

PEER-REVIEW REPORT ANSWERS

First of all, we would like to take this opportunity to thank the reviewer of this manuscript for his/her timely review. We have made changes according to questions asked wherever we could and tried to justify and explain why where we couldn't.

#1st Comment

- The major issue is that a recent meta-analysis containing 35 studies assessed the diagnostic accuracy of MR-imaging techniques in the evaluation of treatment responses in patients with high-grade glioma (van Dijken BRJ et al. Eur Radiol. 2017) already analyzed the techniques evaluated in this study (DSC-MRI and DCE-MRI).
- Moreover, this meta-analysis is based only on six studies and the data obtained cannot be addressed to precise and conclusive results.

1st Comments' Answer

We would like to start by pointing out the key differences between our study from the recently published meta-analysis which contained 35 studies:

- i. They assessed the **1st time treatment response in high-grade glioma** while our assessment focused on **treatment response in recurrent glioma**.
- ii. They included studies in which patients underwent **radiotherapy or chemotherapy** as their treatment of choice whereas we only included studies where patients were treated with **antiangiogenic (anti-VEGF) therapy**.
- iii. They assessed **both anatomical MR (12 studies) and perfusion MR (23 studies) techniques in high-grade glioma** while ours focused on **perfusion MR techniques in recurrent glioma**.

We believe these differences had a major impact on our findings thus making our two meta-analyses different.

We also agree that having few studies raises several issues such publication bias. But we think it's not a problem because several experts all over the world have argued that you can even do a meta-analysis with just 2 studies. Also there is several meta-analyses published in respected journals some with 4 studies and others with 5 studies. We strongly believe that our meta-analysis managed to answer the research question.

2nd Comment

The analysis was done using, Meta-Disc (version 1.4). However, this software has strong limitation for meta-analysis of diagnostic study. In fact, MetaDisc software is now under development and the software Author's state: "We are working to implement current recommended statistical methods (hierarchical models) for the

meta-analysis of Diagnostic Test Accuracy studies into MetaDisc 2.0. Old version of MetaDisc uses outdated statistical methods and should be used only for explorative purposes and not for making inferences. Please refer to the web site of the Cochrane DTA methods group for other software alternatives (<https://methods.cochrane.org/sdt/welcome>)

2nd Comments' Answer

Thank you for the update. This is the new information to us because when we used Meta Disc 1.4 software for analyzing our data it was not undergoing any updates. Plus, as we all know there are no simple criteria for picking the best diagnostic test accuracy (DTA) among the several available statistical package. Another factor is that all of these statistical packages gives similar results, albeit obviously not identical.

We picked Meta Disc because it was highly recommended and have been used more compared to other packages. Choosing another software at this time is a big challenge and we believe Meta Disc 1.4 served its purpose and produced good results which tackled and answered our main objective excellently by showing that PW-MRI can be used for assessing treatment response in recurrent glioma patients on antiangiogenic therapy.

3rd Comment

The Authors should provide the PRISMA check-list

3rd Comments' Answer

We included a 2009 PRISMA checklist in a revised manuscript

4th Comment

The Authors should provide a full search strategy.

4th Comments' Answer

We did this in **Material and Methods** section under the heading *Study Selection* and further outlined on **Figure.1**

5th Comment

In "Data Extraction" the Authors should specify which items have been used in the Excel spreadsheet and provide the detailed tools used in QUADAS-2

5th Comments' Answer

We addressed this in a revised manuscript

6th Comment

I would suggest use the Funnel plot methods (e.g. Deek's method) to assess publication bias. The validity of a meta-analysis depends on minimizing bias in the identification of studies, otherwise the conclusions of the analysis can be compromised by publication bias

6th Comment's Answer

We didn't use the funnel plot because it's not advised to do so if you have less than 10 studies. From the 10.4.3.1 Cochrane Recommendation on Testing for Funnel Plots Asymmetry they state that **"As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry"** ("10.4.3.1 Recommendations on testing for funnel plot asymmetry," n.d.).

7th Comment

Another issue is that different reference tests have been used as gold standard in the studies evaluated; this can lead to a reasonable bias in the results of meta-analysis

7th Comments' Answer

It's true that different reference standards were used, but technically they are the same because **Response assessment in neuro-oncology criteria (RANO) criteria** which was published in 2010 assess glioblastoma treatment as well as lower grade astrocytoma and **is an update to Macdonald criteria** which was published in 1990 and assess treatment response for glioblastoma only. RANO criteria have largely superseded Macdonald criteria but both assesses: 1. Complete response 2. Partial response 3. Stable disease 4. Disease progression. **So the only difference is that RANO can assess treatment response in more than one Glioma subtype and Macdonlad can just assess treatment response in glioblastoma so therefore we believe was minimal chance of bias.**

8th Comment

Beside the sensitivity analysis performed, the Authors should conduct a meta-regression analysis to evaluate the impact of moderator variables on study effect size

8th Comment Answer

It's also not advised to do a meta regression if you have less than 10 studies that's why we didn't do it. From the Cochrane book **9.6.4 Meta-regression** 1st paragraph last sentence it states that **"Meta-regression should generally not be considered when there are fewer than ten studies in a meta-analysis"**

9th Comment

In the Forest Plots the Authors should add the variable “patients” with number of patients analyzed in each study.

9th Comment Answer

Every software produces different forest plots, Forest Plots by Meta Disc doesn't include patient number of each study. Also patient number (sample size) of each study is reported in Table of Characteristics we don't think it's a must to be shown on the forest plot.