Evaluation of Voxel Based Analysis of Intravoxel Incoherent Motion (IVIM) Parameters in Breast Cancer Patients.

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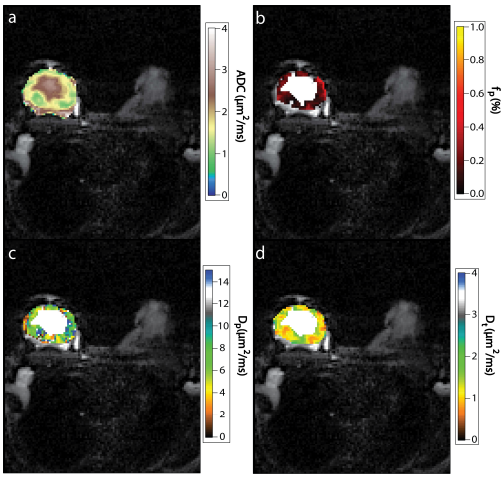

Figure 1. Parametric maps of diffusion biomarkers in a breast cancer patient (IDC) (a) Apparent diffusion coefficient - ADC, (b) perfusion fraction - f_p, (c) pseudodiffusivity - D_p, and (d) tissue diffusivity - D_t. ADC map shows entire lesion, while the others are limited to the VTT region identified in the voxelwise analysis, which excludes the central necrotic region.

Introduction: Half of all men and a third of all women in the US will develop cancer during their lifetimes [1]; as a result, there is an increasing need for accurate noninvasive methods to diagnose, monitor, and guide cancer treatment throughout the body. Diffusion-weighted imaging (DWI) can play an important diagnostic role through its sensitivity to both vascular and cellular components of tumors by the measurement of intravoxel incoherent motion (IVIM) [2-4]. Furthermore, data processing algorithms for IVIM analysis can be optimized by filtered voxelwise analysis of the IVIM biomarker parametric maps. This type of textural analysis has been shown to benefit cancer imaging schemes [5-8]. A voxel-wise IVIM analysis allows the delineation of viable tumor tissue within a typically heterogeneous texture of cellularity, necrosis, and normal tissue [7], improving lesion quantification. In this study, we used highly sampled DWI data to perform voxel based analysis on biexponential IVIM parameters in a cohort of breast cancer patients in a 3T clinical scanner. The extracted biomarkers of tissue diffusivity (D_t), perfusion fraction (f_p), and pseudodiffusivity (D_p) were then compared to biomarkers from an integrated region of interest (ROI) based IVIM analysis as well as with various breast cancer prognostic factors.

Method: 31 patients with confirmed lesions were scanned in a full body Siemens 3T MRI scanner using a 7-channel breast coil in a HIPAA compliant study approved by the local institutional review board (IRB). Patients underwent a standard bilateral MRI breast examination using contrast enhancement along with diffusion-weighted imaging (DWI). DWI protocol used 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/mm^2. Parametric maps and voxel-based analysis for IVIM parameters were derived from custom data analysis (Igor Pro 6, Wavemetrics). ROIs were drawn around the outer tumor border limiting the parametric map 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 in all voxels. The residuals of the monoexponential and biexponential fits were used to calculate Bayesian information criterion (BIC) values [9]; the fit with the lower BIC value is validated for that voxel. A viable tumor tissue (VTT) mask was then generated from all voxels with (a) lower biexponential BIC and (b) ADC < 2 μm^2/ms to exclude necrotic or normal tissue regions. Means of the D_t, f_p, and D_p maps within the VTT mask were then calculated from first moments of histograms of the contained voxels, within the following ranges ($1<f_p<100\%$, $0.1<D_p<30$ μm^2/ms, $0.01<D_t<2$ μm^2/ms). DWI signal intensity decays derived from whole lesion ROIs were used to calculate ROI IVIM biomarkers (f_p, D_p, and D_t) [2-3]. Other clinical data included ultrasound guided fine-needle aspiration (FNA) biopsy for initial diagnosis and/or MRI guided core biopsy for pathological analysis. Biopsy analysis provided percentage expression of molecular prognostic factors PR (progesterone receptor) and ER (estrogen receptor); positive expression was defined as ≥10% and for Her2/neu higher than +1 [10]. Statistical t-tests were performed to compare IVIM biomarkers versus different tumor histological subtypes or different hormone receptor groups. Pearson correlations were performed between IVIM values and various prognostic factors and tumor types.

Table 1	ADC (μm^2/ms)	D_t (μm^2/ms)	f_p (%)	D_p (μm^2/ms)
ROI based	1.329 (±0.122)*	1.126 (±0.108)	10.496 (±1.463)*	15.055 (±3.372)*
Voxel based	1.211 (±0.121)	1.082 (±0.102)	21.839 (±2.388)	6.297 (±0.472)

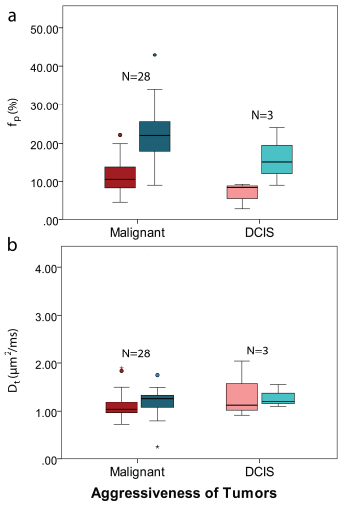

Figure 2. Comparison of ROI based analysis (red) vs voxel based analysis (blue) (a) f_p vs tumor aggressiveness (b) D_t vs. tumor aggressiveness.

Results: Fig. 1 shows the different parametric maps of IVIM biomarkers. In Table 1 and Fig. 2, IVIM and ADC values are compared for different lesion subtypes. Overall, ADC, D_t, and D_p values decreased while f_p increased using the voxel-based technique in comparison to the ROI based analysis. In Table 1, all differences were found significant except D_t with confidence intervals in parentheses. Malignant tumors consisted of those with adenocarcinoma (N=1), invasive lobular carcinoma (N=3), invasive ductal carcinoma (IDC) (N=17), and IDC with DCIS (N=7). The malignant tumors were then compared to ductal carcinoma in situ (DCIS) (N=3). Fig. 3 shows a trend towards separation between the molecular prognostic factor groups via f_p. Her2/neu positve (Her2+) (N=2) showed higher f_p values compared to Her2/neu negative (Her2-) (N=22, p=0.095) (Fig. 3a), while hormone receptor positive (HR+) (N=18) cancers showed a lower f_p value compared to hormone receptor negative (HR-) (N=8, p=0.065) (Fig. 3b); however, neither of these group differences were significant.

Discussion/Conclusion: Voxel based analysis of IVIM parametric maps potentially allows improved quantification and correlation with clinical risk predictors of breast cancer. The voxel-based analysis limits IVIM analysis to viable tumor tissue and excludes necrotic tissue. Correspondingly, the average extracted f_p is higher, and D_t lower, than that obtained with integrated ROIs, consistent with more purely sampling of the hypervascular and hypercellular tumor tissue. While the voxel based IVIM biomarkers did not differentiate tumor types or prognostic factors significantly, some promising trends exist for hormone receptor differentiation, consistent with reports that HR+ cancers have higher cellularity and less angiogenic activity while Her2+ cancers are more aggressive and vascular [11-13]. In conclusion, voxel-based IVIM analysis using parametric mapping may help maximize the potential for IVIM MRI as a diagnostic tool in breast cancer; however, a larger study will help to investigate whether these promising trends hold true.

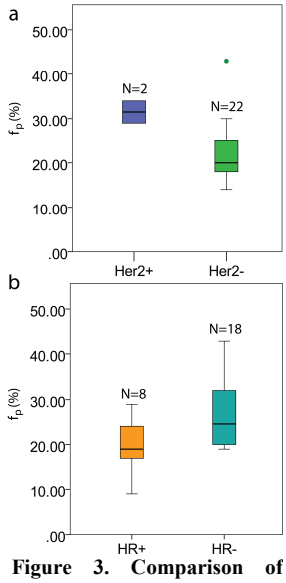

Figure 3. Comparison of prognostic factors with (a) Her2/neu and (b) Hormone receptors.

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