Title: Combined use of the automated breast volume scanner and the US elastography for the differentiation of benign from malignant lesions of the breast

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Version: 3
Date: 24 September 2014

Author's response to reviews: see over
Dear Dr Yuanyi Zheng and Ms Roselyn Remoto:
On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “Combined use of the automated breast volume scanner and the US elastography for the differentiation of benign from malignant lesions of the breast”. (MS: 1593359496136966). We have studied reviewers’ comments carefully and have made revision with marked in red in the paper. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration.
We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.
Thank you and best regards.
Yours sincerely,
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List of responses
Dear Ms Roselyn Remoto and Reviewers:
Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Combined use of the automated breast volume scanner and the US elastography for the differentiation of benign from malignant lesions of the breast”. (MS: 1593359496136966). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made corrections which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewers’ comments are as following:
Responds to the reviewers’ comments:
Reviewer Ji-Bin Liu 1:
1. **Response to the comment:** the comma after “US elastography (UE)” should be deleted.
   **Response:** Page 2, line 43-44, the comma after “US elastography (UE)” was deleted.
2. **Response to the comment:** use “Forty-one” instead of “41”.
   **Response:** Page 2, line 49, “41” had changed as “Forty-one”, “46” had changed as “forty-six”.
3. **Response to comment:** Authors should provide more description of study design and technique in the method section.
**Response:** In page 2, line 50-53, “ABVS images were acquired by medial and lateral scans for each breast and classified a BI-RADS category based on the distribution, size, shape, echogenicity and microcalcification of the lesions. UE images were assigned an elasticity score according to the distribution of strain induced by light compression.” was added to the description of study design and technique in the method section.

4. **Response to the comment:** the conclusion section is repeated twice in the text.
   **Response:** Page 2, line 74, the repeated conclusion section was deleted.

5. **Response to the comment:** “ago” should be added up after “60 years”.
   **Response:** Page 3, line 89, “ago” was added up after “60 years”.

6. **Response to the comment:** “hybrid echo” should be replaced by “complex echogenicity”.
   **Response:** Page 4, line 166-167, “hybrid echo” was replaced by “complex echogenicity”.

7. **Response to the comment:** “the malignant lesions” should be reworded as “hard lesions” and the “benign lesions” should be reworded as “soft lesions”.
   **Response:** Page 4, line 172, “malignant lesions” was reworded as “hard lesions”, and “benign lesions” was reworded as “soft lesions”.

8. **Response to the comment:** the statement should be reworded and clarified in page 6, line 217-221.
   **Response:** Page 6, line 217-221, “redefined the category of ABVS…..” mean ”reassess the lesions”, and the statement of “two examiners compared each image of ABVS with UE to get more information to add accuracy for diagnosis. They redefined the category of ABVS and the score of UE of every lesion and identified the nature of lesions with more details” was clarified as “the information of ABVS image and UE image were provided for the two examiners to make comprehensive assessment of all lesions. They redefined the category of ABVS and the score of UE of every lesion and identified the nature of lesions with both the morphological and the stiffness details. Therefore, the diagnosed accuracy would be increased”.

9. **Response to the comment:** the paragraph of “According to BI-RADS category….as malignant lesions (Figure 5)” describes the diagnostic performance of ABVS and UE, so it should be moved to the Diagnostic performance section.
   **Response:** Page 6, the paragraph of “According to the BI-RADS category”’”’” as malignant lesions (Figure 5)” was moved to the Diagnostic performance section. The details of the description were displayed in page 6, line 231-239 as “Compare BI-RADS category with pathological results, there were 14(14/18) benign lesions consistent with pathological results and the malignant lesions were 28(32/28), 4 benign lesions were misdiagnosed as malignant lesions (Figure 3). As respect to the UE results, 14 benign lesions and 27 malignant lesions were correctly diagnosed while 1 malignant lesion was misdiagnosed as benign and 4 benign lesions misdiagnosed as malignant (Figure 4). When ABVS and UE combined, only two benign lesions were misdiagnosed as malignant lesions (Figure 5). According to these results, the accuracy, sensitivity, specificity, PPN and NPN of
ABVS, UE, and ABVS combined with UE were calculated”.

10. **Response to the comment:** “time-save” should be “time saving”.
    **Response:** Page 8, line 319, “time-save” was reworded as “time saving”.

11. **Response to the comment:** the full spelling of the acronyms should be provided in the figure legends.
    **Response:** Page 12, line 497, line 507, line 512, line 518 and line 524, the full spelling of the acronyms “ABVS, UE, US” were provided in the figure legends.

12. **Response to the comment:** the sentence below Table 4 should be deleted.
    **Response:** Page 14, line 538, the sentence below Table 4 was deleted.

13. **Response to the comment:** the statement below Table 5 and Table 6 should be deleted.
    **Response:** Page 14, line 542, the statement below Table 5 “ABVS and ABVS+UE both obtained an almost perfect agreement with pathological findings, while UE reached a substantial agreement. Examiner variability was reduced from UE to ABVS, and to ABVS+UE” was changed as “The inter-rater reliability coefficients of ABVS, UE and ABVS+UE were calculated” and line 545, the statement below Table 6 “Though there was no statistically significance in any of the diagnostic performance index among these three methods, the diagnostic performance of ABVS+UE was better than, or at least equal to, that of ABVS or UE alone” was changed as “The diagnostic performance of ABVS, UE and ABVS+UE was evaluated”.

Special thanks to you for your good comment.

Reviewer Tang Jie 2:

1. **Response to comment:** rewrite the results.
    **Response:** In page 2, line 60-73, the results were changed as “Inter-examiner reliability with ABVS ($\kappa=0.62$, 95% confidence interval (CI):0.44-0.80) and UE ($\kappa=0.65$, 95%CI: 0.48-0.82) was substantial. With respect to the pathology results, the inter-rater coefficient of concordance was $\kappa=0.81$ (95%CI: 0.64-0.98) for ABVS, $\kappa=0.77$ (95%CI: 0.58-0.96) for UE, and $\kappa=0.90$(95%CI: 0.77-1.00) for combination of ABVS and UE. Examiner variability was reduced from UE to ABVS, and to ABVS+UE.

The diagnostic accuracy, sensitivity, and specificity for the combination of ABVS and UE were 95.7%(95%CI:84.0-99.2 ), 100%(95%CI:85.9-100), and 87.5%(95%CI:60.4-97.8 ), respectively. When comparing, the diagnostic performance of ABVS combined with UE was better than, or at least equal to, that of ABVS (accuracy 91.3%(95%CI:78.3-97.2), sensitivity 100%(95%CI:85.0-1.00), specificity 77.8%(95%CI:51.9-92.6) ) or UE (accuracy 89.1% (95%CI:75.6-95.9), sensitivity 96.4%(95%CI:79.8-99.8), specificity 77.8%(95%CI:51.9-92.6)) alone, though the improvement was no statistically significance.”

2. **Response to comment:** how is the picture quality of ABVS compare with HHUS.
    **Response:** Page 3, line 95-98, the “the operator variability is reduced and the reproducibility is improved” was changed as “the resolution of image is increased
by providing better demonstration of breast anatomy and proper orientation. And
the operator variability is reduced while the reproducibility is improved.” to
describe the picture quality of ABVS when comparing with HHUS.

3. **Response to the comment:** 10min is not short.
   **Response:** Page 3, line 94, we do agree 10min is not short. However, with respect
to HHUS, the scan time of ABVS is controllable no matter in the simple or
complicate cases so that the operating process will achieve optimization and
standardization.

4. **Response to the comment:** the good way to get good picture.
   **Response:** Page 4, line 136, the gaps between breast and the compression paddle
can be reduced by filling the gaps with ultrasound gel, but this solution is only
partial because some women are too skinny. If the picture is not good, we will try
padding with pillow under the shoulders of the patient. If this solution is not
effective, HHUS may be more beneficial for the patients.

5. **Response to the comment:** how to minus the statistical error if the patient id too
   fat or too thin.
   **Response:** Page 4, line 145, if the patient is too fat or too thin, according to
reports, multivariable analysis showed that there was no correlation of image
quality with age, BMI, mammographic density or distance from the nipple.
However, in our opinion, if the patient is too fat or too thin, he/she will be
excluded from our study.

6. **Response the comment:** what should we do if the lesion is smaller than the ROI
   area.
   **Response:** Page 4, line 147, the size of the ROI is depend on the size of the lesion.
In principle, the top of the ROI was set to include the subcutaneous fat, and the
bottom of the ROI was set to include the pectoral muscle, the lateral borders were
set more than 5mm from the boundary of the lesion. If the lesion is much smaller,
the quality of the image will be affected and the valid strain information will fail
to obtain. Therefore, if the lesion is to smaller, it cannot be evaluated by
elastography.

7. **Response to the comment:** how to do with the lesions describe category 0.
   **Response:** Page 4, line 159, the lesions describe category 0 were evaluated
incompletely, we cannot find any positive manifestations with ultrasound.
Therefore, other imaging methods such as CT, MRI were needed for evaluation.

8. **Response to the comment:** it is not objective when the two examiners discussed.
   **Response:** Page 5, line 196 and line 210, the kappa statistics was used to evaluate
the concordance between examiners with ABVS and UE in the beginning of our
study, and we obtained good results. In order to make it better to compare with
pathologic results, the equivocal lesions were needed to reach an agreement,
therefore, the two examiners discussed and made sure the category and score of
the equivocal lesions.

9. **Response to the comment:** it is not very clear in page 6, line 217
   **Response:** Page 6, line 217-221, the statement of “two examiners compared each
image of ABVS with UE to get more information to add accuracy for diagnosis.
They redefined the category of ABVS and the score of UE of every lesion and identified the nature of lesions with more details” was clarified as “the information of ABVS image and UE image were provided for the two examiners to make comprehensive assessment of all lesions. They redefined the category of ABVS and the score of UE of every lesion and identified the nature of lesions with both the morphological and the stiffness details. Therefore, the diagnosed accuracy would be increased”.

10. **Response to the comment:** the needle is 18G or 16G.
    **Response:** Page 6, line 224, the “core needle” was changed as “16G core needle”

11. **Response to the comment:** what are the short comes of ABVS and US.
    **Response:** Page 6, line 258-267, we added the shortcomings of ABVS, UE, and US: “We propose that this may be because ABVS is inability to immediately adjust the modifying factors such as compression, the orientation of the probe, and the machine’s setting while acquiring the image in real-time when exploring further a questionable lesion. Though HHUS and UE may compensate these shortcomings, HHUS is lacking of standardization in diagnostic for the poor reproducibility of images and high variability of operators. And UE is not specific enough to diagnose lesions in morphology. On the other hand, both ABVS and UE are inability to perform color or spectral Doppler for tissue or lesion vascularity. Therefore, the combination of ABVS and UE provides minimal benefit to diagnostic performance.”
    Special thanks to you for your good comment.

Reviewer Wu Changjun 3:

1. **Response to the comment:** suggest the author to use figure and figure legends to illustrate the criteria of UE.
    **Response:** Page 4, line 173, the scoring criteria were changed in a table form in page 13, line 527

<table>
<thead>
<tr>
<th>score</th>
<th>Chromatic code</th>
<th>Possible lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>entirely pink</td>
<td>Prevalently elastic: prevalently in the benign lesions</td>
</tr>
<tr>
<td>2</td>
<td>a mosaic pattern of purple mixed with a small amount of green</td>
<td>Prevalently rigid: prevalently in the malignant lesions</td>
</tr>
<tr>
<td>3</td>
<td>a mosaic pattern of green mixed with a small amount of yellow</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>almost the entire lesion in yellow, but mixed with a small amount of red</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>both the lesion and surrounding area are red mixed with a small amount of yellow</td>
<td></td>
</tr>
</tbody>
</table>

2. **Response to the comment:** the statement below Table 4 should be displayed in the results section.
    **Response:** Page 14, line 540-542, the statement below Table 4 “ABVS and ABVS+UE both obtained an almost perfect agreement with pathological findings,
while UE reached a substantial agreement. Examiner variability was reduced from UE to ABVS, and to ABVS+UE” was changed as “The inter-rater reliability coefficients of ABVS, UE and ABVS+UE were calculated”.

3. **Response to the comment:** the results in the result section should be showed simply.
   **Response:** It is really true as professor Wu suggested that we should showed the results simply in line 241-246, but we thought that the results in line 241-246 were in order to display a complete result, and the results in Table 6 were used for a better comparison.

4. **Response to the comment:** why the author mentioned strain ratio.
5. **Response:** Page 8, line 321-324, we mentioned the strain ratio because some studies reported that the inter-observer variability in data acquisition and interpretation has been shown as a limitation of the use of UE, and to overcome this limitation, they suggested that the fat to lesion strain ratio could be used an objective and constant characteristic regardless of data acquisition or interpretation variability. We thought that strain ratio might be help to improve the UE diagnostic performance.
   Special thanks to you for your good comment.

We appreciate for editor’s and reviewers’ warm work earnestly, and hope that the correction will meet with approval.
Thank you very much for your comments and suggestions.