Optimization of the Percent Enhancement Threshold for Breast MRI Tumor Volume Measurement During Neoadjuvant Treatment of Breast Cancer for Predicting Recurrence Free Survival Time

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Introduction: Dynamic Contrast Enhanced (DCE) MRI has been reported in a number of recent studies to be useful for assessing breast tumor response to neoadjuvant chemotherapy (NACT). In preliminary results of the ACRIN 6657 multi-center trial of breast MRI for assessing tumor response to NACT, tumor volume measured by DCE-MRI was shown to be more effective than clinical exam or mammography for predicting pathologic outcomes following NACT [1]. DCE tumor volume measurements show promise for risk prediction, but the establishment of optimal benign/malignant thresholds is challenging. Previous work [2] indicated that MRI pre-treatment volume and change in volume over treatment were significant predictors of recurrence free survival (RFS). In this study we systematically reanalyzed MRI data for the same neoadjuvant breast cancer cohort with 6-10 years of RFS data, examining the effects of varying the percent enhancement threshold (PE_{thresh}) on the predictive value of different tumor volume measures based on the signal enhancement ratio (SER) DCE-MRI method.

Subjects and Methods: Between 1995 and 2002 68 women (29–72, median 48.6 years old) undergoing NACT for stage II or III locally advanced invasive breast cancer, defined as tumors that had not spread beyond the breast and regional lymph nodes, and diagnosed by core biopsy or fine needle aspiration, were enrolled. The study was IRB approved and all subjects gave informed consent. Two patients who did not undergo surgery were omitted from these analyses. The chemotherapy regimen for all patients consisted of four cycles of doxorubicin and cyclosphosphamide given every 3 weeks, followed by 12 weekly cycles of taxane in 12 patients. The subjects were imaged on a 1.5-T Signa scanner (GE Healthcare) using a bilateral phased-array breast coil before treatment (V1, n=66), after the first cycle of chemotherapy (V2, n=50), and at completion of treatment pre-surgery (PS, n=65). High spatial resolution (.7x.94x2.0mm^3), fat-suppressed, DCE scans were performed with a 3DFGRE sequence (TR/TE 8/4.2ms, flip 20°). One pre- and 2 post-contrast scans were acquired (S0,S1,S2). Centric phase encoding with a scan time of 5 minutes gave effective post-injection times of 2.5 and 7.5 minutes. A 3D rectangular analysis region including the entire enhancing lesion was defined manually and a background intensity threshold applied to S0 to eliminate fat regions. PE=100*(S1-S0)/S0 was calculated for each voxel and a malignant tissue map, $PE>PE_{thresh}$, was generated for values of PE_{thresh} between 50% and 220%. SER=(S2-S0)/(S1-S0) was used to classify these voxels as persistent-enhancing (blue (B), SER<0.9) or tumor (red (R), SER>0.9). Total volumes for each category were calculated for each value of PE_{thresh}. A Cox proportional hazard model was used to calculate risk ratios per unit change (1cm^3 volumes, 1% percent changes) for disease recurrence.

Results: Figure 1 shows a 2D slice of an early post-contrast volumetric breast image with a color overlay showing the high (red) and low (blue) SER ranges of the tumor for a PE threshold of 70%. Tumor morphology and size varied widely in the study subjects, initial MRI tumor longest diameters ranging 1.1–11.4cm. Figure 2 shows the RFS curve for n=66 subjects. 2-year RFS rate was 74%, median time to recurrence 24 months (n=26), and median RFS time 80 months (n=40). Figure 3 shows the Cox proportional risk ratios (RR) for RFS for total enhancing volume (R+B, SER>0.0) and high SER tumor volume (R, SER>0.9) for baseline (V1), pre-surgery (PS), and percent change from V1 to PS. Only significant ($p<0.05$) points are included. The RR for change in volume from V1 to PS showed a broad peak at PE_{thresh}=70% with high significance (RR=1.017, p~0.01). All single visit volume measures showed a steady increase in RR with threshold, though with decreasing significance at both high and low thresholds. Tumor (Red) volume showed the most significant results with $p<.0001$ for PE_{thresh}=110-130%. Final MRI (pre-surgery) volumes gave significant very high RR at high thresholds (RR=4.5 (R+B) 4.9 (R), p=.006, at PE_{thresh}=200%). However, at this threshold only 26 of 66 scans gave a nonzero volume. Early treatment percent change in volume from V1 to V2 did not give significant risk ratios at any threshold investigated.

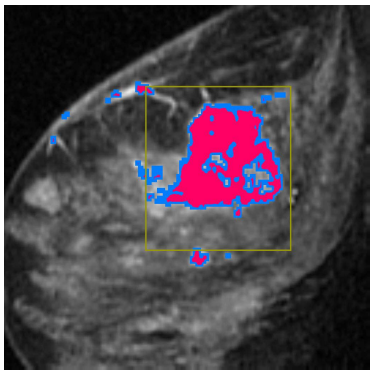

Figure 1. Image with SER color overlay.

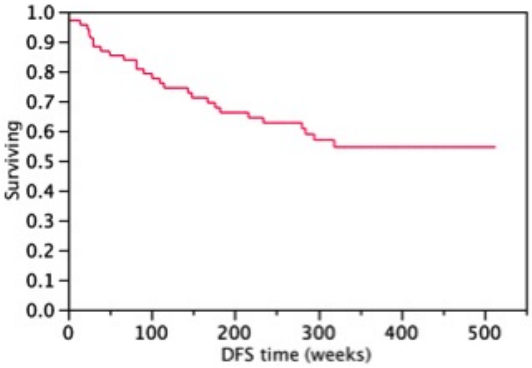

Figure 2. RFS curve for n=66 patients.

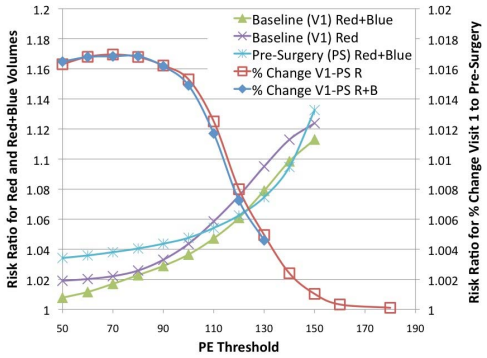

Figure 3. Cox risk ratios v PE_{thresh}.

Discussion: Optimization of the PE cutoff for malignant tissue significantly affects the RFS prediction value for MRI tumor volume measurements for patients undergoing NACT, and the best threshold may depend on the parameter measured. In this pilot study we found a peak in risk ratio for volume change over treatment PE_{thresh}=70%, while single visit volume measures showed monotonically increasing RR with increasing threshold. High RR at high thresholds may indicate an important risk contribution of even small volumes with unusually high PE values and/or small volumes of residual disease post-NACT. Further testing will be performed on a larger cohort of patients with different acquisition timing.

References:

1. Hylton NM et al. *MRI assessment of breast cancer response to neoadjuvant chemotherapy: preliminary findings of the American College of Radiology Imaging Network (ACRIN) trial 6657.* 94th Scientific Assembly and Annual Meeting of the RSNA, November 2008, Chicago, IL
2. Partridge SC et al. *MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence- free survival.* American Journal of Roentgenology AJR 2005; 184:1774–1781.