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.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers’ comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

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<th>TITLE (PROVISIONAL)</th>
<th>Role of diffusional kurtosis imaging in grading of brain gliomas: a protocol for systematic review and meta-analysis</th>
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<td>AUTHORS</td>
<td>Abdalla, Gehad Medhat Abdelfattah Mohamed; Sanverdi, Eser; Machado, Pedro; Kwong, Joey S.W.; Panovska-Griffiths, Jasmina; Rojas-Garcia, Antonio; Yoneoka, Daisuke; Yousry, Tarek; Bisdas, Sotirios</td>
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VERSION 1 – REVIEW

| REVIEWER             | Nikoletta Szabó, MD, PhD Department of Neurology, University of Szeged, Szeged, Hungary |
| REVIEW RETURNED      | 31-Jul-2018 |
| GENERAL COMMENTS     | This study protocol is well designed addressing actual questions. DKI acquisition parameters have a great influence on MRI images and on data processing (b-values and diffusion directions). It would be necessary to extract and compare this information from the selected studies. How these parameters could help the grading of brain gliomas. |

| REVIEWER             | Anna Falk Delgado Department of clinical neuroscience, Karolinska Institutet, Sweden |
| REVIEW RETURNED      | 02-Aug-2018 |
| GENERAL COMMENTS     | Dear authors,
Thank you for the opportunity to review this protocol. I agree with the authors that this research question is of high interest.

I do have some minor comments on how the authors can clarify their protocol.

1. Abstract: "random-effects model if substantial statistical heterogeneity is found”. Heterogeneity is expected in diagnostic accuracy meta-analysis.

2. Strengths and limitations of the study. This is just a personal reflection but heterogeneity with associated well performed sensitivity analysis can give valuable information in a meta-analysis. |
3. Introduction. The authors refer to the recently published meta-analysis on a very similar topic as published in 2007, this study was in fact published in April 2018. Please correct. It is thus a short interval since the last similar study was performed.

4. Search strategy: will the search also include studies with only astrocytomas or only oligodendrogliomas?

5. Data synthesis and analyses: Do you have a cut-off to define significant heterogeneity? Please elaborate.

6. The authors state that “A fixed-effect meta-analysis as well as aggregation of data using the hierarchical summary receiver operator characteristics will be pursued, if the studies do not show significant heterogeneity.” From my perspective I imagine you can perform a summary ROC curve even though you will have high heterogeneity but then you will refrain from stating cut-offs.

REVIEWER
Sofie Van Cauter
Department of Medical Imaging, Ziekenhuizen Oost-Limburg, Genk, Belgium Department of Medical imaging, University Hospitals of Brussels, Brussels, Belgium

REVIEW RETURNED
13-Aug-2018

GENERAL COMMENTS
Interesting study

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments:

DKI acquisition parameters have a great influence on MRI images and on data processing (b-values and diffusion directions). It would be necessary to extract and compare this information from the selected studies. How these parameters could help the grading of brain gliomas.

This is a useful comment and we totally agree. Therefore, we have prepared a state-of-the-art spreadsheet for extracting the relevant data, incl. image acquisition parameters and processing software used. We do believe that this information will correlate to some point to the degree of the test accuracy and of course, we will highlight these results in the discussion of the upcoming paper. It is in example very obvious that the different range of b-values will capture in a different way the kurtosis phenomenon. Notably, there have already been attempts to create guidelines for kurtosis acquisition parameters in the scientific community.

Reviewer 2 comments:

1. Abstract: “random-effects model if substantial statistical heterogeneity is found”. Heterogeneity is expected in diagnostic accuracy meta-analysis.

Yes, we do agree with this comment. We revised the manuscript accordingly (highlighted in red colour).

2. Strengths and limitations of the study. This is just a personal reflection but heterogeneity with associated well performed sensitivity analysis can give valuable information in a meta-analysis.
Addressing also the essence of the next comment (see below 5. Data synthesis and analyses), we would like to stress that the issue of heterogeneity in sensitivity/specificity has not been well studied in the field of biostatistics. Especially, the traditional $I^2$ statistic has been not recommended for quantifying heterogeneity in sensitivity/specificity because it is a univariate measure that does not account for potential threshold effects. In our opinion, heterogeneity can be only considered graphically by plotting sensitivities and specificities from the studies as points on a receiver operating characteristic (ROC) plot.

3. Introduction: The authors refer to the recently published meta-analysis on a very similar topic as published in 2007, this study was in fact published in April 2018. Please correct. It is thus a short interval since the last similar study was performed.

We revised accordingly the publication date in the new version and highlighted in red colour. We acknowledge that a meta-analysis was published quite recently but our endeavour differs as it extends the interrogation of the method’s accuracy in more tumours (we aim to include studies that also compared DKI between gliomas and other intra-axial brain tumours) reflecting the increased use of DKI in brain tumours and the momentum it has gained the last years.

4. Search strategy: will the search also include studies with only astrocytomas or only oligodendrogliomas?

There will be an exhaustive search that will contain all primary brain tumours, irrespective of histology. In the Discussion, we will interpret the findings in light of the histology and the possible impact of the different tumour microenvironments on the diffusional kurtosis accuracy.

5. Data synthesis and analyses: Do you have a cut-off to define significant heterogeneity? Please elaborate.

As aforementioned, it is difficult to check the heterogeneity in sensitivity/specificity (in contrast, there are many methods such as $I^2$ to check the heterogeneity of mean/odds ratio). Our proposed methodology includes the use the random-effect model to incorporate the potential heterogeneity for meta-analysis of sensitivity and specificity; and the use the random-effect or fixed-effect model for meta-analysis of mean difference. According to the Cochrane handbook: $I^2$ =0-40% indicates that might not be important heterogeneity; $I^2$ =30-60%: may represent moderate heterogeneity; $I^2$ =50-90%: may represent substantial heterogeneity; and $I^2$ =75-100% suggests considerable heterogeneity.

6. The authors state that "A fixed-effect meta-analysis as well as aggregation of data using the hierarchical summary receiver operator characteristics will be pursued, if the studies do not show significant heterogeneity." From my perspective I imagine you can perform a summary ROC curve even though you will have high heterogeneity but then you will refrain from stating cut offs.

Yes, this is our intention. We have clarified it in the manuscript (highlighted in red colour),

### VERSION 2 – REVIEW

| REVIEWER | Anna Falk Delgado  
| Karolinska Institutet, Stockholm |
| REVIEW RETURNED | 09-Oct-2018 |

| GENERAL COMMENTS | Thank you for your revision of the protocol. |