**Functional Diffusion Mapping (fDM) for Quantitative DW-MRI to Predict Breast Cancer Response to Neoadjuvant Chemotherapy**

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**PURPOSE** Diffusion weighted MRI (DW-MRI) reports on tissue cellular characteristics and has been used to predict treatment response in breast cancer¹. The functional diffusion mapping (fDM) method has been used to correlate changes in the apparent diffusion coefficient (ADC) with the response of various brain tumors to therapy,² ³ but there is only one study applying the fDM method to breast cancer.⁴ The goal of this study is to determine if the fDM analysis applied to ADC changes from pre- to post-one cycle of chemotherapy can be used to improve predictive accuracy over a region-of-interest based analysis.

**METHODS** Thirty-three patients with Stage II/III breast cancer were enrolled in an IRB-approved clinical trial in which DW-MRI data were acquired before \( t_1 \) and after one cycle of chemotherapy \( t_2 \). At surgery, 12 patients achieved a pathological complete response (pCR) while 21 patients were non-responders (i.e., non-pCR). Imaging was performed on a 3.0T MR scanner (Philips Healthcare, The Netherlands). DW-MRI was acquired with a single-shot spin echo (SE) echo planar imaging (EPI) sequence, with two \( b \)-values (0 and 500 s/mm² for 13 patients, and 0 and 600 s/mm² for 20 patients), \( TR/TE = 3080 \text{ ms}/43 \text{ ms} \) and NSA = 10 for a total scan time of 4 m and 40 s.

A longitudinal registration algorithm⁵,⁶ with a tumor volume-preserving constraint was employed to register the ADC maps from \( t_1 \) to \( t_2 \). A set of thresholds, from \( 0.1 \times 10^{-3} \text{ mm}^2/\text{s} \) to \( 0.8 \times 10^{-3} \text{ mm}^2/\text{s} \) with a \( 0.1 \times 10^{-3} \text{ mm}^2/\text{s} \) increment, were evaluated to detect the voxels with a significant increase in ADC. The percentage of tumor voxels with ADC changes above the threshold was calculated \( V_i \) for each patient and receiver operating characteristic (ROC) analysis was performed to test the ability of \( V_i \) to predict pCR. The Wilcoxon rank sum test was also employed to evaluate whether \( V_i \) between responders and non-responders was significantly different.

A region-of-interest (ROI) analysis, in which the ROC was directly applied to the change in mean ADC from \( t_1 \) to \( t_2 \), instead of \( V_i \), was also performed to evaluate whether the fDM approach improved the ability to predict treatment response.

**RESULTS** The optimal threshold to detect the voxels with a significant ADC increase was \( 0.4 \times 10^{-3} \text{ mm}^2/\text{s} \), resulting in the best area under ROC curve (AUC) of 0.75. Figure 1 shows the ROC curve for \( V_i \) estimated from the ADC values. The AUC, sensitivity, specificity, accuracy, and precision were 0.75, 0.75, 0.70, 0.72, and 0.60, respectively. The p value was 0.02, indicating that the percentages of voxels with increased ADC between responders and non-responders were significantly different. For comparison, the ROI analysis conducted on the change in mean ADC yielded an AUC of 0.62, with sensitivity, specificity, accuracy, and precision of 0.50, 0.76, 0.67, and 0.55, respectively.

**DISCUSSION** We applied the fDM approach on DW-MRI data obtained in 33 breast cancer patients. When compared to the ROI analysis with an AUC of 0.62, the fDM analysis improved the predictive ability by achieving an AUC of 0.75. The optimal threshold of significant ADC changes was \( 0.4 \times 10^{-3} \text{ mm}^2/\text{s} \), similar with the threshold \( 0.5 \times 10^{-3} \text{ mm}^2/\text{s} \) derived from short interval exams in the study of Ma et al⁴.

**CONCLUSION** The study indicates that the spatial analysis of the DW-MRI data after registration retains the information of tumor heterogeneity, therefore allowing for an improved ability to predict treatment response. Future work includes investigating a multi-parameter predictive model based on a larger cohort of patients.


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