group over estimates the acceptance rate and eligibility of this group.

I also believe this is important research to conduct especially in the area of rehabilitation which is often not offered to these patients due to the nature of their condition.
to the uncertainty of prognosis but significant care of this group needs to be considered and the burden of the research taken into account.

**REVIEWER**
Dirven, Linda  
VU University Medical Center, Amsterdam, the Netherlands

**REVIEW RETURNED**
15-Jul-2014

**GENERAL COMMENTS**

* The abstract explicitly describes phase I and phase II, but this is not mentioned in the paper. Maybe the authors could add this in the protocol for clarity.

* Background: The authors describe that ‘Primary brain tumors is the cause of 2% of all cancer-related deaths and can in accordance with the WHO be divided into low-grade glioma (LGG) (WHO grades I/II) and high-grade glioma (HGG) (WHO grades III/IV)’. I would suggest that the authors revise this sentence slightly, because gliomas (including LGG and HGG) are the most common type of primary brain tumors, but not the only ones.

* Background: In the last sentence, the authors state that ‘The results of the present RCT will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer or LGG’. I wonder why the authors mention explicitly LGG? They also include patients with HGG. I would therefore suggest to change ‘LGG’ into ‘glioma’ (or something similar).

* Primary and secondary outcomes are clearly defined, but it would be helpful if the authors provide a rationale for the chosen primary outcome measure.

* Objectives: The authors describe the secondary objective as ‘to investigate if the rehabilitation programme has an effect on HRQoL, fatigue and median survival rate between the groups’. It is unclear to which ‘groups’ the authors refer to. Is it LGG versus HGG? Or grade I, versus grade II, versus grade III and versus grade IV?

* Sample size: An effect size of 15%, can this be considered as clinically relevant?

* Randomisation: ‘Stratified by tumor grade’. Does this imply all four WHO grades? Or LGG versus HGG?

* Data collection methods: The description of the EORTC QLQ-C30 questionnaire is not complete. One of the symptoms scales is ‘nauseau and vomiting’ instead of only ‘nausea’. Moreover, ‘global health status’ should be called ‘global health status/QoL’, because it comprises two items.

* Data collection methods: For fatigue, the symptom scale from the EORTC QLQ-C30 is used. However, if this is a outcome measure on its own, it might be worth considering to use the Fatigue Severity Scale instead?

* Missing data: Did the authors consider to use Linear Mixed Models or Generalised Estimating Equations models to deal with missing data instead of using last observation carried forward?
The paper of Hansen and colleagues describes the protocol for an interdisciplinary, outcome assessor blinded, randomised 12 week parallel group rehabilitation study comparing physical function, HRQoL, fatigue and survival rates among glioma patients. This is an interesting study and the results may be valuable for future research and/or clinical practice. Moreover, the methodology that is described is robust.

I only have some minor issues that need to be addressed.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name Dr. Gaye Moore
Institution and Country St Vincent's Hospital, Melbourne, Australia
Please state any competing interests or state ‘None declared’: None declared

* This paper has highlighted a significant gap in the literature around RCTs conducted for glioma patients and rehabilitation programs. The challenge is conducting this research with such a vulnerable population and the additional burden placed on them, especially for those who receive standard treatment.

* The ethically issue about conducting the RCTs for this group has not been adequately addressed and I believe that even the phase 1 program should have ethics approval.

Respond: The protocol has been approved by the Regional Scientific Ethical Committees for Southern Denmark under Project-ID: S-20140108.

We certainly share the reviewers' consideration regarding the vulnerability of the study population. To deal with this concern, we have conducted a feasibility study to evaluate the participant burden, safety and ability to cope with the offered physical training. The content described in this protocol has been informed based on the results of the feasibility study. The feasibility study will be published in a separate paper, unfortunately not yet available.

Action: “The project was approved by the Regional Scientific Ethical Committees for Southern Denmark under Project-ID: (S-20140108) and by the Danish Data Protection Agency (J. no.2008-58-0035)”.

* It concerns me that under ethical considerations this protocol states ‘this study poses no serious ethical issues in general’. I am also concerned that the glioma patient will be approached on Day 1 post-operatively.

Respond: The amount of training placed on the patients is similar to intervention studies among other cancer groups (Adamsen et al.1), there are no similar studies of glioma patients to lean against. However, a systematic review of current knowledge indicates that no physical training studies reported adverse events as a direct result of testing or training2. A study by Jones et al.3 has reported that functional performance measures (e.g. cardiopulmonary exercise testing and maximum voluntary muscle contraction) are safe and acceptable methods to quantitatively assess functional status in patients with newly diagnosed and untreated, postsurgical, primary malignant glioma.

The feasibility study registered an attendance of 89% of training at OUH (averaging 16 of 18 possible sessions, range 10-18) and patients did not feel that the intervention was too burdensome evaluated by a questionnaire.
The training at OUH is considered safer than municipality services because the patient is under constant observation from therapists and nurses, and a physician can be called within minutes. The feasibility study registered a clinical safety of 100%.

Regarding contact on the first day after surgery: The project leader or nurse will before approaching patients seek information on the patients’ emotional status by the caring nurse. If the patient is emotional or physical compromised, the patient will be approached the following day. Guidelines at Neurosurgical ward at Odense University Hospital states that patients should be evaluated by therapists within 24 hours after returning from the intensive recovery room. Our opinion is that approaching patient with information within this particular time will be safe. The sentence has been revised.

Action: “The study leader/nurse approaches eligible patients at the neurosurgical department within 24 hours after returning from the intensive recovery room, when the first contact with the therapist normally is scheduled” has been added under the recruitment section.

*I believe there needs to be clearer guidelines in place to assess if the patient is not longer able to participate due to disease progression or burden/impact of research on their well-being. Also there needs to be stipulated a clear referral system to counselling etc if required.

Respond. We thank the reviewer for this comment. The Physical and emotional status of the patients are evaluated before every training session. Patients who exceed the set of specified requirements based on Adamsen et al.1 are referred to the study nurse or neurologist for further evaluation and possible exclusion.

The project co-operates with rehabilitation-, neurological-, neurosurgical-, oncology department including the radiation department and ‘Kraeften Bekæmpelse’ (Against Cancer) a private cancer counselling providing support groups located at the hospitals. Patients can be referred to all professional groups affiliated with the mentioned departments, including speech-therapists, psychologists, neuropsychologists and social workers ect. Patients will be referred to municipality rehabilitation if the specialised treatment does not meet the patients’ expectations.

Actions: “Temperature above 38°C, respiration frequency at rest >20, infection requiring treatment with antibiotics, ongoing bleeding; fresh petecchiae, bruises, blood-leukocytes <5×10⁹/L and blood-thrombocytes <5 x 10³/µL” has been added in the safety section.

“Patients are referred to municipality rehabilitation if the specialised treatment does not meet the patients’ expectations” has been added under the Criteria for discontinuing allocated intervention for a given trial participant section.

* Besides the intervention it is important to identify the commitment of time for the assessment tools for both groups and importantly what possible follow-up and gain the control group may receive from this research.

Respond. The feasibility study indicates that time of assessment was done within 90 minutes. The physical tests and questionnaires were completed within 60 minutes and 30 minutes was used for patient contact (talking etc.). The AMPS-test was accomplished in 60 minutes.

At follow-up assessments the control-group patients are evaluated by health professionals. In case of progression or complication, the therapists or nurses will register the change and actions will be initiated. If a patient is slightly functional or cognitive compromised the patient will be referred to a
suitable rehabilitation facility.

Actions: “All physical assessment tools and questionnaires are set to be conducted within 90 minutes and occupational tests within 60 minutes. This is done to decrease the symptom burden and avoid risk of bias due to fatigue” have been added under the outcome section.

* Due to the nature of this intervention I think an additional qualitative component is required to elaborate on the psycho-social aspect of this intervention.

Respond: We appreciate the comment. However, a qualitative evaluation to understand psycho-social aspects and experience of attending the intervention lies beyond the scope of this particular study.

* I believe the anticipated sample size anticipated for this group over estimates the acceptance rate and eligibility of this group.

Respond. Throughout May 1, 2013 to March 31, 2014 a feasibility study were conducted. A total of 24 patients were recruited out of 29 approached patients. All patients met the inclusion criteria (100%). Five patients declined to participate, all due to lack of motivation or they failed to see the possible benefits which equal an acceptance rate of 83%. Based on these results the anticipated acceptance rate and eligibility is considered obtainable.

As a consequence of the results of the feasibility study, we have elaborated on the primary and secondary outcomes. Due to process and scientific feasibility criteria the primary outcome has been changed into a more appropriate QoL.

Actions: The background section has been re-written according to the primary outcome of QoL and a new sample size has been estimated based on QoL-outcome and result from the feasibility study. The method section has thus been revised and now is worded.

"According to the scoring manual for EORTC QLQ-30 a change of 10 points or more is considered to be a moderate to large clinically significant change. Based on this assumption and the pilot studies results (n=24) a sample size is calculated. At an expected "effect size" of at least 10 points (SD ±24,6) increase in the EORTC QLQ-30 General Health Scale/QoL (paragraphs 29 and 30) with a statistical power of 80% and a of 0.05, the study requires 48 subjects in each arm. To meet an expected dropout-rate of approximately 15% a total of 56 participants will be included in each group. Based on 90 new cases annually in the Region, an >80% acceptance rate and fulfilment of inclusion criteria based on the feasibility study, approximately 64 patients will be included per year. Enrollment is thus expected to extend for 22 months."

* I also believe this is important research to conduct especially in the area of rehabilitation which is often not offered to these patients due to the uncertainty of prognosis but significant care of this group needs to be considered and the burden of the research taken into account.

Reviewer: 2
Reviewer Name L. Dirven
Institution and Country VU University Medical Center, Amsterdam, the Netherlands
Please state any competing interests or state ‘None declared’: None declared

* The abstract explicitly describes phase I and phase II, but this is not mentioned in the paper. Maybe the authors could add this in the protocol for clarity.

Respond: We thank the reviewer for the comment.
Actions: The sentence has been rewritten. The description of the phase I and II have been deleted in the abstract.

* Background: The authors describe that 'Primary brain tumors is the cause of 2% of all cancer-related deaths and can in accordance with the WHO be divided into low-grade glioma (LGG) (WHO grades I/II) and high-grade glioma (HGG) (WHO grades III/IV). I would suggest that the authors revise this sentence slightly, because gliomas (including LGG and HGG) are the most common type of primary brain tumors, but not the only ones.

Respond: Again we thank the reviewer for the comment.

Actions: The sentence has been revised to avoid misunderstandings as advised.

"Primary brain tumor is a complicated condition due to complex diagnostic and treatment regimes. It has a progressive nature and a poor prognosis causing 2% of all cancer-related deaths. Gliomas are the most frequent primary neoplasm in the CNS and according to World Health Organization histologically categorized into low-grade glioma (LGG) (WHO grades I/II) or high-grade glioma (HGG) (WHO grades III/IV)."

* Background: In the last sentence, the authors state that 'The results of the present RCT will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer or LGG'. I wonder why the authors mention explicitly LGG? They also include patients with HGG. I would therefore suggest to change 'LGG' into 'glioma' (or something similar).

Respond: LGG is theoretical not considered as cancer, but we thank the reviewer for making a notice.

Actions: The sentence has been rewritten to avoid misunderstandings.

"The results of the present RCT study will add to the growing body of literature investigating the potential role of exercise as a supportive therapeutic intervention for patient with cancer."

* Primary and secondary outcomes are clearly defined, but it would be helpful if the authors provide a rationale for the chosen primary outcome measure.

Based on results from the feasibility study we have elaborated on the primary and secondary outcome.

Primary outcome has been changed to the more appropriate QOL estimate.

Median survival time is removed from this trial due to an inadequate sample size.

Training in their home environment was not considered feasible and patients were unsatisfied with not having a therapist supervising the training. The 2nd phase of training in their home environment has thus been omitted.

Fatigue has been deleted as a secondary outcome – as it may just contribute to the overall symptom burden evaluated through EORTC-QLQ-30.

Physical activity levels measured by MET is removed due to the problems the participants had with responding on this particular part of the questionnaire. It has been replaced by a simpler question of
physical activity in leisure time and at work.

Actions: These key alterations are incorporated throughout the paper from the background section to method section.

The following section has been added in the background section “Since the vast majority of patients cannot be cured outcome measures in clinical cancer research have traditionally been focusing on prolonging the overall survival, progression-free survival or response to the medical treatment10-13. Today there is a general agreement that HRQoL measures are increasingly important and The American Society of Clinical Oncology has suggested, that QoL measurements are important primary endpoint in any Phase III study14. However research on glioma patients’ perception on HRQoL is sparse compared to other patient categories with neoplasms11 15”

* Objectives: The authors describe the secondary objective as ‘to investigate if the rehabilitation programme has an effect on HRQoL, fatigue and median survival rate between the groups’. It is unclear to which ‘groups' the authors refer to. Is it LGG versus HGG? Or grade I, versus grade II, versus grade III and versus grade IV?

Respond. We see the need for clarification. “Groups” referred to intervention group versus control group.

Actions. The sentence has been revised.

“The primary objective is to investigate if a structured rehabilitation program of intensive specialised physiotherapy and occupational therapy versus standard care has effect on HRQoL. Secondary objective is to investigate if the rehabilitation program can reduce the symptom burden and maintain or delay regression in physical function”.

* Sample size: An effect size of 15%, can this be considered as clinically relevant?

Respond. Primary outcome has been changed to QoL and a new sample size has been conducted. The rationale is stated previously.

Actions. The sample size calculation has been re-written.

*Randomisation: ‘Stratified by tumor grade’. Does this imply all four WHO grades? Or LGG versus HGG?

Respond: Again, we see the need for clarification. We referred to LGG versus HGG.

Actions: The sentence has been revised to avoid misunderstandings.

“Participants are randomly assigned to a control or intervention group (with a 1:1 allocation) by block randomisation stratified by LGG versus HGG.”

* Data collection methods: The description of the EORTC QLQ-C30 questionnaire is not complete. One of the symptoms scales is ‘nauseau and vomiting’ instead of only ‘nausea’. Moreover, ‘global health status’ should be called ‘global health status/QoL’, because it comprises two items.

Respond. We thank the reviewer for highlighting.

Actions. This has been corrected throughout the paper.
* Data collection methods: For fatigue, the symptom scale from the EORTC QLQ-C30 is used. However, if this is a outcome measure on its own, it might be worth considering to use the Fatigue Severity Scale instead?

Respond: As stated above fatigue has been deleted as a secondary outcome – but will contribute to the overall symptom burden through EORTC-QLQ-30.

Actions. Fatigue has been removed from the title and throughout the paper as a secondary outcome.

* Missing data: Did the authors consider to use Linear Mixed Models or Generalised Estimating Equations models to deal with missing data instead of using last observation carried forward?

Respond. We thank the reviewer for these highly appropriate advise.

Actions. This has been implemented in the method section as advised.

“Linear Mixed Models & Generalised Estimating Equations are used for handling non-ignorable dropouts in the longitudinal study”.

* The paper of Hansen and colleagues describes the protocol for an interdisciplinary, outcome assessor blinded, randomised 12 week parallel group rehabilitation study comparing physical function, HRQoL, fatigue and survival rates among glioma patients. This is an interesting study and the results may be valuable for future research and/or clinical practice. Moreover, the methodology that is described is robust.

I only have some minor issues that need to be addressed.

We thank the reviewer for the positive and encouraging comments as well as for the very helpful and detailed review that have clearly improved the paper.

10. van den Bent MJ, Carpenter AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and


**VERSION 2 – REVIEW**

| REVIEWER | Linda Dirven  
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- The reviewer completed the checklist but made no further comments.
The effect of an interdisciplinary rehabilitation intervention comparing HRQoL, symptom burden and physical function among patients with primary glioma: an RCT study protocol

Anders Hansen, Lisbeth Kirstine Rosenbek Minet, Karen Søgaard and Jens Ole Jarden

BMJ Open 2014 4:
doi: 10.1136/bmjopen-2014-005490

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