Spatial Heterogeneity Analysis of DCE- and DW-MRI Using the Logistic Ridge Regression to Predict Breast Cancer Response to Neoadjuvant Therapy

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TARGET AUDIENCE Basic and clinical scientists studying breast cancer

PURPOSE Dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted MRI (DW-MRI) report on tumor vascular and cellular properties, respectively, and have been used to predict the response of breast cancer to neoadjuvant chemotherapy[1,2]. However, most studies track changes during treatment in these parameters averaged over the tumor region of interest (ROI) and these approaches cannot capture tissue heterogeneity and therefore discard all spatial information. In this study, we applied longitudinal registration to spatially align DCE- and DW-MRI parametric maps obtained during NAC in order to perform a novel voxel-by-voxel analysis based on a logistic ridge regression model. We hypothesized that explicitly incorporating spatial heterogeneity would increase the ability to separate pathologic complete responders (pCR) from non-responders (non-pCR) when compared with the ROI-based analysis.

METHODS *Data Acquisition* Thirty-three patients with Stage II/III breast cancer were enrolled in an IRB-approved clinical trial where DCE- and DW-MRI data were acquired before (t_1), after one cycle of chemotherapy (t_2), and after all cycles of treatment (t_3). At surgery, 12 patients achieved a pCR while 21 patients were non-responders. Imaging was performed on a 3.0T MR scanner (Philips Healthcare, The Netherlands); DCE-MRI employed a 3D spoiled gradient echo sequence, while DW-MRIs were acquired with a single-shot spin echo (SE) echo planar imaging (EPI) sequence.

Data Analysis The efflux rate constant k_{ep} was estimated from the DCE-MRI data using the extended Tofts model, while the apparent diffusion coefficient (ADC) was obtained from the DW-MRI data. For the ROI-based approach, the mean k_{ep} and ADC in the whole tumor ROIs were calculated and input into the logistic regression (LR) model. For the voxel-based analysis, a longitudinal registration algorithm[3,4] with a tumor volume-preserving constraint was first applied to register the k_{ep} and ADC maps from t_1 to t_2, respectively. Then the subsets of voxels with increased k_{ep} and decreased ADC were detected and the histograms of these subsets were calculated for each patient. Redundancy analysis was performed to select the most non-predictable percentiles from the remaining percentiles for the given histogram and these were input to the logistic ridge regression (LRR) model in the voxel-based analysis. The difference between the LR and LRR models is that a penalty is added in the cost function in the LRR model to handle a large number of parameters with a relatively small number of samples. A third analysis incorporated the mean ROI values, the histogram data, patient age, and tumor grade into the LRR model. Receiver operating characteristic (ROC) analysis was performed to test the abilities of the three approaches to predict pCR. The bootstrap method was performed with 500 replicates to calculate 95% confidence intervals (CI) for the area under ROC curve (AUC).

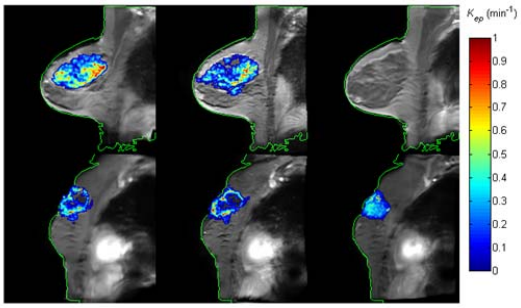

Figure 1. The k_{ep} parametric map superimposed on the post-contrast DCE-MRI data at three time points for one pCR (top row) and one non-pCR (bottom row). For each patient, the maps obtained at each time point were registered to the same image space.

	ROI	Voxel	ROI+Voxel+Clinical
k_{ep}	0.77	0.81	0.91
ADC	0.79	0.90	0.97
k_{ep} + ADC	0.90	0.92	0.98

Table 1. The AUCs for different parameters using the ROI-, voxel-, and all information based analyses in the logistic ridge regression model.

RESULTS Figure 1 shows the k_{ep} parametric map superimposed on the post-contrast DCE-MRI data at three time points (three columns) for one pCR (top row) and one non-pCR (bottom row) after registration. Table 1 shows the mean AUCs of the 500 replicates from the bootstrap for the three different approaches. For each single parameter, the AUC was improved through adding the histogram and clinical information to the regression model; in particular, for the combination of k_{ep} and ADC, the AUC was improved from 0.90 by the ROI analysis to 0.98 when including all data. The AUCs between ADC in the ROI analysis and ADC in the analysis integrating all information were significantly different (95% CIs of difference in AUCs: -0.42 to -0.05). No significant difference was found for the other cases.

CONCLUSION The study indicates that incorporating changes in the spatial heterogeneity in DCE- and DW-MRI data improves the ability to predict treatment response for breast cancer patients receiving NAC.

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