Intravoxel Incoherent Motion MRI for Tumor Subtype Differentiation in Locally Advanced Breast Cancer

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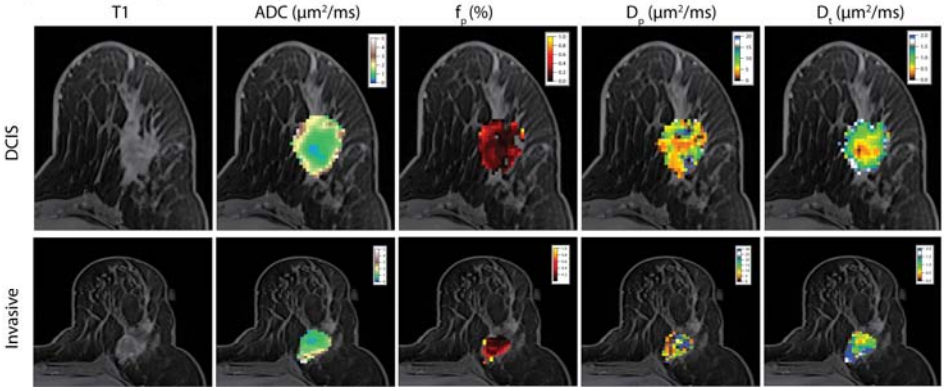
Introduction: Many oncological imaging techniques focus on improving imaging tools through resolution and increased sensitivity to facilitate early detection and accurate localization of the malignant tumor. However, another powerful role for imaging is its potential capability to identify the precise classification of a lesion. Determination of tumor subtypes through imaging can be advantageous in the strategic planning of therapy and limit the need for invasive biopsy procedures. In magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI) can play an important role in this goal and is most commonly employed due to its sensitivity to tumor cell density, a component of aggressiveness. Several studies have shown subtype differentiation via apparent diffusion coefficient (ADC) [1-3]. More generally, both vascular and cellular components of tumors can be sensed through the measurement of intravoxel incoherent motion (IVIM) [4-7]. IVIM parameters can quantify lesion characteristics and present a clearer understanding of the tumor microenvironment [4]. This study tests diagnostic accuracy by comparing patients with different tumor subtypes in terms of IVIM parameters. Highly sampled DWI data is used to perform biexponential IVIM analysis in a cohort of breast cancer patients in a 3T clinical scanner. The extracted biomarkers of apparent diffusion coefficient (ADC), tissue diffusivity (D_t), perfusion fraction (f_p), and pseudodiffusivity (D_p) are then compared between breast cancer histological subtypes.

Figure 1. IVIM parameter maps of two different breast cancer



Methods: This HIPAA compliant, IRB-approved retrospective study evaluated 62 patients (50 confirmed cancer diagnosis - 31 invasive (invasive ductal carcinoma - IDC or invasive lobular carcinoma - ILC) tumors, 12 mixed tumors, and 7 ductal carcinoma in situ (DCIS); along with 12 benign lesions) in a full body Siemens 3T MRI scanner using a 7-ch breast coil (Invivo Corp). 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. Analyses for IVIM parameters were derived from custom data analysis (Igor Pro 6, Wavemetrics). ROIs were drawn around the outer tumor border limiting IVIM analysis within the tumor region. Monoexponential analysis was performed to generate ADC maps. Similar to a previous study [8], segmented biexponential IVIM analysis was performed to estimate D_t, f_p, and D_p. Three types of ROI sampling were performed: (1) integrated single slice signal analysis, (2) integrated whole lesion signal analysis, and (3) whole lesion voxelwise analysis. Single slice analysis used the tumor slice with the largest cross-sectional area, while whole lesion analysis included all slices. Integrated signal analysis derived one set of signal intensities from the lesion for IVIM fitting, while voxelwise analysis determined the average of all voxel fits. Statistical analysis (SPSS) included t-tests to compare IVIM biomarkers versus different tumor histological subtypes and ROC curves to obtain area under curve (AUC) values for only the malignant versus benign comparisons.

Results: Figure 1 shows two patients with different tumors and the corresponding IVIM parameter maps. The mean values of the ADC and IVIM parameters are shown between malignant and benign patient groups (Table 1). For all three methods of analysis, significant differences ($p < 0.05$) were seen between the malignant and benign lesions when comparing ADC and D_t values. ADC and D_t values were much lower in malignant lesions for all three analysis methods. In addition, f_p also was significantly different ($p = 0.03$) between the two groups for the integrated single slice analysis with f_p being much higher in the malignant group. ADC and D_t values were also overall higher in DCIS patients versus the invasive carcinomas. When comparing between tumor subtype using the whole lesion voxelwise analysis, ADC ($p = 0.017$) and D_t ($p = 0.025$) once again differentiated between the invasive lesions and DCIS. D_p also differentiated between different malignant lesions (Invasive, Mixed, and DCIS). Significant D_p differences were seen between the Mixed subtype group and DCIS ($p=0.008$) as well as between Mixed and Invasive ($p = 0.007$).

Discussion/Conclusions: Diffusion MRI with improved quantification through IVIM shows significant differences when comparing benign with malignant lesions and between different tumor subtypes. Invasive breast cancers (IDC and ILC subtypes) displayed lower ADC and D_t. This is expected as these cancers are more aggressive cancers with generally higher cell density, to which ADC and D_t are inversely sensitive [9]. Furthermore, pseudodiffusivity - D_p shows promise as a biomarker as it can separate out the heterogenous mixed tumor type which contains both DCIS and invasive cancer cells, apparently on the basis of differences in vascular flow rates in the two entities. Discerning the mixed type from the other two subtypes can be confounded by its heterogeneous makeup; therefore, the less specific ADC is suboptimal. Using single slice analysis also adds value with the perfusion fraction (f_p) parameter's distinction between malignant and benign groups. Given the typically heterogeneous lesion characteristics on imaging, the focal single slice analysis of the most aggressive regions is evidently key to differentiating subtypes' vascularity. While single slice analysis shows significant malignant/benign differentiation via both D_t and f_p, the whole lesion voxelwise analysis shows slightly better differentiation of types within the malignant class. Given the dependence of diagnostic performance on sampling method, we expect incorporating heterogeneity metrics to increase the efficacy of IVIM in breast cancer characterization. In summary, these results show the potential for IVIM MRI as a diagnostic tool in breast cancer and motivate a larger study to corroborate these findings.

Table 1. Mean values between malignant and benign patient groups using whole lesion voxelwise analysis. *indicates significant differences between malignant and benign groups.

Method	Integrated Single Slice			Integrated Whole Lesion			Whole Lesion Voxelwise		
Type	Malignant	Benign	AUC	Malignant	Benign	AUC	Malignant	Benign	AUC
ADC	1.410±0.542*	1.919±0.385	0.85	1.529±0.601*	2.024±0.521	0.79	1.496±0.500*	1.934±0.386	0.76
D_t	1.308±0.528*	1.972±0.411	0.85	1.407±0.623*	1.930±0.611	0.78	1.371±0.496*	1.840±0.340	0.80
F_p	14.23±6.77*	6.85±8.97	0.81	8.23±4.93	7.15±4.29	0.62	11.17±5.25	11.26±6.39	0.55
D_p	8.96±3.18	20.78±23.28	0.54	18.56±13.43	25.64±19.69	0.58	18.38±6.46	22.12±11.98	0.59

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