

# DIFFUSION MRI OF MALIGNANT BREAST LESIONS USING MULTIPLE B-VALUES: MONOEXPONENTIAL AND BIEXPONENTIAL APPROACHES

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## INTRODUCTION

Diffusion-weighted imaging (DWI) characterizes the random microscopic motion of molecules and enables assessment of tissue microstructure without the use of contrast agents<sup>1</sup>. Malignant breast lesions exhibit a higher cellular density and hence lower diffusivity when compared to benign lesions and normal breast parenchyma<sup>2,3</sup>. This technique has been widely used to characterize malignant and benign breast lesions<sup>4,7</sup>; however, most studies only involve implementation of monoexponential model which assumes free and unrestricted water diffusion. While perfusion can contribute significantly to the diffusion measurements because of the incoherent motion of blood in pseudorandom capillary network at macroscopic level, intravoxel incoherent motion (IVIM) analysis utilizing biexponential model was developed to quantify the diffusion and perfusion effects separately<sup>8,9</sup>. Recently, this IVIM approach has been applied to investigate the clinical significance of the derived parameters in detecting various types of tumors<sup>10-14</sup>. In this study, we aim to compare the conventional monoexponential and IVIM biexponential approaches in detecting malignant breast lesions at 3 T.

## METHODS

**Subjects and Lesions:** This study was conducted with the approval of the institutional review board and with informed consent. Twenty-two female patients (age: mean = 41.7 years; range = 26 - 56 years) with 24 known biopsy-proven malignant lesions were retrospectively evaluated. **MRI:** All MRI examinations were performed on a 3 T Siemens MRI scanner (MAGNETOM Tim Trio; Siemens Medical Solutions, Erlangen, Germany) using a dedicated 4-channel phased array coil (In Vivo Devices, Pewaukee, Wis). High resolution anatomical  $T_1$ - and  $T_2$ -weighted images were acquired. The DW images were acquired using single-shot SE-EPI with 8 b-values (0, 50, 100, 150, 200, 400, 600, 1000 s/mm<sup>2</sup>) and single diffusion gradient direction, TR/TE = 5800/102 ms, acquisition matrix = 192 × 192, spatial resolution = 1.82 × 1.82 × 3 mm<sup>3</sup>, NEX = 4, parallel imaging technique using acceleration factor = 2 and total scan time of 3'25". Dynamic contrast-enhanced MRI (DCE-MRI) was then performed to confirm the localization of the malignant lesions. **Data Analysis:** A region-of-interest (ROI) was defined to encompass the breast malignant lesions. Care was taken to avoid adjacent normal tissue or cystic components. The same ROI was then used for apparent diffusion coefficient (ADC), true diffusion coefficient ( $D_{true}$ ), blood pseudodiffusion coefficient ( $D_{pseudo}$ ) and perfusion fraction ( $P_{fraction}$ ) measurements. Similarly, ROI with same size was also placed over normal fibroglandular tissue for ADC and IVIM measurements. ADC value was calculated over the ROI with a least-square nonlinear monoexponential fitting. To examine the individual contributions of molecular water diffusion and blood microcirculation to the apparent diffusion changes,  $D_{true}$ ,  $D_{pseudo}$  and  $P_{fraction}$  were estimated using a least-square nonlinear fitting in Matlab by fitting the DW signal decay in the ROI to the IVIM bi-compartmental model as follows:  $SI / SI_0 = (1 - P_{fraction}) \times \exp(-b D_{true}) + P_{fraction} \times \exp(-b D_{pseudo})$ . Two-tailed Wilcoxon matched pairs test was employed to compare the ADC,  $D_{true}$ ,  $D_{pseudo}$  and  $P_{fraction}$  measurements between breast carcinomas and normal tissues, with  $p < 0.05$  considered as statistically significant. The diagnostic performance of all parameters was evaluated with Receiver Operating Characteristic (ROC) analysis.

## RESULTS AND DISCUSSIONS

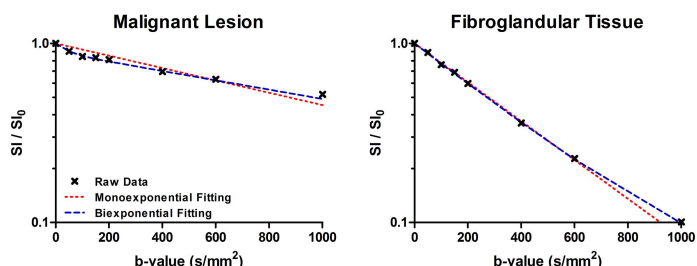
Fig. 1 illustrates the decay of normalized DW signals typically observed in the malignant breast lesion and normal fibroglandular tissue ROIs with the multiple b-values acquisition. The blood perfusion manifested the fast pseudodiffusion effect within the small b-value regime. It can be clearly seen that the biexponential model (blue) provided better fitting than the monoexponential model (red) in cancerous tissue. Fig. 2 shows the ADC,  $D_{true}$ ,  $D_{pseudo}$  and  $P_{fraction}$  values of normal fibroglandular tissue and malignant lesions for all patients. ADC and  $D_{true}$  were observed to be significantly lower ( $p < 0.001$ ) in malignant lesions, likely due to the increased cellularity in cancerous tissue. Change in ADC could also be associated with the alterations in vascularity, which has also been suggested in several DWI studies<sup>2,15</sup>. Significant decrease ( $p < 0.05$ ) in  $P_{fraction}$  of malignant lesions was observed, likely due to change in tissue perfusion in carcinomas. In both malignant lesions and normal fibroglandular tissue, the ADC from the monoexponential model was significantly higher ( $p < 0.001$ ) than the  $D_{true}$  from the IVIM biexponential model. This is likely due to the inclusion of the large-scale intravoxel movement in the calculation of ADC. The ADC and  $D_{true}$  threshold values for breast carcinomas were determined as  $1.45 \times 10^{-3}$  mm<sup>2</sup>/s (sensitivity / specificity / accuracy = 95.8 / 83.3 / 89.6%) and  $0.90 \times 10^{-3}$  mm<sup>2</sup>/s (sensitivity / specificity / accuracy = 91.7 / 83.3 / 87.5%) respectively, suggesting both diffusion parameters may serve as sensitive markers in detecting breast carcinomas. Note that  $D_{pseudo}$  and  $P_{fraction}$  have large associated standard deviations within the sampling patients, possibly inferring physiologically based variability. Their clinical utility may therefore be limited, and exclusion of such highly variable perfusion component from diffusion measurements may be essential in enhancing its clinical utility for better patient management. Nevertheless, IVIM quantitation can be affected by SNR, choice of b-values used and fitting algorithms<sup>16-19</sup>, technical optimizations and studies of a larger patient cohort may provide insights for future clinical applications.

## CONCLUSIONS

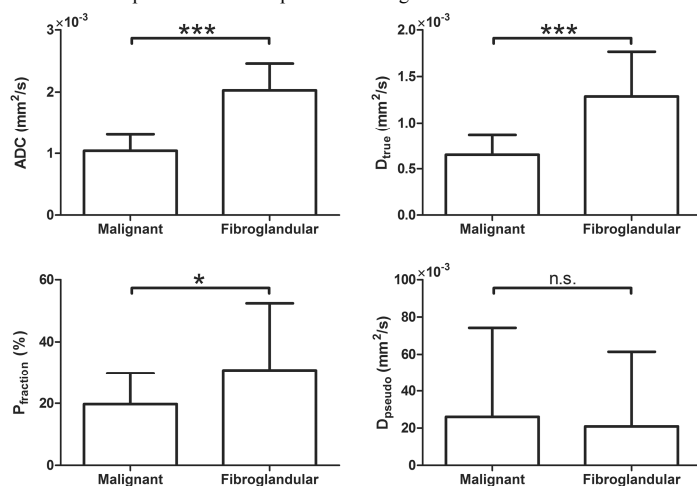
In this study, the results showed that both molecular water diffusion and blood microcirculation contributed to the alteration in apparent diffusion changes observed in malignant breast lesions. ADC from monoexponential model and  $D_{true}$  from the IVIM biexponential model showed comparable diagnostic performance in detecting breast carcinomas. With the capability to quantify the diffusion and perfusion effects separately, IVIM analysis may be valuable for characterizing in malignant breast lesions *in vivo* non-invasively without the use of contrast agents.

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**FIG. 1.** Normalized diffusion-weighted (DW) signal versus b-value in the malignant breast lesion and normal fibroglandular tissue ROIs with the multiple b-values acquisition. The non-monoexponential decay behavior was demonstrated in malignant lesion. Monoexponential and biexponential fittings are also shown.



**FIG. 2.** ADC,  $D_{true}$ ,  $D_{pseudo}$  and  $P_{fraction}$  values of malignant lesions and normal fibroglandular tissue for all patients. Error bars represent standard deviations. Two-tailed Wilcoxon matched pairs test was performed with \*\*\* for  $p < 0.001$ , \* for  $p < 0.05$  and n.s. for insignificance.