Author’s response to reviews

Title: Apparent Diffusion Coefficient cannot predict molecular subtype and lymph node metastases in invasive Breast Cancer. A multicenter analysis

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Version: 1 Date: 19 Oct 2019

Author’s response to reviews:

Reviewer reports:
Matthias Dietzel (Reviewer 1): This study aims to re-investigate the potential role of DWI as a biomarker in the context of predicting lymph node MTX and molecular subtype. The authors performed a retrospective multicentric DWI study in a high number of breast cancers. They conclude that DWI is not able to discriminate molecular subtypes and cannot be used as a surrogate marker for disease stage or proliferation activity.

The material - I am convinced of that - is of high scientific value. However the presentation of the material is limited by nearly all central aspects of STARD criteria. Most of all

- Patient selection: unclear
- MRI: protocol not clearly enough described. Methodology of harmonization of ADC measurements among the centers missing a study with expected faint differences in my eyes a must (. In a clinical setting not necessary.)
- MRI analyzes: Not specified

Dear reviewer, thank you very much for the helpful comments.
As suggested, we added additional information regarding DWI into the manuscript.

In fact, there were different MR scanners, protocols, b values, slice thickness, and ADC measurements. However, our aim was to provide evident data about relationships between ADC and clinical relevant features like hormone receptor status and tumor stage based on a large multicenter cohort. Therefore, our sample reflects a real clinical situation. In clinical setting also different scanners etc. are used. Therefore, we need a general statement independent on numerous technical details.

Intro

Please provide more background on dwi and the rationale that it might be used as a biomarker.

Epidemiological data on breast cancer less important in this article

Dear reviewer, the information regarding DWI/ADC is given in the discussion as follows:

DWI measures diffusion of water molecules in tissues (16). Numerous reports indicated that DWI can reflect several histopathological features of malignant and benign lesions (17-19). It has been shown that ADC correlated inversely with cell count and proliferation index Ki 67 (17-19). Furthermore, some authors suggested that ADC may be also associated with expression of epidermal growth factor receptor (EGFR) (20, 21), vascular endothelial growth factor (VEGF) (22), epidermal growth factor receptor 2 (HER2) (23), tumor suppressor protein p53 (20, 21), programmed cell death protein (PD L1) (24), nucleic content (25), and membrane permeability in several tumors (25). Therefore, it might be possible that ADC may also depend on hormone receptor status in BC.

We think, BMC Cancer is a journal predominantly for oncologists but not for radiologists or biophysicist and, therefore, a more detailed technical information regarding DWI is unnecessary.

M&M

Explain indications for breast MRI

Insufficient description of MRI parameters:

- in plane resolution.
- Number of b-Values (probably 2 but a range is given).
- Fat saturation?
- quality management in terms of ADC standardization explorative/formal comparison, phantoms etc.)
Dear reviewer, unfortunately, the data about quality management in terms of ADC standardization explorative/formal comparison, phantoms etc. were not available. As indicated above, our aim was to provide evident data about relationships between ADC and clinical relevant features like hormone receptor status and tumor stage based on a large multicenter cohort. Therefore, our sample reflects a real clinical situation. In clinical setting also different scanners etc. are used. Therefore, we need a general statement independent on numerous technical details.

Our previous results suggested that some MR/DWI parameters like b values, Tesla strength, measure (whole lesion or single ROI) did not influence

- Multiple multicentric lesions?

We added this information into table 1.

There were no patients with multiple breast lesions.

No description of MRI analysis:

- how were lesions identified?

- how were lesions measured?

- DWI?

We added this information into table 1.

- DCE? If yes add details on DCE.

Dear reviewer, DCE findings were not analyzed in the study and were not available.

- Reader: experience, blinding etc.

This information was added in the table.

Stats:

- Any power analysis considered, as this will impact the key result of your study

- Predictive performance addressed (odds ratio or similar value).

Dear reviewer, because our results did not show really significant associations between ADC and histopathological features in breast cancer, it was impossible/unnecessary to perform other statistical analyses.
Results, Discussion, Abstract, Tables: Revision recommended acc. to issues raised above

As suggested, we added some points into the manuscript.

Hee Jung Shin (Reviewer 2): This paper evaluated the relationship between ADC and molecular subtype and lymph node metastasis in invasive breast cancer from multicenter data analysis. This topic may be important in order to recognize ADC as a biomarker of breast cancer assessment. However, there was vague and important methodological problem in the ADC analysis and DWI acquisition because this study was retrospective analysis and they did not analyze the external validation. Several specific comments are as follows;

1. Abstract: There was mismatch between the title and conclusion regarding LN metastasis. In the conclusion, there was no description about prediction of LN metastasis. Please clarify and modify the description.

Thank you very much for the helpful comment. As suggested we corrected/modified the conclusion.

2. Methods: There was no detailed description about DWI acquisition of multiple institutions. DWI acquisition including number of b value and spatial resolution can influence the ADC measurement. So please describe in detail about DWI acquisition protocol.

Dear reviewer, we added this information into the table 1.

3. Methods: There was no detailed description about ADC measurement. ADC values could be significantly influenced by ADC measurement methods; 2D vs. 3D; manual vs. semiautomatic; one representative slice vs. whole tumor..etc. Did one radiologist draw ROI or did two or more radiologists draw ROI in consensus?

Dear reviewer, we added also this information into the table 1.

4. Results: Subgroup analysis may not be enough. For example, was there a difference of ADC values between different T or N stage among the same molecular subtype? I think that the addition of subgroup analysis of each molecular subtype may be needed to clarify the conclusion.

As suggested, we performed additional analyses and added the new data into the results.