

Apr 04, 2017

To,
Dr. Lian-Sheng Ma,
Editor-in-Chief,
World Journal of Hepatology.

Respected Dr. Ma,

We are herewith submitting a revised version of the invited manuscript (ESPS Manuscript NO: 32290) entitled “**Diffusion Weighted MR Imaging of Liver: Principles, Clinical applications and recent updates**” for consideration of publication as “Review Article” in your esteemed journal. We kindly appreciate the critical review by the reviewers and have tried to address the reviewer’s comments in the revised version of the manuscript. We would like to confirm that this article has not been published or under consideration for publication elsewhere. There are no conflicts of interest. We would appreciate your kind review.

Thanking you,

Respectfully,

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RESPONSE TO REVIEWERS COMMENTS

Reviewer's code: 02926997

Comment 1- There is no data regarding search strategy.

Response- Thank you so much for your comment. The articles were searched from Google search engine and PubMed database using key terms like, diffusion weighted imaging, diffuse liver disease, response assessment in liver cancer etc. All recent relevant articles were filtered and stored in an online library. Since this is a general review of the topic and not a meta-analysis; the methodology of search was not described in the paper.

Comment 2- The keywords are not selected based on MeSH terms.

Response- The reviewer's indeed raised a very valid point and the keywords have been changed in the revised manuscript.

Comment 3- The references are not provided according to the journal format.

Response- Thank you so much for your comment. Reference style and citation format have been changed in the revised manuscript.

Comment 4- The draft needs a great deal of English editing.

Response- Thank you for pointing it out. In accordance with the reviewer comments, we have thoroughly revised the content of the manuscript and improved the quality of the language used.

Comment 5- The acknowledgment section is not meaningful.

Response- Thank you for pointing it out. We do not have any acknowledgements and we have modified our comment in this section.

Comment 6- The sources of figures are missing.

Response- The figures are from Abdominal Imaging division of Massachusetts General Hospital.

Reviewer's code: 03647916

Comment 1- The manuscript is too long. It would be better to make an article short and conclusive. The important things are mixed with a lot of unnecessary and sometimes not understandable writings.

Response- Thank you for your thoughtful comments. The reviewer's indeed raised a very valid point and we have thoroughly revised the manuscript and a lot of text has been cut down.

Comment 2- The Authors made many simply description of already published papers. Please avoid writing in the manner: in the Topic 1, the First Author wrote ..., the Second Author

wrote ..., the Third Author wrote, ... In the Topic 2, The Fourth Author wrote ... and so on. The review article should summarize current knowledge rather than simply describe other published papers.

Response- Thank you for pointing it out. In accordance with the reviewer comments, we have changed the manner of description of earlier work throughout the manuscript, in a way that it summarizes the current knowledge of the subject.

Comment 3- It should be clearly stated what is currently known on DW MRI application and what is considered as not proven hypothesis. 1. Especially the role of quantitative assessment by means of ADC should be clarified for the reader who may be not familiar with DW MRI. The Authors wrote in the introduction: "DWI allows quantitative evaluation of the apparent diffusion coefficient (ADC), which is helpful not only in lesion characterization but also in follow-up" but further in the text the Authors wrote: "The reproducibility of quantitative ADC values has also been questioned" "substantial degradation of image quality and systemic errors in the calculations of ADC values" "The cut-off values reported have high variability likely due to the difference in scanners and parameters used to obtain DW MR images and ADC maps" "high degree of overlap between solid benign and malignant lesions" "the use of absolute ADC values or ADC value cut-off for characterization of focal hepatic lesions should be avoided" Please clarify the current state of knowledge in the quantitative assessment of diffusion (i.e. ADC).

Response- Thank you for your thoughtful comments. The reviewer's indeed raise a very valid point. We have given a clear description under the lesion characterization section; that use of absolute ADC values or ADC value cut-off for characterization of focal hepatic lesions should be avoided and DW images always be interpreted as a complimentary technique to conventional MR sequences..

Comment 4- The Authors wrote: "DW MRI has been shown to compliment and substitute multiphase contrast enhanced MRI for a wide array of clinical application." 2. What does "compliment" mean in this context? 3. In patients with impaired renal function ($GFR < 30$) DW MRI can substitute contrast enhanced phases in focal lesion detection. With DW MRI it is also possible to differentiate solid lesions and simple cysts. Do exist other applications? What does "wide array" mean in this context? In this context, are there more applications than focal lesion detection?

Response- Thank you for pointing it out. In accordance with the reviewer comments, we have modified the introduction to remove the subjectivity and have changed it to a more objective description.

Comment 5- The Authors wrote: “DWI allows quantitative evaluation of the apparent diffusion coefficient (ADC), which is helpful not only in lesion characterization but also in follow-up of changing histological tumor characteristics after cancer related therapies” The usage of the term “histological” is inappropriate - the term related to the microscopic not radiological evaluation.

Response- Thank you for pointing it out. In accordance with the reviewer comments, the word “histological” has been removed from the revised manuscript.

Comment 6- Please enumerate high cellular tissues that restrict diffusion – this would be of clinical importance.

Response- As per reviewer comments, these have been included as the examples (lymphoma, carcinoma, abscess) in the revised manuscript.

Comment 7- The sophisticated technical terms and sentences should be avoided thorough the whole article. Example: “DW MRI is performed by applying a symmetric pair of diffusion sensitizing bi-polar gradients on the either side of a 1800 refocusing pulse of a T2-weighted echo planar sequence.”

Response- Thank you for your thoughtful comments. The reviewer’s indeed raise a very valid point. We have removed the deeply technical descriptions throughout the manuscript considering the target audience of the journal.

Comment 8- The Authors compared breath-hold and free breathing sequences. This paragraph should be shortened. It could be limited to the list of advantages and disadvantages. In the present form this paragraph contains 220 words.

Response- Thank you for pointing it out. In accordance with the reviewer comments, this section has been trimmed down significantly.

Comment 9- The authors wrote: “The differences of the diffusion properties in different tissues provide information on tissue density/cellularity and the integrity of cellular membranes.” Density is not the same as cellularity. DW MRI does not show tissue density. The word density was used improperly.

Response- Thank you for your thoughtful comments. In accordance with the reviewer comments, the word “density” has been removed from the revised manuscript.

Comment 10- The subsection “Intravoxel incoherent motion (IVIM) imaging” is very unclear. Is this a DW MRI principle or the future trend? Section: Clinical applications in liv

Response- We agree that IVIM is a relatively newer application. The section of future trends has been removed from the revised manuscript in the interest of word limits. This section was more technical and seemed inappropriate for the audience of the journal. So IVIM is still retained in the technique section.

Reviewer’s code: 03700164

Comment 1- Please use an acronym consistently ie, either DW-MRI or DWI throughout the manuscript.

Response- Thank you for pointing it out. In accordance with the reviewer comments, we have used the acronym DWI uniformly in the revised manuscript.

Comment 2- Secondly, the limitations of DW-MRI need to be discussed in greater depth.

Response- Thank you for your thoughtful comment. The reviewer’s indeed raise a very valid point. We tried to include as many limitations as we can, but in interest of the word limits we could not expand this section.

Comment 3- Also, its role/experience in children, who may need anesthesia/deep sedation etc, could be discussed.

Response- Thank you for your thoughtful comment. The reviewer’s indeed raise a very valid point. DWI can be acquired with free breathing mode and with reparatory triggering, so it can be obtained in patients who are under sedation or anesthesia.

Reviewer’s code: 03646639

Comments-

1) On page 9 line 7, the description of hyperintensity on DWI

2) On page7 line 8, ‘intravenous gadolinium however it is’ should be ‘intravenous gadolinium.

Response- Thank you for pointing it out. These sections have been revised and the typing errors have been fixed.