Author's response to reviews

Title: Meta-analysis of quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesions.

Authors:

Xin Chen (chen_x129@163.com)
Wenling Li (lwlwl_szs@126.com)
Yili Zhang (yilizhang1975@hotmail.com)
Qian Wu (wugian@mail.xjtu.edu.cn)
Youmin Guo (cjr.guoyoumin@vip.163.com)
Zhilan Bai (bzl8216@yahoo.com)

Version: 7 Date: 1 December 2010

Author's response to reviews: see over
Dear Mr. Cochrane and Dr. Madabhushi,

Thank you very much for your letter and advice. We have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers’ comments are listed as below:

**Reviewer 1: Matthew DiFranco**

**Major Compulsory Revisions**

None

**Minor Essential Revisions**

1. **Selection of Articles, paragraph 3** - make it "Studies were excluded to exclude the stability..."

   **Answer:** Revised as the two reviewers’ comments.

2. **Quality Assessment, paragraph 2** - make it "...using the quality assessment of diagnostic studies (QUADAS)..."

   **Answer:** Revised per suggestion.

3. **Quality Assessment, paragraph 4** - make it "Values for true-positive (TP), false-positive (FP), ..., ...(NLR) in the detection of ..."

   **Answer:** Revised per suggestion.

4. **Quality Assessment, paragraph 4** - spelling: radio -> ratio

   **Answer:** Revised per suggestion.

5. **Quality Assessment, paragraph 4** - Accuracy formula is wrong. Numerator should be (TP + TN).

   **Answer:** Revised per suggestion.

6. **Meta-Analysis, paragraph 1** - "... if the differences across the studies were greater than..."

   **Answer:** Revised per suggestion.
7. Meta-Analysis, Publication-bias analysis - "...whereas a skewed and asymmetric..." This is redundant, use one or the other. Skewness is a measure of asymmetry.

Answer: “Skewed” has been removed.

8. Results, paragraph 4 - spelling: homogeneity -> homogeneity

Answer: Revised per suggestion.

9. Results, paragraph 4 - make it "Therefore, notable heterogeneities..."

Answer: Revised per suggestion.

10. Discussion, paragraph 5 - confusing wording "...should be used in screening crowd to early detect nonpalpable lesions.." This sentence needs to be fixed.

Answer: “Should” has been changed to “could” as the reviewers’ suggestions.

11. Discussion, paragraph 7 - "The significant variance of threshold values..." This implies a statistically significant variance. Better to change to "substantial", or "large", or something similar.

Answer: Revised per suggestion.

12. Discussion, paragraph 7 - make it "For example, a relatively higher threshold value..."

Answer: Revised per suggestion.

13. Discussion, paragraph 7 - remove "out", "...to minimize missing malignance in screening breast cancers."

Answer: The sentence has been revised as “For example, a relatively higher threshold value may be recommended to minimize missing malignancy in breast cancer screening.”

14. Discussion, paragraph 7 - Last sentence has a few grammar errors as well.

Answer: Last sentence has been revised as “If DWI is appended to the contrast-enhanced MRI, a relatively lower threshold value may be recommended to reduce false positive results.”

Discretionary Revisions
The Discussion section could be better organized to get the key points across better. I leave it up to the authors to pursue this.

Answer: The discussion section has been revised as the reviewer’s suggestions. We combined fourth and fifth paragraphs, and break sixth paragraph into 2 paragraphs.

Reviewer 2: Shannon Agner

Minor essential revisions:

1. In Discussion, fifth paragraph, sentence 9: This sentence is too bold a conclusion to be drawn from meta-analysis results. I suggest changing “should” to “could.”

Answer: Revised per suggestion. Thank you.

2. In the Conclusion, a comment should be made on why a threshold for benign/malignant lesions classification could not be made based on this study and how this could be rectified.

Answer: Amended as suggested.

3. In Methods, Selection of Articles, how is “sufficient data” to calculate TP, FP, TN, and FN defined?

Answer: The sentence may be confusing. Here, “sufficient data” means that we should know the total number of lesions, the number of malignant/benign lesions diagnosed by DWI and pathology. We revised it as “sufficient information”.

4. In the Abstract, Conclusions: “Quantitative DWI has a higher specificity to differentiate between benign and malignant breast lesions…”

Answer: Revised per suggestion.

5. In Background, first paragraph, second sentence: “…application of mammography and ultrasound, differentiation between benign and malignant breast lesions remains a difficult diagnosis problem, especially in dense fibroglandular breasts.”

Answer: Revised per suggestion.

6. In Background, third paragraph, third sentence, “Comparison of the diagnostic performance of breast quantitative DWI among the studies may have been compromised by differences in the patient characteristics, MR imaging
techniques, and diagnostic criteria for malignancy in the studies.”

Answer: Revised per suggestion.

7. In Background, third paragraph, last sentence, the authors should state the purpose of the study, not the conclusions. For example, “In this study, we pool a number of DWI studies of the breast to evaluate the diagnostic performance of DWI in breast lesion characterization.”

Answer: Revised per suggestion.

8. In Methods, Literature Search, third sentence: “We limited our search to publications in English and Chinese languages…” (leave word languages in).

Answer: Revised per suggestion.


Answer: Revised per suggestion.

10. In Methods, Selection of Articles, first sentence: “Inclusion criteria were: varied pathology within the dataset; total number of lesions # 30, with the number of both malignant and benign lesions each # 10; histopathologic analysis (performed at surgery and biopsy) and follow-up by ultrasound, mammography, or MRI used as the reference standards…”

Answer: All revised per suggestion.

11. In Methods, Selection of Articles, third paragraph, first sentence: remove “to verify that stability and reliability of pooled analysis”

Answer: Revised per suggestion.

12. In Meta-Analysis, Threshold effect, third sentence: log (SEN) instead of “log sensitivity” and log(1-SPE) instead of log 1-specificity

Answer: All revised per suggestion.

13. In Meta-Analysis, Publication bias analysis, last sentence, change “nil” to “zero.”

Answer: Revised per suggestion.
14. In Results, first paragraph, third sentence: “The objective of studies was…”

Answer: Revised per suggestion.

15. In Results, second paragraph, first sentence: “were included from 13 studies.”

Answer: Revised per suggestion.

16. In Results, second paragraph, sentence 5: “The abstracted data of these individual studies are summarized in Tables 1 and 2.”

Answer: Revised per suggestion.

17. In Results, second paragraph, sentence 6: “used to perform breast DWI in Baltzer et al. [40]; Marini et al. [18] used…in Rubesova et al. [8].

Answer: All revised per suggestion.

18. In Results, fourth paragraph, second sentence: “A homogeneity test…”

Answer: Revised per suggestion.

19. In Results, fourth paragraph, sentences 6-7: “A Spearman rank correlation is performed as a further test for threshold effect. The Spearman correlation coefficient was equal to 0.097 (P=0.66) and indicates…”

Answer: All revised per suggestion.

20. In Results, sixth paragraph, first sentence: “Having found notable heterogeneity beyond threshold…” (remove “the”).

Answer: Revised per suggestion.

21. In Results, fifth paragraph, first sentence: “Heterogeneity, the pooled weighted sensitivity and specificity, and AUC are analyzed again when [46] and [47] were excluded…”

Answer: All revised per suggestion.

22. In Discussion, second paragraph, first sentence, “in a ROC space, and Spearman correlation coefficient is computed between log (SEN) and log (1-SPE).”
23. In Discussion, second paragraph, remove “Comprehensive literature search may reduce publication biases.” In next sentence: “is supplemented by checking references of relevant studies in order to reduce publication bias [25].”

Answer: All revised per suggestion.

24. In Discussion, third paragraph, “Because b values used in the included studies varied, we needed to explore whether b values were the source of heterogeneity.”

Answer: Revised per suggestion.

25. In Discussion, third paragraph, “Furthermore, sensitivity analysis is performed in the subgroup of b = 1000 s/mm². When the studies…”

Answer: Revised per suggestion.

26. In Discussion, combine fourth and fifth paragraphs.

Answer: All revised per suggestion.

27. In Discussion, fifth paragraph: “The significance of Peter et al. [6] lies in…”
28. In Discussion, fifth paragraph, sentence 9: “Because MR is one of the important methods for breast cancer diagnosis, DWI, having the advantages of a short examination time and …”

Answer: All revised per suggestion.

29. In Discussion, the sixth paragraph is very long. Consider breaking it into 2 paragraphs.

Answer: All revised per suggestion. Thank you.

30. In Discussion, sixth paragraph, first sentence: remove “considered to be combinable”

Answer: Revised per suggestion.

31. In Discussion, sixth paragraph, sentence 9: “As the index test, DWI was always performed first, and interpretation of the results of the DWI was usually done without knowledge…”
We hope that the revised version of the manuscript is now acceptable for publication in your journal.
We look forward to hearing from you soon.

With best wishes,

Yours sincerely,

Xin Chen and You-min Guo