**Tumor Heterogeneity Patterns of DCE-MRI Parametric Response Maps May Augment Early Assessment of Neoadjuvant Chemotherapy: A Pilot Study of ACRIN 6657/I-SPY 1**

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Character Count: 1911/2000

*Purpose:* (character count: 321) To investigate the performance of tumor heterogeneity metrics derived from parametric response mapping (PRM), in their capacity to predict early pathologic complete response (pCR) to breast neoadjuvant chemotherapy (NAC), based on longitudinal assessment of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).

*Materials and Methods*: (character count: 777) A subset 27 patients from ACRIN 6657/I-SPY 1 TRIAL were retrospectively analyzed. Four kinetic features (i.e., signal enhancement ratio, peak enhancement, wash-in and wash-out slope) were computed separately from DCE-MRI acquired before chemotherapy and at the first treatment visit. For each feature, voxel-wise measures of variation during chemotherapy were assessed via PRM, and the degree of spatial heterogeneity for these voxel-level variations were quantified by selected statistical texture-based indices. The resulting heterogeneity-based PRM-index was compared with current standard measures in predicting pCR using logistic regression, where each model was adjusted for age and tumor subtype and performance was assessed via receiver operator curve (ROC) analysis.

*Results:* (character count: 573) After adjusted for patient's age and tumor subtype, the heterogeneity-based PRM-index outperformed current standard measures (AUC = 0.93 (95% CI: 0.83 – 1.00), PRM-index p-value = 0.08), including the "hot spot" signal enhancement ratio (SER) (AUC = 0.87 (95% CI: 0.71 – 1.00), SER p-value = 0.76), tumor longest diameter (LD) (AUC = 0.89 (95% CI: 0.67 – 1.00), LD p-value = 0.13), and tumor volume (AUC = 0.87 (95% CI: 0.71 – 1.00), volume p-value = 0.34). A similar trend was observed for unadjusted models, although performance was generally lower across all models.

*Conclusion:* (character count: 239) Our study provides preliminary evidence that metrics of spatial tumor heterogeneity are valuable in revealing patterns of early tumor response to NAC, and could augment pCR prediction based on standard MRI measures, age and tumor subtype.

*Clinical Relevance* (character count: 197/200): Patterns derived from quantitative tumor heterogeneity analysis by voxel-level DCE-MRI kinetic feature changes may augment early

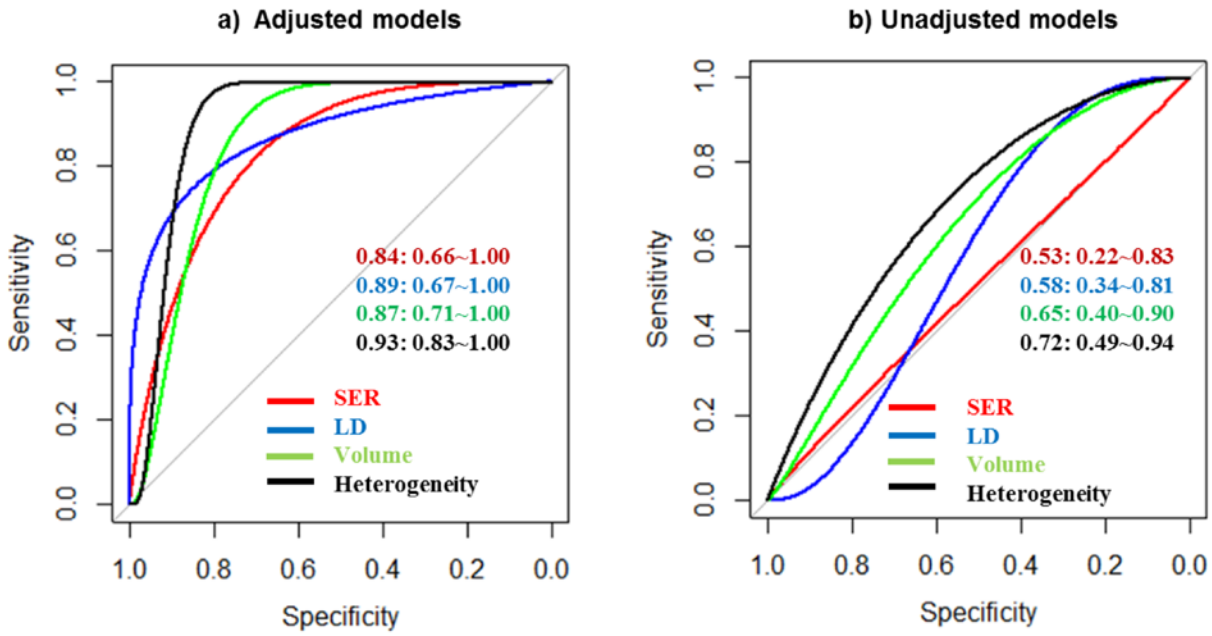


Figure 1: ROC curves comparing the tumor heterogeneity based model, to models based on tumor volume, longest diameter (LD) and signal enhancement ratio (SER), a) with and b) without adjustment for age and tumor subtype. The ROC AUCs and 95% confidence intervals are shown in corresponding color schemes.