Title: Diffusion-weighted imaging: a valuable aid for the evaluation of the tumor aggressiveness in breast carcinoma

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Author's response to reviews: see over
1. The results and threshold may be different with smaller lesions.

   Response: This work is mainly a methodological study. Our aim is to study the change of ADC value from tumor to peri-tumor tissue to normal tissue by this novel MRI technique. After that, our next stage study is designed to compare the DWI change with the molecular biological/pathological change in breast cancer. Thus, the specimen from mastectomy including tumor, peri-tumor tissue, and normal tissue are most suitable for our study purpose mentioned above. At present in clinical work, most patients with large breast tumor would be possibly performed mastectomy. That is the reason the lesions recruited in our study were relatively large in size.

   At the end of the Discussion section, we had added a new paragraph to address this issue: Besides, since this work was basically a methodological study and our aim was to study the change of ADC values from tumor to peri-tumor tissue to normal tissue by the novel MRI technique, all the lesions recruited in our study were from mastectomy and relatively large in size. Therefore, further researches are needed to assess whether the results and threshold in the present study could be also applied to the smaller lesions.

2. The authors draw the conclusion from their results that there existed “another margin”, which they regarded as “molecular margin”. As the authors didn’t compare their results with the histological specimen this conclusion definitely cannot be made.

   The conclusions of the authors regarding tumor margins are not reflected in the results.
   The conclusions regarding tumor margins are mere guesses.

   For these reasons I recommend rewriting the manuscript substantially for its purpose and conclusion and adding limitations.

   Response: We admit it is too early to directly determine the so-called molecular margin, since our study results lacked the support of pathological evidence. Therefore, we have re-written some of the manuscript--- changed the second aim from “identifying molecular margin of tumor” to “evaluating the aggressiveness of tumor in breast cancer by DWI”, which is more objective, according to our results--- ADC values increased gradually from the tumor to peri-tumor to normal tissues and there existed a region with a thickness of about 5 mm surrounding the border of tumor (by routine MRI), which has an abnormal ADC value, while beyond this region, the ADC value of tissue return to a normal range gradually. Based on these
findings, our next stage study will be to compare the examination of DWI with that of pathological histology about tumor aggressiveness in breast carcinoma and study the correlation of diagnosis between these two methods.

3. Change title:

**Response:** We had changed the title to “Diffusion-weighted imaging: a valuable aid for the evaluation of the tumor aggressiveness in breast carcinoma”.

4. Choose other words than “precisely” and “accurate” as this sounds exaggerated.

**Response:** We have deleted or replaced words such as “precisely” and “accurate” in manuscript which sounds exaggerated.

5. 10 mm outwards from the anatomical margin of breast carcinoma could be viewed as a safe margin for excision. But how was it proved in the study as no comparison with histological specimen was made.

**Response:** Same with question 2.

6. P3, Line 6: “However, because” correct English?

**Response:** We have searched online and found “However, because” is indeed correct English.

7. P3, Line 8: “previous study” correct “studies”

**Response:** We have changed study to “studies”.

8. The study cited deals with hepatocellular carcinoma which can not be compared to breast cancer.

**Response:** We had substituted the reference about hepatocellular carcinoma with another one about breast cancer.

9. Higher resolution than that of mammography and ultrasonography. If you write this statement please cite the resolution of the different methods.

**Response:** The sentence “MRI has a higher resolution than that of mammography and ultrasonography (US)” is inexact. In fact, much like x-ray mammography, breast MRI relies on anatomical or structural information, but provides much more detailed images. Ultrasound is also commonly utilized as a next-step after a questionable mammogram and is good at determining if a suspect mass is solid or fluid-filled. However, ultrasound demonstrates a low specificity that can produce misleading results and indicate biopsy where one may not be needed. So, the sentence in the paper has been changed to: “MRI has a high resolution and can
Point-by-point response to the concerns from Evelyn Wenkel

provide much more detailed images than mammography and ultrasonography (US)”.
10. “minute” choose another word as this sounds exaggerated.
   Response: We have deleted the “minute” from manuscript.
11. How were patients recruited for the study? Please define inclusion criteria.
   Response: We have added our inclusion criteria in the Materials and methods section.
12. Lymph node metastasis in malignant lesions was observed in 13 cases. Shouldn’t it be plural?
   Response: We have changed it to “Lymph nodes”.
   Response: We have corrected it.
14. Tumor? Or tumors?
   Response: We have changed it to “tumors”.
15. Based: correct spelling.
   Response: We have changed it to “based”.
16. second paragraph: results are repeated
   Response: Since we needed compare our results with that of other researchers and explain the
   reasons for the differences between ours and theirs, we had to repeat parts of our results.
17. slightly: please correct
   Response: We have changed it to “slightly”.
18. incassation: please use a different word
   Response: We have changed it to “densification”.
19. Readers: please correct
   Response: We have changed it to “readers”.
20. Figure 1: A: with hyperintense (missing word?)
   Response: We have changed it to “with hyperintense signal”.
21. Speculate, do you mean speculation
   Response: We had changed it to “picule sign”
22. Figure 1: D: missing words?
   Response: We have added “found”.
23. Figure 2: B: Hyperintense Add lesion
   Response: We have added “lesion”.
24. Figure 2: D: correct isointensel to isointense  
   **Response:** We have changed it to “isointense”.

25. Figure 5 and 6: following not followings  
   **Response:** We have changed it to “following”.