Blazeby, J., Jacobs, M., & Pusic, A. (2014). The level of patient-reported outcome reporting in randomised controlled trials of brain tumour patients: A systematic review. *European Journal of Cancer*. <https://doi.org/10.1016/j.ejca.2014.06.016>

Peer reviewed version

Link to published version (if available):
[10.1016/j.ejca.2014.06.016](https://doi.org/10.1016/j.ejca.2014.06.016)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via ELSEVIER at <https://www.sciencedirect.com/science/article/pii/S0959804914007606?via%3Dihub>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

The level of patient-reported outcome reporting in randomized controlled trials of brain tumour patients: A systematic review

Linda Dirven¹, Martin J.B. Taphoorn^{1,2}, Jaap C. Reijneveld^{1,3}, Jane Blazeby⁴, Marc Jacobs⁵, Andrea Pusic⁶, Edoardo La Sala⁷, Roger Stupp⁸, Peter Fayers^{9,10}, Fabio Efficace⁷. On behalf of *EORTC Quality of Life Group (Patient Reported Outcome Measurements Over Time In ONcology-PROMOTION Registry)*

¹VU University Medical Center, Department of Neurology, Amsterdam, The Netherlands

²Medical Center Haaglanden, Department of Neurology, The Hague, The Netherlands

³Academic Medical Center, Department of Neurology, Amsterdam, The Netherlands

⁴University of Bristol, Centre for Surgical Research and Division of Surgery, Head & Neck, University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom

⁵Academic Medical Center, University of Amsterdam, Department of Medical Psychology, Amsterdam, The Netherlands

⁶Memorial Sloan Kettering Cancer Center, Department of Surgery, New York, NY, USA

⁷Italian Group for Adult Hematologic Diseases (GIMEMA), Data Center and Health Outcomes Research Unit, Rome, Italy

⁸University Hospital Zurich, Department of Oncology and Cancer Centre, Zurich, Switzerland

⁹University of Aberdeen, Institute of Applied Health Sciences, Aberdeen, United Kingdom

¹⁰Norwegian University of Science and Technology, Department of Cancer Research and Molecular Medicine, Faculty of Medicine, Trondheim, Norway

Keywords: Brain tumour; patient-reported outcome; clinical trial; quality of life; clinical decision-making

Corresponding author:

L. Dirven, PhD

VU University Medical Center, Department of Neurology

PO BOX 7057

1007 MB Amsterdam

The Netherlands

Tel: +31 2044 45292; Fax: +31 2044 42800

Email: l.dirven@vumc.nl

Word count: 2973

Abstract: 248

Abstract

Background: To determine the net clinical benefit of a new treatment strategy, information on both survival and patient-reported outcomes (PROs) is required. However, to make an adequately informed decision, PRO evidence should be of sufficiently high quality.

Objective: To investigate the methodological quality of PRO reporting in randomized controlled trials (RCTs) in patients with brain tumours, and to assess the proportion of studies that should impact clinical decision-making.

Methods: We conducted a systematic literature search in several databases covering January 2004 to March 2012. We selected relevant RCTs and retrieved the following data: (1) basic trial demographics and PRO characteristics, (2) quality of PRO reporting, and (3) risk of bias. Studies that should impact clinical decision-making based on their methodological robustness were analysed systematically.

Results: We identified 14 RCTs, representing over 3000 glioma patients. Only two RCTs (14%) satisfied sufficiently many key methodological criteria to provide high-quality PRO evidence, and should therefore impact clinical decision-making. Important methodological limitations in other studies were lack of reporting of the extent (43%) and reasons (86%) of missing data and statistical approaches to handle this (71%). PRO results were not interpreted in 79% of the studies and clinical significance was not discussed in 86%. Studies with high-quality PRO evidence generally showed lower risk of bias.

Conclusions: Investigators involved in brain tumour research should pay special attention to methodological challenges identified in current work. The level of PROs reporting should continue to improve in order to facilitate a critical appraisal of study results.

1 Introduction

Although primary brain tumours constitute only 2% of all adult cancers[1], they result in a disproportionate share of cancer morbidity and mortality. Gliomas are the most frequent primary brain tumours in adults, and prognosis depends on histological tumour type, grade and tumour genetics.[2] Typically, patients with low-grade gliomas live longer than patients with higher grade gliomas. However, despite multimodal treatment with surgery, radiotherapy and chemotherapy, gliomas remain largely incurable.[2, 3]

Traditional outcome measures in randomized clinical trials (RCTs) are overall and progression-free survival. The incurable nature of gliomas has led to the recognition that palliation and maintenance or improvement of health-related quality of life (HRQoL) are just as important as prolonged survival. Consequently, HRQoL has become an important outcome measure in clinical brain tumour research.[4-7] HRQoL is a patient-reported outcome (PRO), reflecting the patient's perspective[8], and is a multidimensional concept covering physical, psychological and social domains as well as symptoms induced by the disease and its treatment.[9] Several PRO measures are available, ranging from one-dimensional (measuring a single aspect of HRQoL, such as fatigue) to multidimensional measures.

To determine the net clinical benefit of a new treatment strategy, information on both survival and HRQoL is required. The benefits of a new treatment strategy in terms of prolonged survival have to be carefully weighed against the side-effects of this treatment. HRQoL measurements should therefore be included in RCTs. In addition, it is important that PROs generate high-quality evidence to be of value. Inadequate or poorly designed RCTs including PRO measurements, or simply reporting insufficient PRO information, may limit their ability to inform clinical decision-making. In 2002, a systematic review showed that many RCTs in brain tumour patients which included PRO had methodological limitations, hampering the interpretation of the results.[10]

The primary objective of this study was to investigate the methodological quality of PRO reporting in RCTs of primary brain tumours published since 2004. The secondary objective was to assess the proportion of studies that should impact clinical decision-making based on their methodological robustness.

2 Methods

2.1 Search strategy for identification of studies

We conducted a systematic literature search in the e-resources PubMed/Medline, the Cochrane Library, PsycINFO, and PsycARTICLES covering January 2004 to March 2012. The search strategy consisted of a combination of two strings, one related to PRO measures and one related to primary brain tumours (see supplementary file for full search string).

In PubMed/Medline, the search strategy was restricted to RCTs. Moreover, only English-language articles were considered. All retrieved titles and abstracts were screened, and full-texts of potential relevant articles were read and the reference lists of these articles were screened for additional studies. In addition, experts in the field were contacted to identify possible relevant articles that were not retrieved in the electronic search.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to document details on the search strategy and selection processes.[11]

2.2 Criteria for considering studies

2.2.1 Type of participants

Studies were considered to be eligible if adult (≥ 18 years) patients were included with histologically confirmed primary brain tumours, or those with recurrence, regardless of the type and grade of the tumour. Studies involving patients with brain metastases were excluded.

2.2.2 Type of intervention

Any RCT comparing conventional treatments (i.e. chemotherapy, radiotherapy, surgery and target therapy) was eligible for inclusion. Studies comparing psychosocial interventions or complementary and alternative medicine were excluded.

2.2.3 Type of outcome measures examined

All studies including a PRO measure, either as primary or secondary outcome measure, were considered eligible. Measures assessing the impact of the disease and treatment-related effects were considered, including both multidimensional HRQoL measures as well as other types of PRO measures. Studies evaluating adherence to therapy or satisfaction were excluded.

2.2.4 Type of studies

Only original studies were considered and they were eligible if they described an RCT comparing different conventional medical treatment modalities or symptom management strategies, and if a minimum of 50 primary brain tumour patients (overall) were included. When the RCT comprised a heterogeneous population, consisting of different cancer types, the study was excluded because of possible difficulties in interpreting PRO results relating specifically to primary brain tumour patients.

2.3 Methods of study evaluation

Data were gathered through the EORTC Quality of Life Group PROMOTION (Patient-Reported Outcomes Measurements Over Time in Oncology) Registry (<http://promotion.gimema.it/>) which stores information on cancer RCTs having included a PRO evaluation. More details on this project have been previously published.[12] Two reviewers (E.S. and M.J.) independently reviewed all identified studies. When disagreements occurred, the paper was reviewed again and remaining discrepancies were solved by consensus or by consulting a third reviewer (F.E.).

On several trials, multiple articles were published. In these cases, relevant data from all articles were combined.

2.4 Type of information extracted and definition of high quality PRO study

We extracted different types of information from each RCT. First, basic trial demographics and clinical and PRO characteristics were extracted, such as the overall study sample size, types of intervention, type of PRO questionnaire used, and main PRO and clinical outcomes.

Second, the level of PRO reporting was assessed using the recently published recommendations by the International Society for Quality of Life Research (ISOQOL).[13] The ISOQOL checklist consists of 17 items that should be reported in all RCTs, irrespective of the type of PRO and whether the PRO is used as primary or secondary endpoint. When a PRO is the primary endpoint, an additional 11 items should be reported.[13] As exception to the checklist, we divided the item about 'missing data' into two items (extent of missing data and statistical approaches to deal with missing data), to better investigate the possible discrepancies between reporting of actual missing PRO data as opposed to reporting of statistical methods to address this issue. To estimate the potential impact of PRO evidence on clinical decision-making, we needed a definition of 'high-quality' for PRO evidence. In line with previous work[12], we propose that at least two-thirds of the recommended ISOQOL criteria must be satisfied in order to be classified as high-quality evidence. Additional details have been previously reported.[14]

Third, using the Cochrane Risk of Bias Tool, the RCTs were assessed for risk of bias.[15] Types of bias assessed were selection bias, performance bias, detection bias, attrition bias and reporting bias. The risk of bias was divided into three categories using previously reported definitions: low risk, unclear or high risk of bias.[12]

3 Results

The literature search yielded 3404 records published between January 2004 and March 2012 which were screened for eligibility. A total of 18 papers was identified, comprising 14 RCTs which enrolled over 3000 glioma patients. Figure 1 shows a detailed description of the selection procedure.

3.1 Overview of study demographics and patient-reported outcomes assessment

In all 14 RCTs, PRO measurements were a secondary endpoint. Most (64%) RCTs were multi-centre international studies and half (50%) of the RCTs had a sample size of >200 patients. Patients with glioblastoma were mostly studied (86%).

All studies used previously validated PRO instruments. The two most frequently used PRO instruments were the European Organisation of Research and Treatment of Cancer (EORTC) QLQ-C30 and the Functional Assessment of Cancer Therapy-General (FACT-G) in nine (64%) and four studies (29%), respectively. These instruments were used alone or in conjunction with tumour-specific measures (EORTC QLQ-BN20 and the FACT-Brain). A difference in PRO results between the treatment arms was found in three RCTs (23%). Further details are depicted in Table 1.

3.2 Overview of methodological PRO quality according to ISOQOL criteria

According to the predefined criteria, two RCTs[6, 7, 16-19] provided 'high-quality' evidence (Table 2). Major limitations in reporting included the lack of documentation of the rationale for the PRO instrument used (86%) and lack of a description of the PRO hypothesis and specification of the relevant PRO domains that were analysed (86%). Moreover, none of the trials documented the mode of PRO administration (i.e. on paper, by telephone, electronically) and the methods of data collection. The level of documentation of details on missing data was highly variable: only two studies (14%) reported reasons for missing data, four studies (29%) described the statistical approaches to deal with missing data, while eight studies (57%) reported on the extent of missing data. Furthermore, the majority of the trials (57%) did not describe the baseline PRO characteristics. The clinical significance of PRO findings was discussed in only two trials (14%), whereas four trials

(29%) discussed PRO findings in the context of other clinical outcome measures. Lastly, a minority of the trials discussed the limitations of the PRO components in the trial (29%) or the generalizability issues uniquely related to the PRO results (14%).

In contrast, most studies did report whether the PRO was a primary or secondary outcome measure (93%). Also, details on PRO data collection schedule were provided in the majority of the studies (93%).

3.3 Risk of bias

For several types of bias, the risk across RCTs was similar for studies that provided high- and low-quality PRO evidence (Figure 2). Nevertheless, two studies with low-quality PRO evidence (17%) had a high risk of performance bias, where neither of the two studies with high-quality PRO evidence had a high risk for this type of bias. Moreover, most studies with low-quality PRO evidence (67%) had a high risk of reporting bias and attrition bias (58%), while both studies with high-quality PRO evidence were attributed a low risk.

3.4 Overview of treatment recommendations based on high-quality PRO studies

We identified two RCTs that provided ‘high-quality’ PRO evidence and should therefore be considered to adequately influence clinical decision-making. The first RCT compared radiotherapy alone with radiotherapy plus concomitant and adjuvant temozolomide in patients with newly diagnosed glioblastoma.[17, 18] This study showed that the combination of temozolomide and radiotherapy led to clinically meaningful and significant longer overall and progression-free survival rates. This prolonged survival was achieved without a lasting negative impact on HRQoL. Although patients undergoing treatment with temozolomide plus radiotherapy reported significant lower social functioning compared to patients undergoing radiotherapy alone, this decline in HRQoL was temporary. Similar results were found for nausea and vomiting, appetite loss, and constipation: radiotherapy plus temozolomide resulted in a temporary higher symptom burden. Other HRQoL scales did not differ between the two treatment arms during follow-up.[6] Concomitant and adjuvant radiochemotherapy with temozolomide is now the standard of care for newly diagnosed glioblastoma patients[20]; this study showed that the benefits of prolonged survival outweigh the temporary negative effects of this treatment on HRQoL.

The second RCT compared radiotherapy alone with radiotherapy plus adjuvant procarbazine, lomustine and vincristine (PCV) chemotherapy in patients with newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas.[19] After a median follow-up of 60 months, overall

survival rate was similar for the two treatment arms while progression-free survival was significantly longer in patients treated with radiotherapy plus PCV chemotherapy.[19] A recent update on this study has shown that, after median follow-up of 140 months, both overall and progression-free survival rates were significantly prolonged in the radiotherapy plus PCV chemotherapy arm, in particular in patients with co-deleted 1p/19q.[21] Addition of PCV chemotherapy to radiotherapy resulted in a decreased HRQoL during and shortly after receiving PCV chemotherapy: patients reported more nausea and vomiting, appetite loss and drowsiness.[7] However, this decline in HRQoL was clinically not meaningful, and transient. Based on the survival benefit, treatment with radiotherapy plus PCV chemotherapy is recommended for patients with 1p/19q co-deleted anaplastic oligodendrogliomas and oligoastrocytomas[20]. The 'high-quality' PRO results support the choice for this treatment strategy: the temporary negative effects of the experimental treatment strategy on HRQoL seem to be outweighed by the survival benefit. For those without co-deletion, radiotherapy alone remains the standard of care.[20]

4 Discussion

In the last decade, more than 3000 glioma patients have been included in 14 RCTs to obtain information on the impact of different treatment strategies, both in terms of survival and PROs. This systematic literature review showed that two RCTs could be classified as 'high-quality' studies with respect to PRO evidence[6, 7] and could therefore facilitate critical appraisal and interpretation of the results necessary for clinical decision-making.[22]

Compared to the previous systematic review[10], which identified only five RCTs including a PRO measure in a period >20 years, the absolute amount of RCTs including a PRO measure has increased in the last decade. However, current data indicate that level of PRO reporting has not improved much. Previously, issues such as documentation of missing data, description of PRO hypothesis, description of clinical significance of PRO findings, and a description of the methods of administration were reported in 60%, 40%, 20% and none of the RCTs, respectively.[10] Similarly, the current review reveals that these issues were reported in 57%, 7%, 14% and none of the RCTs. On the other hand, where previously poorly validated instruments were used, all RCTs in the current review used validated and reliable PRO instruments. Awareness of sufficient reporting of PRO results is still warranted, and key guidelines on how to conduct and report PRO measures are available.[13] This applies not only to brain tumour research, because similar methodological limitations were found in other cancers, such as prostate or lung cancer.[12, 23]

A major limitation of all RCTs, regardless of publication date, is an adequate description of missing data. Missing data is a major source of bias and a common problem in many research

areas.[24] Frequent reasons for missing data in brain tumour trials are administrative failure, patient refusal and poor health status of the patient.[25] As a result, patients with poor prognostic factors and a poor response to treatment are underrepresented during follow-up.[26] This has implications for the interpretation of the results. It is therefore of utmost importance that studies report the amount of missing data and their methods of analysis. From a practical point of view, the amount of missing data can be decreased by using electronic data capture[27] or proxy measures.

Another major limitation is that the majority of RCTs lacks an interpretation of PRO findings, especially in terms of clinical significance. A significant difference in PRO between two treatment arms does not necessarily imply that this difference is also clinically meaningful for patients.[28] Moreover, when no differences in survival are found between treatment arms, PRO results can be highly informative to evaluate the net clinical benefit of a new treatment strategy. Also, in many studies PROs are assessed up to, but not beyond, tumour progression. This will hamper the evaluation of late treatment effects, especially in trials where a difference in progression-free survival leads to a difference in observation time. Data collection after tumour progression should therefore be included in future trials.[29, 30]

Although the quality of reporting of PRO evidence was classified as low in most RCTs published since 2004, this does not mean that the trial design was poor. These RCTs may have assessed and analysed PROs correctly, but failed to report the procedures and results adequately, resulting in PRO evidence classified as low-quality. A possible explanation for the poor reporting of PRO procedures and results is that PROs are used as secondary outcome measures. This means that results on PRO assessment are included in the main paper, next to outcome measures such as overall and progression-free survival, leaving limited room for a detailed description of PRO results. Therefore, researchers need to become aware of the recommended methodologies for reporting PRO-related outcomes, in order to facilitate critical appraisal and interpretation of the results necessary for clinical decision-making. We therefore suggest reporting PROs in a separate publication, possibly in the same journal to reach the same target audience. Moreover, both RCTs that provided high-quality PRO evidence were conducted by the EORTC, an organization with a longstanding tradition in HRQoL research. Indeed, the EORTC Quality of Life Group implemented standardized procedure for HRQoL implementation cancer trials already several years ago.[31]

This paper has limitations. Although a comprehensive search strategy was used, it is possible that not all RCTs comprising PRO components were identified. Moreover, this review covers RCTs published between 2004 and 2012, thereby excluding more recently published RCTs[32-35] and those published between 2002 (previous review covers years <2002[10]) and 2004. This may result in an underestimation of the amount of studies with high-quality PRO evidence, and therefore a lack to detect an improvement in PRO reporting over time. It will thus be important to keep monitoring and

evaluating future studies to possibly find a quality improvement over time. Another limitation of this study is that the definition of 'high-quality' PRO evidence is based on methodological grounds solely. However, evaluation of the methodological quality of PRO evidence is based on recommendations that are generated by an international task force endorsed by a major scientific society.[13, 36] A challenge, however, is to determine the tangible impact of 'high-quality' PRO studies on clinical decision-making. Although treatment recommendations in oncology endorse that quality of life is of highest priority and should guide clinical guidance[37], most recommendations seem to be based on survival outcomes only. Moreover, the actual impact on clinical decision-making also depends on the specific findings of a study, implying that studies with low-quality PRO evidence might have had a large impact as well. Lastly, we have to acknowledge that with only 14 studies, the estimates may not be very accurate.

In conclusion, quality of PRO reporting was evaluated in 14 RCTs in patients with primary brain tumours and found to be of sufficient quality to be valuable for clinical decision-making in two RCTs. High-quality PRO evidence is necessary to determine the net clinical benefit of treatment strategies, in conjunction with survival data. Both RCTs that included high-quality PRO evidence resulted in treatment recommendations, showing that the new treatment strategies were not only effective in terms of survival, but also without a (lasting) detrimental effect on HRQoL. Overall, this systematic review indicates the need to keep improving PRO reporting in brain tumour trials, in order to facilitate critical appraisal and interpretation of results necessary to better inform clinical decision-making.

Conflict of interest

Roger Stupp and Martin J.B. Taphoorn have been involved in the conduct of several randomized controlled trials that were identified in this paper, but they were not involved in the data extraction process. All other authors have declared no conflicts of interest.

Role of the funding source

This paper stems from a larger project (i.e., Patient Reported Outcome Measurements Over Time In ONcology-PROMOTION Project) funded by a research grant from the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group. Also, additional support for the conduct of the study was provided by the Italian Group for Adult Hematologic Diseases (GIMEMA).

Acknowledgments

The authors acknowledge Alessandro Perreca and Salvatore Soldati, from the GIMEMA, for their contribution to data management.

Reference List

1. Stupp R, Gander M, Leyvraz S, Newlands E. Current and future developments in the use of temozolomide for the treatment of brain tumours. *Lancet Oncol.* 2001;2:552-60.
2. Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro Oncol.* 2013;15 Suppl 2:ii1-56.
3. Ricard D, Idbaih A, Ducray F, Lahutte M, Hoang-Xuan K, Delattre JY. Primary brain tumours in adults. *Lancet.* 2012;379:1984-96.
4. Aaronson NK, Taphoorn MJ, Heimans JJ, Postma TJ, Gundy CM, Beute GN, et al. Compromised health-related quality of life in patients with low-grade glioma. *J Clin Oncol.* 2011;29:4430-5.
5. Malmstrom A, Gronberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol.* 2012;13:916-26.
6. Taphoorn MJ, Stupp R, Coens C, Osoba D, Kortmann R, van den Bent MJ, et al. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. *Lancet Oncol.* 2005;6:937-44.
7. Taphoorn MJ, van den Bent MJ, Mauer ME, Coens C, Delattre JY, Brandes AA, et al. 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.* 2007;25:5723-30.
8. US Department of Health and Human Services Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims [Internet]. 2009 Dec. [cited 12 May 2014]. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
9. Aaronson NK. Quality of life: what is it? How should it be measured? *Oncology: Williston Park*; 1988, p69-76.

10. Efficace F, Bottomley A. Health related quality of life assessment methodology and reported outcomes in randomised controlled trials of primary brain cancer patients. *Eur J Cancer*. 2002;38:1824-31.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006-12.
12. Efficace F, Feuerstein M, Fayers P, Cafaro V, Eastham J, Pusic A. Patient-reported Outcomes in Randomised Controlled Trials of Prostate Cancer: Methodological Quality and Impact on Clinical Decision Making. *Eur Urol*. 2013(Oct 30):S0302-2838(13)01090-7.
13. Brundage M, Blazeby J, Revicki D, Bass B, de Vet H, Duffy H, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. *Qual Life Res*. 2013;22:1161-75.
14. Efficace F, Bottomley A, Osoba D, Gotay C, Flechtner H, D'haese S, et al. Beyond the development of health-related quality-of-life (HRQOL) measures: a checklist for evaluating HRQOL outcomes in cancer clinical trials--does HRQOL evaluation in prostate cancer research inform clinical decision making? *J Clin Oncol*. 2003(21):3502-11.
15. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
16. Mirimanoff RO, Gorlia T, Mason W, van den Bent MJ, Kortmann RD, Fisher B, et al. Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol*. 2006;24:2563-9.
17. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-96.
18. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. 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*. 2009;10:459-66.

19. van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJ, Bernsen HJ, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol*. 2006;24:2715-22.
20. Stupp R, Tonn JC, Brada M, Pentheroudakis G. High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21 Suppl 5:v190-3.
21. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol*. 2013;31:344-50.
22. Calvert M, Brundage M, Jacobsen PB, Schunemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. *Health Qual Life Outcomes*. 2013;11:184.
23. Zikos E, Ghislain I, Coens C, Ediebah DE, Sloan E, Quinten C, et al. Health-related quality of life in small-cell lung cancer: a systematic review on reporting of methods and clinical issues in randomised controlled trials. *Lancet Oncol*. 2014;15:e78-e89.
24. Dirven L, Reijneveld JC, Aaronson NK, Bottomley A, Uitdehaag BM, Taphoorn MJ. Health-related quality of life in patients with brain tumors: limitations and additional outcome measures. *Curr Neurol Neurosci Rep*. 2013;13:359.
25. Walker M, Brown J, Brown K, Gregor A, Whittle IR, Grant R. Practical problems with the collection and interpretation of serial quality of life assessments in patients with malignant glioma. *J Neurooncol*. 2003;63:179-86.
26. Vordermark D. Avoiding bias in the prospective evaluation of patients with brain metastases. *J Clin Oncol*. 2007;25:4023-5.
27. Walther B, Hossin S, Townend J, Abernethy N, Parker D, Jeffries D. Comparison of electronic data capture (EDC) with the standard data capture method for clinical trial data. *PLoS One*. 2011;6:e25348.

28. Maringwa J, Quinten C, King M, Ringash J, Osoba D, Coens C, et al. Minimal clinically meaningful differences for the EORTC QLQ-C30 and EORTC QLQ-BN20 scales in brain cancer patients. *Ann Oncol*. 2011;22:2107-12.
29. Mauer ME, Bottomley A, Taphoorn MJ. Evaluating health-related quality of life and symptom burden in brain tumour patients: instruments for use in experimental trials and clinical practice. *Curr Opin Neurol*. 2008;21:745-53.
30. Reijneveld JC, Klein M, Taphoorn MJ, Postma TJ, Heimans JJ. Improved, personalized treatment of glioma necessitates long-term follow-up of cognitive functioning. *Pharmacogenomics*. 2012;13:1667-9.
31. de Haes J, Curran D, Young T, Bottomley A, Flechtner H, Aaronson N, et al. Quality of life evaluation in oncological clinical trials - the EORTC model. The EORTC Quality of Life Study Group. *Eur J Cancer*. 2000;36:821-5.
32. Armstrong TS, Wefel JS, Wang M, Gilbert MR, Won M, Bottomley A, et al. Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. *J Clin Oncol*. 2013;31:4076-84.
33. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:709-22.
34. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol*. 2013;31:4085-91.
35. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:699-708.
36. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013;309:814-22.

37. NCCN Clinical Practice Guideline in Oncology; Central Nervous System Cancers [Internet]. 2014 [cited May 12 2014]. Available from: http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf
38. Wick W, Puduvalli VK, Chamberlain MC, van den Bent MJ, Carpentier AF, Cher LM, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol*. 2010;28:1168-74.
39. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer*. 2012;48:2192-202.
40. Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M, Lustig R, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys*. 2004;60:853-60.
41. Levin VA, Phuphanich S, Yung WK, Forsyth PA, Maestros RD, Perry JR, et al. Randomized, double-blind, placebo-controlled trial of marimastat in glioblastoma multiforme patients following surgery and irradiation. *J Neurooncol*. 2006;78:295-302.
42. Henriksson R, Malmstrom A, Bergstrom P, Bergh G, Trojanowski T, Andreasson L, et al. High-grade astrocytoma treated concomitantly with estramustine and radiotherapy. *J Neurooncol*. 2006;78:321-6.
43. Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol*. 2004;22:1583-8.
44. Keime-Guibert F, Chinot O, Taillandier L, Cartalat-Carel S, Frenay M, Kantor G, et al. Radiotherapy for glioblastoma in the elderly. *N Engl J Med*. 2007;356:1527-35.
45. Reardon DA, Fink KL, Mikkelsen T, Cloughesy TF, O'Neill A, Plotkin S, et al. Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. *J Clin Oncol*. 2008;26:5610-7.

46. Kocher M, Frommolt P, Borberg SK, Ruhl U, Steingraber M, Niewald M, et al. Randomized study of postoperative radiotherapy and simultaneous temozolomide without adjuvant chemotherapy for glioblastoma. *Strahlenther Onkol.* 2008;184:572-9.
47. Grabenbauer GG, Gerber KD, Ganslandt O, Richter A, Klautke G, Birkmann J, et al. Effects of concurrent topotecan and radiation on 6-month progression-free survival in the primary treatment of glioblastoma multiforme. *Int J Radiat Oncol Biol Phys.* 2009;75:164-9.
48. Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Onco.* 2012;13:707-15.

Table 1. RCT demographic characteristics of studies identified.

Table 2 Level of Patient-Reported Outcomes (PRO) reporting

Table 3. Randomized Controlled Trials: basic study characteristics.

Fig.1 - Schematic breakdown of literature search results of Brain Randomized Controlled Trials (Preferred Reporting Items for Systematic Reviews and Meta-analysis).

* *PRO= patient-reported outcomes.*

Figure 2. Risk bar chart showing risk of bias across RCTs by quality of PRO reporting.