

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical and economic evaluation of modulated electro-hyperthermia concurrent to dose-dense temozolomide 21/28 days regimen in the treatment of recurrent glioblastoma: a retrospective analysis of a two-center German cohort trial with systematic comparison and effect-to-treatment analysis
AUTHORS	Roussakow, Sergey

VERSION 1 – REVIEW

REVIEWER	John Bianco Universite catholique de Louvain, Belgium
REVIEW RETURNED	08-Jun-2017

GENERAL COMMENTS	<p>The authors present an exhaustive comparison of cohort trials evaluating the clinical and economical relevance of dose-dense TMZ and the use of modulated electro-hyperthermia in the treatment of recurrent GBM. They present a large pool of background data and results to back their claim that modulated electro-hyperthermia can be introduced as an enhancer to current standards of care or used as a salvage treatment when chemotherapy is not effective. The conclusions proposed by the authors are interesting, and do warrant further investigation. However, the manuscript needs to be improved dramatically to clarify the text before publication can be recommended.</p> <p>Remarks:</p> <p>Overall, the manuscript needs major revision for grammar. I recommend either a professional service or a native English speaker to review and correct the manuscript. I have outlined some grammatical errors below, but do not list them all.</p> <p>The list of abbreviations should be moved to the beginning of the text. In addition, quite a number of abbreviations are missing from the list, such as: WA, ETA, CUR, KPS, RF, KME, WHO, FDA, MAC, DALY, MPFS, etc. These should be added. Likewise, mEHT in the list has the definition first followed by the abbreviation. This should be reversed. Also, both MR and MRI are listed together with the same meaning in the abbreviation list. One should be removed to limit confusion in the already numerous abbreviations present within the manuscript.</p>
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	<p>Page 5, line 19: capital T. Also, it should read “estimated at 10.10 months” and not “estimated of 10.10 months”</p> <p>Page 5 (line 33), 29 (lines 29 and 36), 38 (lines 33 and 39): remove the letter “a” in front of mEHT.</p> <p>Page 5, line 33: should read “device over an eight-year period”.</p> <p>Page 5, 34, 37, and 38: the word “fail” should be replaced with “failure”.</p> <p>Pages 6, 8, 11, 22, 36, 37: replace word at with the word in (in front of recurrent)</p> <p>Page 7, line 30: The standard of care for GBM is briefly described. However, the waiting period of approximately one month following surgery to commencement of chemotherapy is not mentioned. This should be discussed.</p> <p>Page 7, line 40: non methylated</p> <p>Page 8, line4: Bevacizumab (BEV)</p> <p>Page 8, line 8: survival limited to 15</p> <p>Page 8, line 16: Remove the word any from “no any progress”</p> <p>Page 8, line 31: remove the word bevacizumab and thus brackets around BEV</p> <p>Page 8, line 54: define PFS-6m</p> <p>Page 8, line 55: recent III phase should be inverted to “phase III” and define “RCT”</p> <p>Page 8, line 54 to page 9, line 9: This entire sentence is too complicated and long. I suggest you end this sentence on page 9, line 6 after the bracket, and begin the next sentence there with “However, the trial showed improved PFS-6m..... Also, remove the words “progression-free survival at 6 months” as they should be page 8, line 54 (see comment above).</p> <p>Page 9, line 20: one author not one authors</p> <p>Page 9, line 32: define KPS</p> <p>Page 9, line 42: remove the word bevacizumab. Also, who granted accelerated approval? Where?</p> <p>Page 9, line 52: define FDA</p> <p>Page 10, line 20: define OS. Remove overall survival from line 22.</p> <p>Page 11, line 13: define ICER</p> <p>Page 11, line 20: define ICUR</p> <p>Page 11, line 34: non MGMT</p> <p>Page 11, line 54: invert III phase to phase III</p>
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	<p>Page 12, line 6: define QoL</p> <p>Page 12, line 15: replace which with “whose”, invert I/II phase to “phase I/II trials”</p> <p>Page 13, line 28: remove the word been before “underwent”</p> <p>Page 13, line 54: temozolomide with a z</p> <p>Page 14, line 14: define “p.o.” and “t.i.d.”</p> <p>Page 14, line 20: mEHT already defined earlier</p> <p>Page 15, lines 23-33: Sentence way too long.</p> <p>Page 15, line 52: symbol not clear after the number 42.</p> <p>Page 16, lines 1-13: This paragraph is poorly written and should be reworded.</p> <p>Page 16, lines 27-38: The use of “ : “ is not good. They should be removed and the sentences improved.</p> <p>The use of the colon (:) throughout the manuscript could be minimised, and even removed at places. If the sentences are structured better, they would not be needed.</p> <p>Page 17, lines 7-11: Rephrase</p> <p>Page 17, lines 47-57: This is a terrible paragraph. Reword</p> <p>From page 14, “Intervention of Interest” to page 18, line 18: This whole section read more like additional background, although it is present in the materials and methods section.</p> <p>Page 22, lines 25-29: reword this sentence</p> <p>Page 25, line 6: figure 6B is referenced. There are two figure 6 (on page 95 and 96) which have the exact same legend, but no designation which is A and which is B.</p> <p>Page 25, line 27: The sentence beginning with “Since” must be reworded as it is not clear.</p> <p>Page 28, line 16: give data for German model before US model to be consistent in how you have maintained this order throughout the rest of the manuscript.</p> <p>Page 33, line 10: remove cost-effectiveness threshold and just leave CET. Some terms are repeatedly defined throughout the manuscript, others not, while others are completely neglected.</p> <p>Page 36, line 38: mEHT and TMZ, or ddTMZ? Or both?</p> <p>Page 36, line 42: phase III</p> <p>Page 38, line 11: remove cost-effectiveness analysis and just leave CEA</p>
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	Overall, the entire manuscript is riddled with grammatical errors. For example, on page 12, lines 17, 20, 21, 46, 47, 53 all have grammatical errors. The use of singular words instead of plural, and vice versa, is present throughout. In addition, the use of the words such as "the", "an", "a", etc. is missing where appropriate. Also, sometimes sentences are too long and difficult to understand.
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REVIEWER	Dr. B. Suchorska Department of Neurosurgery, Ludwig-Maximilians-University, Munich, Germany
REVIEW RETURNED	16-Jul-2017

GENERAL COMMENTS	<p>The present article by S. Roussakow relates to a an important topic, namely the cost-effectiveness adjuvant chemo-therapy in recurrent glioblastoma.</p> <p>The article is well written, however, it suffers from a couple of insufficiencies, some of which are related to the topic examined. While it is highly interesting to examine the cost efficiency of dose intensified TMZ in recurrent GBM, the concurrent therapy examined here is modulated electro-hypothermia, which plays a marginal role in glioma therapy, at best. I wonder whether the author could include a statement on why he did not choose a comparison of dose-intensified TMZ versus BEV or dose-intensified TMZ versus re-resection or re-irradiation, instead. This would have much more impact for the neuro-oncological community.</p> <p>A second major point is the lack of focus: there are two main points discussed here: one is the comparison of two therapy regimens and the other is the comparison of cost-effectiveness of these two regimens. I would concentrate on one aspect.</p> <p>Minor points:</p> <ul style="list-style-type: none"> - the length of the article has to be reconsidered, the description of modulated electro-hyperthermia should be shortened - descriptions of initial therapies in primary GBM in the introduction section are not topic-related and should be left out - the result section has a considerable amount of data interpretation, please discuss the results within the discussion section
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment: However, the manuscript needs to be improved dramatically to clarify the text before publication can be recommended. Overall, the manuscript needs major revision for grammar. I recommend either a professional service or a native English speaker to review and correct the manuscript.

Response: English corrected.

Reviewer: 2

Comment: While it is highly interesting to examine the cost efficiency of dose intensified TMZ in recurrent GBM, the concurrent therapy examined here is modulated electro-hypothermia, which plays a marginal role in glioma therapy, at best. I wonder whether the author could include a statement on why he did not choose a comparison of dose-intensified TMZ versus BEV or dose-intensified TMZ versus re-resection or re-irradiation, instead. This would have much more impact for the neuro-oncological community.

Response: Our idea is that it is oncothermia which can significantly improve the treatment of recurrent GBM.

Comment: A second major point is the lack of focus: there are two main points discussed here: one is the comparison of two therapy regimens and the other is the comparison of cost-effectiveness of these two regimens. I would concentrate on one aspect.

Response: To our opinion, the combination approach is more informative and convenient. It allows reader to receive a comprehensive information from one source. Also, it prevents a multiple publication bias.

Minor points:

Comment: the length of the article has to be reconsidered, the description of modulated electro-hyperthermia should be shortened

Response: Somewhat shortened.

Comment: descriptions of initial therapies in primary GBM in the introduction section are not topic-related and should be left out

Response: Done

Comment: the result section has a considerable amount of data interpretation, please discuss the results within the discussion section

Response: Done – the discussion-related points are transferred into discussion section.

Further remarks:

1. Please ensure that the Funding statement in your main document and Scholar One submission system are the same.

Response: The same.

2. Please embed your Data sharing statement on your main document file as shown in scholar one.

Response: The same

3. Please include Figure legends at the end of your main manuscript.

Response: Done

4. Please place Tables where its cited.

Response: Done

5. Combined Figure 6a and 6b in one Figure file.

Response: Done

6. Please cite your Figures starting at Figure 1 and so on and cite them as such.

Response: Done

7. Please re-upload your supplementary files in PDF format.

Response: Done

8. Please embed your Table on your main document file and placed them where its cited.

Response: Done

9. Aside from the clean copy, please also provide a marked copy of your manuscript with 'tracked changes' and upload it under the file designation 'marked copy'. This is to show all the changes you have made for your paper.

Response: Done

10. Please cite all your uploaded Supplementary files on your main document file if Supplementary file is not intended to be part of the main manuscript file, kindly change the File designation to 'Supplementary file for Editors only'.

Response: Done