Author's response to reviews

Title: Real-time ultrasound elastography in 180 axillary lymph nodes: elasticity distribution in healthy lymph nodes and prediction of breast cancer metastases

Authors:

Sebastian Wojcinski (s@wojcinski.de)
Jennifer Dupont (Jennifer.Dupont@web.de)
Werner Schmidt (werner.schmidt@uks.eu)
Michael Cassel (michaelcassel@web.de)
Peter Hillemanns (hillemanns.peter@mh-hannover.de)

Version: 2 Date: 10 November 2012

Author's response to reviews: see over
Re-Submission after revisions

“Real-time ultrasound elastography in 180 axillary lymph nodes: elasticity distribution in healthy lymph nodes and prediction of breast cancer metastases”

Dear Editors and Reviewers,

Thank you very much for your review of the manuscript. I really appreciate the energy and time that you have spent and your very helpful recommendations.

We have carried out a revision of the manuscript. As proposed, the new version is much shorter (about 1000 words shorter with only 4 tables and 6 images left). All of your detailed comments and suggestions have been incorporated into the revised draft. In order to facilitate the review process, relevant changes and new sections are highlighted in “bold” within our revised manuscript.

Thank you again for your suggestions – we hope that our revision covers all the necessary aspects.

With best regards,

Dr. Sebastian Wojcinski

Email s@wojcinski.de
### Reviewer 1

<table>
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<tr>
<td>The authors present an interesting concept of real-time elastography in axillary lymph nodes.</td>
<td>Thank you very much for your pleasant comments.</td>
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<tr>
<td>Unfortunately, the authors have produced an overly long paper. I think the paper would be better 'slimmed down' and resubmitted.</td>
<td>According to your suggestion, the main text has been reduced from ~4,100 words to ~3,240 words.</td>
</tr>
<tr>
<td>The uses of English are sometimes a little clumsy and so it is not always entirely clear what is being said.</td>
<td>We have tried our best to improve the language. If it is still not acceptable, we will consider using the proposed language editing service (Edanz).</td>
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<tr>
<td>Introduction, materials, results, and discussion are so long and redundant.</td>
<td>According to your suggestion, the main text has been reduced from ~4,100 words to ~3,240 words.</td>
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<td>Furthermore, there are so many tables and figures. For instance, I do not think the weight and BMI are needed at the Table 1, and whole Table 7. And I think authors can combine 3 tables (Table 3-5).</td>
<td>According to your suggestion, there are only 4 tables remaining.</td>
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<td>I do not think Figure 1 and 2 are necessary as the concept of elastography in axillary lymph nodes.</td>
<td>According to your suggestion, we have excluded figure 1 and figure 2.</td>
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### Reviewer 2

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<td>The article present a very relevant topic, since staging is of major importance for all cancer forms. The aim of the study was to evaluate the sensitivity, specificity and predictive value of sonoelastographic evaluation of lymph nodes in patients with breast cancer. The study method is well described. The illustrations are all relevant.</td>
<td>Thank you very much for your pleasant comments.</td>
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<td>Major Compulsory Revisions: The study uses a healthy population as the control group. This is a major concern, since it doesn't reflect the actual clinical setting. Especially since reactive inflammation in lymph nodes is common in most cancer forms. This might very well make the lymph nodes harder and therefore sincerely lower the reported specificity. The authors actually had a proper control group in the cancer patients without metastatic lymph nodes, but these patients were excluded?</td>
<td>We have to acknowledge that a group of healthy patients is probably not the best control group for the calculation of specificity, whereas sensitivity is not impaired by this choice. However, we emphasize the primary study objective in the new version of the document: &quot;The primary objective of our study was to determine the typical color distributions of healthy LNs in the elastogram.”</td>
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<td>Furthermore, we have now chosen a careful formulation concerning the calculation of the performance: &quot;The secondary study objective was an exploratory analysis of the method’s potential value in the prediction of LN metastases when used as an adjunct to conventional B-mode ultrasound.”</td>
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**Note:** The text is formatted as a table for easier readability. The content is a natural representation of the document, consistent with the guidelines provided.
This should point out that the focus of the study is on the mere elasticity distribution and that the analysis of the performance is limited by the mentioned point:

“Finally, the analysis of SP, PPV and NPV is limited by the fact, that a group of healthy women is probably not the optimal choice for the control group, as lymph node morphology may differ even between healthy women and node negative breast cancer patients. Furthermore, there are vast confidence intervals due to the small sample size. Further studies with larger collectives consisting exclusively of breast cancer patients may yield more accurate results.”

Furthermore, the study uses three different postulated prevalences of lymph node metastasis between 4 and 36 percent for T1 to T3 tumors. However, the prevalence in the reported data is 15 of 33 (45%). This is not discussed, did the study group have a very high rate of T4 tumors? This could be a major bias to the reported sensitivity, since the risk of advanced lymph node metastasis is increased with the tumor stage and makes the identification easier compared to earlier lesions. Thus, the reported sensitivity could be falsely high compared to a more normal study group.

Thank you for revealing this inaccuracy! The previously given prevalence comes from a small study and refers to Level II involvement. The correct estimation for the prevalence in T1 tumors should be about 25% and in T2 tumors about 48% [Yip et al. 2009]. In mixed collectives the prevalence can be estimated to be about 45% [Chua et al. 2002]. Therefore, our own prevalence seems to be representative. However, we have corrected the calculation of NPV and PPV with respect to the new data. The number now reflects the real situation and the results are more plausible.

The entire paragraph has been revised.

The reported confidence intervals for the sensitivity are very high due to the limited number of patients. This makes the interpretation of the calculated predictive values very hard. A calculation of the predictive values at the outer limits of the sensitivity could be in place, or save the estimation of predictive value for further studies.

We emphasize that the calculation of SE and SP has an exploratory character and is limited by several points. However, we think that even this “model calculation” may be of certain interest, at least as a basis for further studies. Using the outer limits would be an option, but we would prefer to keep our analysis as it is, because the additional numbers would yield no more accuracy as this is a wary “model calculation” and we do not want to assume a high precision of this analysis.

However, we now address this limitation in the discussion:

“Furthermore, there are vast confidence intervals due to the small sample size. Further studies with larger collectives consisting exclusively of breast cancer patients may yield more accurate results.”

And in the conclusions we still use the formulation “may improve”.

I will suggest the authors rewrite and resubmit with an analysis using the results from the group of patients with proven cancer, but benign histology of the evaluated lymph nodes, as the control group. The
reported data for a normal population is of little value, except if the authors can justify that the results are the same in a group of cancer patients with no metastasis.

NPV. We are actively considering investigating this aspect further.

However, in our current study, we would prefer to keep the focus as it is. As previously mentioned, in the revised paper, we point the primary objective of our study and the limitations:

“The primary objective of our study was to determine the typical color distributions of healthy LNs in the elastogram.”

“The secondary study objective was an exploratory analysis of the method’s potential value in the prediction of LN metastases when used as an adjunct to conventional B-mode ultrasound.”

“Finally, the analysis of SP, PPV and NPV is limited by the fact, that a group of healthy women is probably not the optimal choice for the control group, as lymph node morphology may differ even between healthy women and node negative breast cancer patients. Furthermore, there are vast confidence intervals due to the small sample size. Further studies with larger collectives consisting exclusively of breast cancer patients may yield more accurate results.”

Minor Essential Revisions

Regarding the technique, the authors use colors to compare two different part of the same lymph node. There is a possibility to have the machine calculate a ratio (strain-ratio) based on the measured elasticity of two separate areas. The authors needs to address the choice of the use of a predominant color.

We have added a comment concerning the strain-ratio:

“Another option for the interpretation of elastograms is the calculation of the strain-ratio [25, 53]. This mode has not been systematically analyzed in LNs and could be a matter of future research.”

Furthermore, we address our choice:

“...we have chosen a different approach for the evaluation of the elastograms, as we propagate the idea that the cortex and the medulla of an LN should be evaluated separately. Furthermore, we tried to avoid cumbersome scoring systems. For the evaluation of the elastograms we used a simple 5-point color scale describing the predominant color of the distinct structure (red, yellow, green, turquoise, or blue) as it appears in the elastogram.”

The manuscript has been changed according to your suggestion. Thank you again for all your helpful comments!