

Breast Cancer Heterogeneity via Intravoxel Incoherent Motion Histogram Analysis: Correlation with Prognostic Factors

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Introduction: With sufficient specificity and sensitivity, imaging tools can play a key role in the early and accurate detection of cancer as well as in monitoring response to therapy. Despite the widespread use of these technologies, available imaging methods are insufficient in facilitating early detection, precise characterization, and accurate visualization of the heterogeneous tumor microenvironment. Currently, MRI is often used in oncologic imaging to detect morphologic information such as the lesion's shape and margins and enhancement pattern of the tumor. Functional imaging methods such as diffusion MRI with intravoxel incoherent motion (IVIM) analysis provide quantitative biomarkers that correlate to physiological characteristics within the tumor [1-4]. In this study, we calculate advanced diffusion MRI parameters (ADC and IVIM) and statistical metrics from histogram analysis that represent averages, extrema, and heterogeneity (i.e. kurtosis, skewness, standard deviation [5]). We compare and correlate this imaging metric set with clinical tumor markers (i.e. ER, PR, Her2/Neu, and Ki-67) in breast cancer patients. We hypothesize that this analysis may reveal new biomarkers as well as clarifying some of the observed variability in imaging results in the breast cancer population.

Methods: 50 patients with confirmed breast cancer were evaluated in this HIPAA-compliant retrospective study, approved by the local institutional review board (IRB). All patients underwent a standard bilateral MRI breast examination using contrast enhancement along with diffusion-weighted imaging (DWI) in a full body Siemens 3T MRI scanner using a 7-element breast coil array (Invivo Corp). The DWI protocol consisted of a twice-refocused, bipolar gradient single-shot turbo-spin echo (TSE) sequence (TR/TE = 2000/103 ms, 108 x 128 matrix, 18 axial slices, 2.7 x 2.7 x 4 mm voxel, single direction) with b values of 0, 30, 70, 100, 150, 200, 300, 400, 500, 800 s/mm². Analyses for IVIM parameters (tissue diffusivity D_t , pseudodiffusivity D_p , perfusion fraction f_p) were derived from custom data analysis (Igor Pro 6, Wavemetrics). ROIs were drawn around the outer tumor border limiting IVIM analysis to the tumor region. Monoexponential analysis was performed to generate ADC maps of the entire lesion. Segmented biexponential IVIM analysis was performed to estimate D_t , f_p , and D_p with two methods: (1) for the whole lesion and (2) using a vascular tumor tissue (VTT) mask which excludes necrotic or normal tissue regions and selects voxels that are sufficiently vascular to numerically justify the two-compartment fit via Bayesian information criterion (BIC) [6]. Following histogram generation of each parameter, the following metrics were calculated: average, maximum, minimum, and measures of heterogeneity - kurtosis, skewness, and standard deviation. Biopsy analysis provided percentage expression of molecular prognostic factors PR (progesterone receptor) and ER (estrogen receptor); positive expression was defined as $\geq 10\%$ and for Her2/neu higher than +1 [7]. Statistical t-tests were performed to compare IVIM biomarkers between different hormone receptor groups. Pearson and Spearman correlations were performed between IVIM values and molecular prognostic factors.

Results: In Figure 1, an example of a large locally advanced breast cancer in a patient is shown with diffusion parameter maps (ADC and IVIM metrics), integrated signal decay curves of both lesion and normal tissue, and histograms of the diffusion parameters. In total, 27 different correlations out of a possible 192 (~14%, greater than the 5% corresponding to a null hypothesis) were significant between IVIM parameters and the molecular prognostic factors. Figure 2 summarizes the number of significant ($p < 0.05$) correlations found with the whole lesion analysis as opposed to the VTT analysis between the IVIM parameters and molecular markers. The whole lesion analysis shows more correlations overall compared to when using VTT. Table 1 displays the average significant correlation coefficients R for each category and marker. In total, 16 from heterogeneity parameters and 11 from extremal (maximum and minimum) values. No significant correlations were found with HER2/Neu expression.

Discussion/Conclusion: The IVIM histogram analysis has revealed several interesting trends; some findings in this study are analogous to those in the literature (i.e. ER negatively correlating with D_t [8]), while many other findings, particularly in the vascular parameters, f_p and D_p , warrant further study. Interestingly, ER expression has the most significant correlations with diffusion parameters. Within the IVIM parameter set, the parameter contributing the most significant correlations was f_p , and in general, IVIM parameters showed more findings than ADC alone. Also, among the vascular parameters, f_p and D_p , heterogeneity factors were closely related to the prognostic factors, implying that not only the peak value but the spatial distribution of blood supply is affected by the hormonal profile. Finally, the whole lesion analysis has more significant findings than the VTT analysis; evidently, the focus on purely vascular tissue does not globally increase correlation with prognostic factors. In summary, histogram analysis of ADC and IVIM parameters in breast cancer produce metrics correlating with molecular prognostic factors, which suggests the potential of advanced statistical analysis in producing imaging surrogates for high impact clinical markers.

References: 1. Chandarana, H. *Inv Radiol*, 2012. 47(12). 2. Sigmund, E.E. *MRM* 2011. 65(5). 3. Yoshikawa, M.I. *Rad Med*, 2008. 26(4). 4. Sinha, S. *JMRI*, 2002. 15(6). 5. Chandarana H., *Radiol*, 2012; 265 (3):790-798. 6. Cho, G.Y. *ISMRM 2012 Melbourne* #1296.

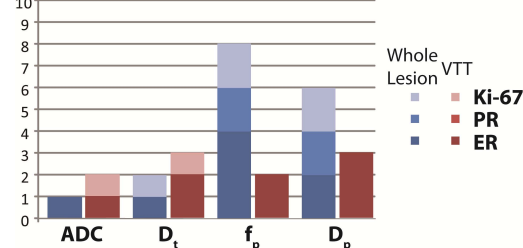


Figure 2. Number of significant correlations between diffusion parameters and molecular markers using whole lesion and VTT analysis.

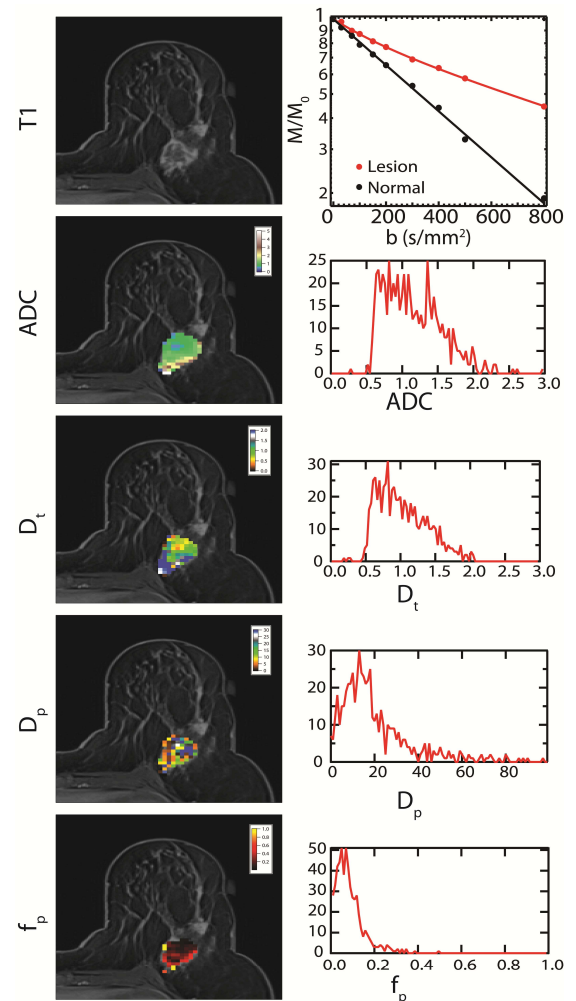


Figure 1. Left: Contrast-enhanced MRI with overlaid IVIM parametric maps in a patient with invasive ductal carcinoma. Right: IVIM parameter full lesion histograms.

Table 1. Average significant correlation coefficients (R) between prognostic factors and IVIM parameters in extrema and heterogeneity parameters for whole lesion voxelwise analysis. Note blank squares indicate no significant correlations.

Marker	Extrema				Heterogeneity			
	Parameters	ADC	D_t	f_p	D_p	ADC	D_t	f_p
Ki-67			0.33					0.41
PR								0.33
ER		0.44	0.41	0.32			0.53	0.42

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