A Feasibility Study Investigating the Use of Quantitative Measures of Spatio-temporal Tumor Heterogeneity Derived from 4D Breast DCE-MRI Registration as a Biomarker of Response to Neoadjuvant Chemotherapy

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INTRODUCTION

Imaging plays a central role in the assessment of breast tumor response to neoadjuvant chemotherapy. Image-based assessment of tumor change via deformable registration is a powerful, quantitative method to potentially explore novel information of tumor heterogeneity, structure, function, and response to treatment. We conduct a pilot study to validate the feasibility of deformable registration as a means to analyze spatio-temporal tumor changes. We also compare the derived registration features as biomarkers of tumor response to neoadjuvant chemotherapy against other prevalent clinical and kinetic features.

METHODS AND MATERIALS

Longitudinal breast DCE-MR images for 12 women with biopsy-proven T2-3 breast tumors were retrospectively collected from the ACRIN 6657 I-SPY trial. All women in this trial underwent standard neoadjuvant chemotherapy, which at the time of the study consisted of four cycles of Adriamycin/Cytoxan, followed by four cycles of Taxotere, over a period of 3 to 4 months. At the end of chemotherapy, the women were evaluated by pathological analysis and classified as either pathologic complete responder (pCR) or pathologic partial responder (pPR). In this study, 6 women were classified as pCR and 6 as pPR; no women in this study were classified as a non-responder. MR imaging parameters were: FOV 18-20 cm, image size 256×256×64,voxel size 0.70×0.70×2.0mm^3, TR=27.0ms, TE=4.76ms, flip angle=45^o. Pre-gadodiamide imaging was performed followed by immediate post-gadolinium images (at 2 minutes) and delayed post-gadodiamide images (at 7 minutes). The baseline image was the image obtained right before the first chemotherapy and final images was acquired after therapy was completed.

First, four state-of-the-art deformable registration algorithms were applied to determine the 3D breast tumor deformation maps of each individual patient throughout the chemotherapy. Evaluated on comparability to the pre-selected anatomical landmarks, an attribute-based deformable registration algorithm known as DRAMMS outperformed other algorithms for longitudinal breast image registration and was therefore selected for subsequent analysis. The previously validated DRAMMS algorithm was applied to assess tumor and normal breast tissue change in each individual patient during the chemotherapy based on MRI-voxel-level correspondence between the pre-chemotherapy and post-chemotherapy DCE-MRI datasets for each individual. Logistic regression models were then applied to predict response to neoadjuvant chemotherapy based on clinical, kinetic and registration-based features. Area under the curve (AUC) of the receiver operating characteristic (ROC) was used to evaluate classification performance, and the three models were compared to assess which set of features are most reflective of pathological response.

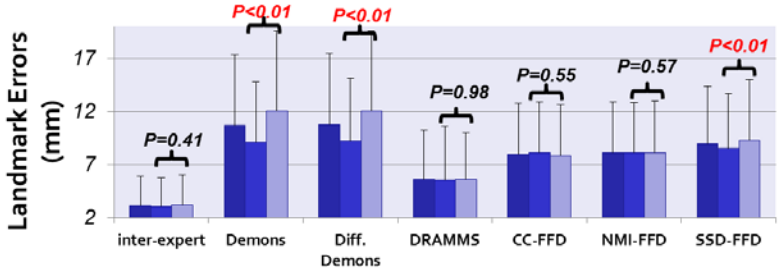

Figure 1. Landmark errors of different deformable registration algorithm at different regions (tumor, normal tissue, or both). The p-value from Students t-test indicate if there is substantial difference between tumor and normal breast tissue area.

RESULTS AND DISCUSSION

Despite the considerable time delay and anatomical structure variation due to the chemotherapy, DRAMMS was still able to accurately build voxel-wised correspondence among two longitudinal MR images of each individual as shown in Figure 1. In detail, compared with the variation between 2 experienced radiologists (noted as inter-expert in Figure 1) which is around 3mm, the landmark error of DRAMMS is 5.5 mm which is relatively close to the uncertainty from two raters.

Figure 2 shows the ROC plot of 4 standard kinetic features (peak enhancement (PE), wash in slope (WIS), wash out slope (WOS), and signal enhancement ratio (SER)) with and without registration, and the registration significantly increases the AUC for all the 4 kinetic features. In general, the best registration associated feature achieves the highest AUC (0.97), which outperformed the best clinical feature (AUC 0.81) and the best kinetic feature (AUC 0.94).

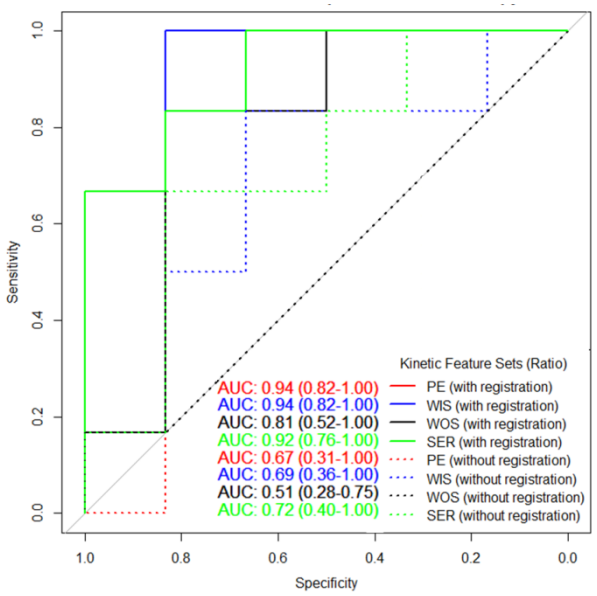

Figure 2. ROC comparison of 4 kinetic features (peak enhancement (PE), wash in slope (WIS), wash out slope (WOS), and signal enhancement ratio (SER)) with and without registration. Note that solid line means feature with registration, dotted line means feature without registration.

CONCLUSION

Registration not only derives distinct deformation associated features but also links the kinetic feature from different time interval at the voxel level which could potentially analyze localized tumor and normal breast tissue change. Deformable registration has been validated in terms of precisely tracking each patient's anatomical structure variation throughout neoadjuvant chemotherapy, and the associated features show the capability to better assess the tumor response to the treatment, in comparison with popular clinical and kinetic features for the selected representative dataset. A larger dataset from the ACRIN 6657 I-SPY trial is currently being acquired and processed to further validate these findings, which could potentially serve as a novel pathway to assess the tumor response to neoadjuvant chemotherapy from its early stage.