

RESPONSES TO REVIEWERS

November 30, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14936-edited.doc). We would like to thank editor and reviewers for their very valuable comments and suggestions that helped us correct errors and improve our manuscript.

Title: Treatment Assessment of Radiotherapy using MR Functional Quantitative Imaging

Author: Zheng Chang, Chunhao Wang

Name of Journal: *World Journal of Radiology*

ESPS Manuscript NO: 14936

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1 Comments:

In this interesting Editorial Comment the authors provide a nice review about the role of MRI in the assessment of patients undergoing radiotherapy. The subject is relevant and the manuscript is well written. It requires only minor language polishing.

Response: Thank you for this suggestion. The revised manuscript has been reviewed and improved by native English speakers.

Reviewer 2 Comments:

Well written review. There are a few topics to consider:

1. Could there be a table that lists the sensitivity/specificity of the method in various tissues?

Response: Thank you for this valuable suggestion. In this manuscript, our scope is limited to radiotherapy assessment using MR functional quantitative imaging, where the tumor stage, shape and location are determined before the treatment course. Up to now, the sensitivity/specificity of MR functional imaging techniques in disease diagnosis has been well investigated. However, due to the varying selection of imaging protocols, radiotherapy regime and patient cohort, few similar sensitivity/specificity investigations have been conducted in the area of radiotherapy assessment. It is

the very motivation of the editorial that more efforts shall be contributed to this emerging and promising research field. We believe that future works, especially multi-center collaborations, are to fulfill the knowledge gap of the sensitivity/specificity investigation of MR functional quantitative imaging in radiotherapy assessment.

2. Should there be a paragraph denoting the limitations of the method being described? A figure with an example would be greatly appreciated

Response: Thank you for this valuable suggestion. We added some examples of MR functional quantitative imaging application in the area of radiotherapy assessment, along with the corresponding pre-treatment and post-treatment images. Please see Figure 1-3. Also, we highlighted current limits and weakness of MR functional quantitative imaging techniques (e.g. DSC, DWI). Please see the sections of interpretation of biomarker and image quality improvement on pages 6 and 7. As suggested by the reviewer, a figure demonstrating the geometrical distortion problem is added. Please see Figure 4.

Reviewer 3 Comments:

The manuscript is well organized and drafted which provides brief and critical information about the treatment assessment of radiotherapy using MRI for functional and quantitative information. Critics on the manuscript: It will be more informative and constructive if there are practical examples and figures (e.g. figures of MRS, DWI and contrast enhanced MRI of brain tumors) for demonstration.

Response: Thank you for this valuable suggestion. In the revised manuscript, we added three examples MR functional quantitative imaging applications (DTI, DWI, and DCE) in the area of radiotherapy assessment. More specifically, figures demonstrating the pre-treatment and post-treatment images of brain tumors have been added for easy appreciation. Please see Figure 1-3.

Reviewer 4 Comments:

General Comments The authors present a review about the significance of functional MRI for the therapy assessment after Radiation Therapy. The topic is noteworthy in the actual clinical contest since dose optimization criterion is being continuously advocated. The paper appears mostly well written and structured correctly. However, some messages are lacking and sometime they delivery misconduct. are clearly It could be of value if revised.

Comments and essential revisions

1. It lacks the information on which kind of neoplasms MRI could be useful since it has not the same sensitivity wherever.

Response: Thank you for this suggestion. As mentioned in Response 2.1, our scope is limited to radiotherapy assessment using MR functional quantitative imaging, where the tumor stage, shape and location are determined before the treatment course. Currently, few sensitivity/specificity

investigations have been reported in the area of radiotherapy assessment. Future works that investigating the sensitivity/specificity of MR functional quantitative imaging techniques in assessing treatment response of different type of diseases are important and in demand. Please see also Response 2.1

2. Figures need.

Response: Thank you for this valuable suggestion. In the revised manuscript, we added three figures demonstrating the pre-treatment and post-treatment MR functional quantitative images (DTI, DWI and DCE). We also added a figure as an example of geometrical distortion effect. Please see Figure 1-4.

3. The information about the avoidance of the use of ionizing radiation is outdated and substantially wrong since we are dealing with diagnostic tools.

Response: Thank you for this valuable suggestion. In this manuscript, we focused on the application of radiotherapy assessment where multiple scans are acquired within a short period of time for possible longitudinal studies. As a result, ionizing radiation may be a potential risk factor for radiotherapy assessment imaging. We revised the text in the first paragraph of the introduction to clarify this point. Please see page 3

4. It cannot be forgotten that PET/CT with conventional and/or new tracers (see FMISO, FLT) constitute at moment a virtual gold standard on this matter. It could be stated clearly.

Response: Please see our response below.

5. To corroborate the #4 comment I'd like just remember to the author that PET/MR exists as a valuable methodology (increasing references on the topic). It should be advocated.

Response: Thank you for these valuable suggestions. In the section of 'Interpretation of biomarker, we added a paragraph of discussion on dynamic susceptibility contrast (DSC) imaging and the gold standard PET measurement in perfusion analysis. Also, the recently available PET/MR imaging is highlighted as a valuable imaging tool for future studies. Please see page 6.

6. Again (according to point #4), the mentioned pitfalls and the lack of reproducibly depend on functional issues already solved since they constitute the matter of the tracers theory in nuclear medicine procedure. Once in a time information could be translated to MRI.

Response: Thank you for this comment. As we know, there are several fundamental differences between MRI and nuclear medicine (NM) imaging including PET and SPECT. For example, NM imaging is based on radioactive tracers, and the distribution of radioactive tracers can be directly measured in NM imaging. In contrast, MR imaging does not depend on the use of contrast agents. The use of contrast agents in MRI simply helps manipulate the imaging contrast to achieve an enhanced capability of investigating physiological processes. The distribution of MR contrast agents is not directly measured, but can be indirectly quantified through rigorous calibrations and post-processing calculations. The pitfalls and challenges often lie in the stage of calibrations and calculations. Currently, it has been well acknowledged that the data reproducibility of MR functional quantitative imaging requires the standardized imaging parameters, pharmacokinetics models and image post-processing methodologies.

In addition, for the radiotherapy assessment studies, patient cohort selection, radiotherapy regime and imaging time are also key factors that should be considered in a standard MR functional quantitative imaging protocol. Indeed, the success of quantitative analysis in NM imaging might provide valuable insights. Future works are in demand to establish and optimize MR functional quantitative imaging for radiotherapy assessment.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Radiology*

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Zheng Chang', with a stylized, flowing script.

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