Author's response to reviews

Title: Prognosis and therapy of tumor-related versus non-tumor-related status epilepticus: a systematic review and meta-analysis

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Author's response to reviews: see over
Utrecht, The Netherlands, June 30, 2014

Dear Dr Strzelczyk, dear Mr De Los Santos,

We are pleased to submit the revised version of our paper entitled ‘Prognosis and therapy of tumor-related versus non-tumor-related status epilepticus: a systematic review and meta-analysis’ (MS: 7398733281261389).

We thank you and the reviewers for the valuable comments and suggestions. Below is a point-by-point response. We have addressed all points, and have incorporated almost all of them in the revised version of the manuscript. Most importantly, we have added an analysis with mortality as the outcome measure, in which we excluded patients with hypoxic/anoxic encephalopathy from the non-tumor group. In this analysis, the difference in mortality between tumor-related SE and non-tumor-related SE is even larger than in the original analysis.

The paper still includes one figure and one table. Also, it still contains three additional components: one figure, one table and one appendix.

All authors contributed to writing of the article and approved the revised version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors declare that they have no conflicts of interest regarding this paper. We hereby state that neither this paper nor any similar paper, in whole or in part, has been or will be submitted to or published in any other source.

We look forward to your response. Again, we thank you for your previous and upcoming efforts.

On behalf of all authors,
Yours sincerely,

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Response to reviewers

Referee #1: Christoph Kellinghaus

Reviewer's report

Major compulsory revisions

1. The authors state that there may be specific pathophysiological mechanisms of epilepsy in brain tumors. Although this may be true, one has to consider that there are several very distinct subgroups of brain tumors such as low-grade and high-grade glial tumors, meningiomas, filiae of systemic cancer etc. which all may act in a different way. In the studies they analyse, it is impossible to distinguish between these subgroups. The mechanisms and thus outcome of tumor-related SE may differ between these tumoral subgroups. This is a severe limitation of the study and has to be discussed.

We thank the reviewer for his valuable comments. We agree with the reviewer that additional data on SE outcome per tumor type would be very valuable. However, such data are not available in the manuscripts we reviewed; given the composition of the study samples (mostly retrospective cohorts, sometimes from population-based databases with a low level of detail), it is unlikely that such data can be retrieved from the original authors. We therefore added a section on this important limitation to our Discussion.

2. Although the authors point to the severe limitations of their study in the discussion part, the methodological problems are not transferred sufficiently into the conclusion part. This should be changed.

We added two (sub-)sentences to the Conclusion to highlight the methodological limitations, and their consequences for the interpretation of the data:

- ‘Pooled data from observational, mostly retrospective, studies show…’
- ‘However, data interpretation is hindered by the heterogeneity between studies and the lack of data on tumor subtypes and possible underlying tumor progression.’

3. Did any of the studies include hypoxic/anoxic etiology of SE? If so, this needs to be clearly marked, and the number of patients need to be reported because this directly influences the outcome of the non-tumor group of patients.

We thank the reviewer for this valuable suggestion. We have now added an extra analysis with mortality as the outcome measure (to Methods, Results and table 1), in which we excluded patients with hypoxic/anoxic encephalopathy from the non-tumor group. In this analysis, the difference in mortality between tumor-related SE and non-tumor-related SE is even larger than in the original analysis.
4. I cannot assess whether the statistics using pooled data from very heterogeneous studies are correct. I recommend to get an assessment from a professional statistician.

In our previously submitted manuscript, we have tried to describe our statistical methods concisely yet thoroughly. We have left this text unchanged. We are open to suggestions if the editor requires further revision of this text.

Minor essential revisions

5. It is unclear why the authors chose the duration of 30 minutes as cut off for inclusion. Most recent studies use 5 minutes or 10 minutes and would be excluded here.

We agree that the time criterion of 30 minutes is outdated. In fact, we did not use this time criterion as an inclusion criterion for our study. We apologize for this incorrect section in the previous version of our manuscript. We have changed this part of the Methods paragraph as follows:

For a paper to be included in this literature review, status epilepticus had to be defined as a single continuous seizure or a series of epileptic seizures with clouded consciousness between ictal events; although most studies used a minimum duration of 30 minutes in the definition (in accordance with traditional guidelines), we did not use this as an inclusion criterion since modern data and guidelines use less stringent time criteria.

Discretionary revisions:

6. It would be recommendable to compare the tumor-etiologies not only to all non-tumor etiologies, but to pick a distinct subgroup for comparison, such as traumatic or ischemic.

The proposed comparison of tumor-related SE with a specific subgroup of non-tumor-SE (e.g. traumatic) may add to the specificity of our findings. However, it is unclear from the available literature which subgroup this should be, since no data are available on prognostic or therapeutic differences between the non-tumor-subgroups (with the exception of hypoxic/anoxic SE). Also, the comparison of tumor-related SE with a specific subgroup of non-tumor-related SE does not address our study question: whether clinical outcome and therapeutic efficacy in tumor-related SE differs from other SE due to other causes (as a whole); selecting a specific subgroup of non-tumor-related SE (e.g. traumatic) for comparison may produce results that reflect characteristics of this subgroup of non-tumor-related SE rather than characteristics of the tumor-related SE. Therefore, we decided not to include such an additional analysis.
Referee #2: Marco Riva

Reviewer's report:

The manuscript addressed a highly interesting topic in the clinical practice of neuro-oncology, encompassing distinct specialities. It also looked into the available literature for the most robust evidence in this regard. The research questions are nicely clarified in the introduction as well as the clinical and biological premises. They are then followed by clear outline of the research methods.

The authors well acknowledged the paucity of the available results to perform a wide meta-analysis, and this is stated in the final remarks.

1. One limitation, which is possibly due to the original reports searched and analyzed, is that brain tumours are considered as a whole entity, while, for instance, intra-axial lesions can have distinct epileptogenic behaviour compared to extra-axial lesions.

We thank the reviewer for his valuable comments. We agree with the reviewer that additional data on SE outcome per tumor type would be very valuable. We refer to our comments to Referee 1, point 1.

2. In addition, the role of the different therapeutic options (surgery, radiation therapy, chemotherapy) is not considered nor mentioned.

We agree that additional information on the relationship between tumor treatment and SE outcome would be valuable; however, these data are not available from the original manuscripts. We have added a short discussion of this item:

In addition, further studies should investigate whether the occurrence and outcome of tumor-related SE is dependent on (previous or current) anti-tumor-treatment such as radio- and chemotherapy, since several anti-tumor treatments are associated with reduction of epilepsy burden [1].

3. Despite the actual results are apparently poor, since no robust conclusions can be drawn to reply to the original research questions given the limited number of heterogenous studies included, points of interests can be found in the current manuscript, which are the following:

- it pushed the continuous effort for refining current clinical practice towards evidence-based decisions
- it stresses the need to further refine the understanding of the clinical and biological aspects of tumour-related epilepsy
- it underline the need to specifically address the therapeutic power of the different commercially available compound, compared to the effect of the different therapeutic options.

Therefore, I think the manuscript to deserve publication to support the discussion and the research in this field.
We thank the reviewer again for his efforts and valuable comments.
Editor's comment

1. The authors are advised to comment on the very distinct subgroups of brain tumors such as low-grade and high-grade glial tumors, meningeomas, filiae of systemic cancer as these may have different prognosis and therapy needs.

We thank the editor for the valuable comments. We agree with the editor and both reviewers that additional data on SE outcome per tumor type would be very valuable. We refer to our comments to Referee 1, point 1.

2. Also it is important to be sure not to include hypoxic or anoxic patients after CPR in the non-tumor group as this will bias the results."

We added an additional analysis to address this point. We refer to our comments to Referee 1, point 3.