Modelling vasculature and cellular restriction in breast tumours using diffusion MRI

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INTRODUCTION: Breast cancers vary in aggressiveness and there are known molecular markers of recurrence[1], but non-invasive imaging markers would allow longitudinal monitoring of patients and better analysis of the spatial distribution of features that may predict invasion and recurrence. Diffusion MRI is sensitive to microstructure and has diagnostic value in breast cancer. Intravoxel incoherent motion (IVIM) shows an increase in the vascular component in invasive ductal carcinomas relative to other malignant subtypes[2]. Diffusion tensor imaging (DTI) finds moderate anisotropy in healthy fibroglandular tissue which decreases in malignant tumours[3]. A model combining IVIM with kurtosis demonstrated a higher perfusion fraction in malignant compared to benign lesions and normal tissue, as well as lower ADC_0 and higher kurtosis[4], suggesting non-gaussian diffusion in high-b diffusion-weighted images (DWI), which may reflect changes in cell density, size or shape. Vascular, Extracellular and Restricted Diffusion for Cytometry in Tumours (VERDICT) is a 3-compartment model that characterizes the restricted diffusion of intracellular water and has shown success in differentiating colorectal cancer xenografts with different cell morphology[5] and in distinguishing benign from malignant prostate tissue clinically[6]. In this study, we test several versions of VERDICT in breast tumours to determine which model best characterizes the structure of cancerous breast tissue and whether model parameters are in agreement with preliminary histological findings.

METHODS: Three patients with 5 breast tumours were imaged on a 3 T Trio (Siemens Healthcare, Erlangen) using a 7-channel InVivo breast coil for receive in compliance with Local Research Ethics Committee approval. DWI was acquired with a 2D fat-saturated Twice-Refocused Spin Echo (TRSE) sequence with 11 b-values (0, 50, 100, 150, 200, 450, 600, 600/1000, 1500, 2000 and 2500 s/mm^2) in three directions (TE/TR = .146/15.7 s, 1.41^2 mm^2, 3.5 mm thick; field of view (FOV) 18 x 36 cm^2, 34 slices; 2 averages). DTI used a 2D TRSE sequence with b=800 s/mm^2 and 20 directions (TE/TR = .102/13.4 s, 1.44-1.53^2 mm^2, 3.5 mm thick; FOV 32.8-34.8 x 34-36 cm^2, 34 slices; 1 average). The two-minute post-contrast dynamic contrast-enhanced image (0.9 x 0.9 x 0.9 mm^3, field of view 34 x 34 x 14.4 cm^3) was used to select a region of interest (ROI) for all slices with visible tumour (ranging from 1-4), which was confirmed by a radiologist.

Motion was corrected by non-rigid registration using an algorithm from NiftyReg with cubic spline interpolation. Three tumours were large enough to be segmented into center and rim ROIs using k-means clustering. The models summarized in Table 1 were fitted to the average signal from each ROI using an iterative optimization procedure that accounts for local minima and Rician noise[5]. Model compartments take the shape of a Ball (B) for isotropic free diffusion, Tensor (T) for anisotropic free diffusion, Zeppelin (Z) for cylindrically symmetric tensor, Stick (I) for diffusion restricted to a single direction and Sphere (S) for isotropic diffusion restricted with radius R. Apparent diffusion coefficient (ADC) and IVIM are equivalent to Ball and Ball-Ball, respectively, in this nomenclature. The minimum of 100 fit iterations was selected to calculate the Akaike Information Criterion (AIC; lower values indicate better fit after adjustment for number of fit parameters) [8]. H&E-stained histology was obtained for two patients and compared with fit parameters.

Table 1 Models tested with fit parameters in parentheses and total number of fit parameters in the last column

Model	Vascular	Extracellular	Intracellular	# pars*
ADC	Ball (D_1)			1
IVIM	Ball (f_p, D_p)	Ball (D_1)		2
T	Tensor (D_1, D_2, D_3, $\vec{e_1}$, $\vec{e_2}$)			6
Z	Zeppelin (D_1, D_2, $\vec{e_1}$)			4
BBS	Ball (f_p, D_p)	Ball (D_1)	Sphere (f_{IC}, D_1, R)	4
BIS	Ball (f_p, D_p)	Stick (D_1, $\vec{e_1}$)		6
BZS	Ball (f_p, D_p)	Zeppelin (D_1, D_2, $\vec{e_1}$)		7

*D_p was fixed to 10^{-2} mm^2/s. Intra- and extracellular diffusivities were assumed to be the equal. Eigenvectors are normalized and orthogonal so that $\vec{e_1}$ is characterized by 2 parameters and $\vec{e_2}$ by 1. Volume fractions (f_x) sum to 1

RESULTS AND DISCUSSION: The BBS model best explained the data in the tumour rim (Figs. 1, 2), whereas the addition of a restricted compartment in the tumour center was not better than traditional IVIM (in P1) or ADC (in P2) models, which is in agreement with the low cellularity observed on histology (eg. Fig 3). DTI signal showed some variation with direction and BZS provided a good fit, but was not superior to BBS, suggesting anisotropy in the tumour may be too low to fit reliably. Parameters from the BBS model (Fig. 4) showed a low perfusion fraction (f_p < 0.08) in all regions, consistent with previous IVIM measurements[2,4] and relatively low cell volume fraction (f_{IC}). Low cellularity makes determination of cell size difficult, but the diameter for cases with f_{IC}>0.05 was estimated as 18 $\pm$ 10 µm in agreement with manual measurements of 8.0 $\pm$ 1.8 µm from P2 histology, particularly considering shrinkage during fixation.

Only two diffusion times were used in this study, which may limit the accuracy of model parameters in the restricted compartment. Additionally, the DTI b-value of 800 s/mm^2 biases determination of anisotropy toward the extracellular compartment. The model also assumes negligible exchange of water between the compartments. Nevertheless, the BBS VERDICT model appears to provide measurements of vascular, intracellular and extracellular volume fractions that are in agreement with histology (cellularity in tumour center vs rim and cell radius). Future work will finalize a VERDICT model for use in breast and validate against histology in a larger number of patients.

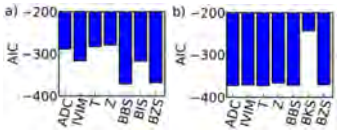

Figure 1 AIC in the tumour (a) rim for patient P1 and (b) center for P2

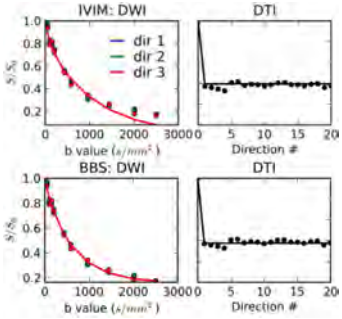

Figure 2 Fits to the IVIM and BBS models for the tumour rim of of P1

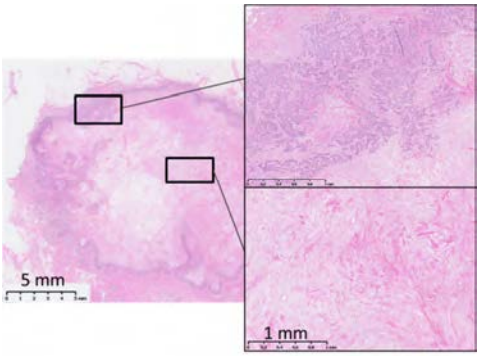

Figure 3 H&E (P2) showed low cellularity in tumour center and higher in tumour rim

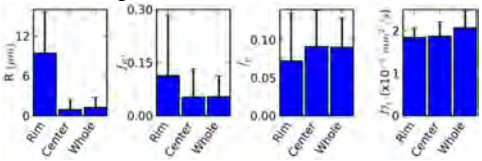

Figure 4 Summary of BBS model parameters (f_{IC}, f_p, tissue diffusion coefficient D_1 are the mean over all patients; R mean of slices with f_{IC} > 0.05)

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