Multi-Component Apparent Diffusion Coefficients in the Rabbit VX2 Tumor Model

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Introduction:

Diffusion-weighted magnetic resonance imaging (DW-MRI) techniques permit quantitative *in vivo* measurement of local water diffusion characteristics within tissues. Multiple studies have demonstrated using DW-MRI to detect early changes in tumor tissue diffusion properties predictive of therapy response [1, 2]. However, most of these studies assumed mono-exponential decay characteristics primarily sensitive to high-mobility extracellular water populations (ADC increases corresponded to therapy response). Recent studies in murine breast cancer models and clinical brain metastases demonstrated bi-exponential diffusion decay properties within tumors [3, 4]. It is hypothesized that these more complex water diffusion characteristics may result from intra- and extra- compartmentalization, water exchange between compartments, or restricted diffusion. DW-MRI over a wider range of *b*-values permits derivation of bi-exponential two-compartment diffusion components and interrogation of both low-mobility (intra-cellular or bound water molecules) and high-mobility (extra-cellular) water populations. For brain metastases, increased parameterization of tissue diffusion properties using the multi-component model permitted improved sensitivity for detecting therapy response. In this study we performed conventional and high *b*-value diffusion weighted imaging in the VX2 rabbit tumor model commonly used to evaluate liver tumor therapies. The purpose of this study was to determine the feasibility of deriving bi-exponential diffusion characteristics in the VX2 tumor model.

Methods:

In this ACUC-approved study, we implanted VX2 carcinoma cells at multiple locations within the hind limbs of 4 New Zealand white rabbits. Rabbits were followed for 2-4 weeks allowing for tumor growth prior to imaging. We subsequently performed MRI using a Magnetom Sonata 1.5T clinical MR scanner (Siemens Medical Solutions, Erlangen, Germany). Rabbits were imaged in the supine position using a one-channel head coil. For each tumor within each rabbit, seventeen diffusion-weighted images over an extended range of b-values (0 to 3,500 s/mm^2) were acquired using a single-shot spin-echo echo-planar imaging (SS-SE-EPI) sequence with imaging parameters: TR/TE = 4000/100ms, 4mm slice thickness, 1.5 kHz/pixel BW, non-selective fat saturation, twice refocused spin-echo diffusion weighting, 2.1x1.3 cm^2 FOV, 128x64 matrix (1.6x1.6x4.0 mm^3 voxel size), 7 averages. First, assuming a simple mono-exponential decay model, conventional ADC values (D_{conv}) were derived from the b=100 and b=1000 s/mm^2 DW images using the following equation: $I/I_o = exp[-bD_{conv}]$. Next, a mono-exponential fit to intensities across all DW images with b ≥ 100 s/mm^2 was performed to derive the mono-exponential ADC value (D_{mono}). Finally, again using all DW images with b ≥ 100 s/mm^2, we derived the bi-exponential fit parameters for the two-population model [5]: $I/I_o = V_{high}exp[-bD_{high}] + V_{low}exp[-bD_{low}]$ with D_{high}, D_{low} and V_{high}, V_{low} the respective ADC and volume fractions for two water populations. The non-linear Levenberg-Marquardt algorithm was employed to fit the bi-exponential function using Matlab software (The Math Works Inc., Natick, MA).

Results:

We imaged a total of ten VX2 hind limb tumors (N=10). An example region of interest (ROI) for mean ADC measurement in two adjacent hind limb tumors is shown in Fig. 1. For each tumor, the r^2 value for the bi-exponential fit was greater than the r^2 value for the mono-exponential fit. The RMSE for each bi-exponential fit was lower than the RMSE for each corresponding mono-exponential fit. Conventional and mono-exponential ADC values, and two-compartment model (bi-exponential) high- and low-mobility ADC values and volume fraction ratios for each tumor are shown in Table 1. Upon subsequent necropsy, tumor 10 was shown to contain primarily necrotic tissue.

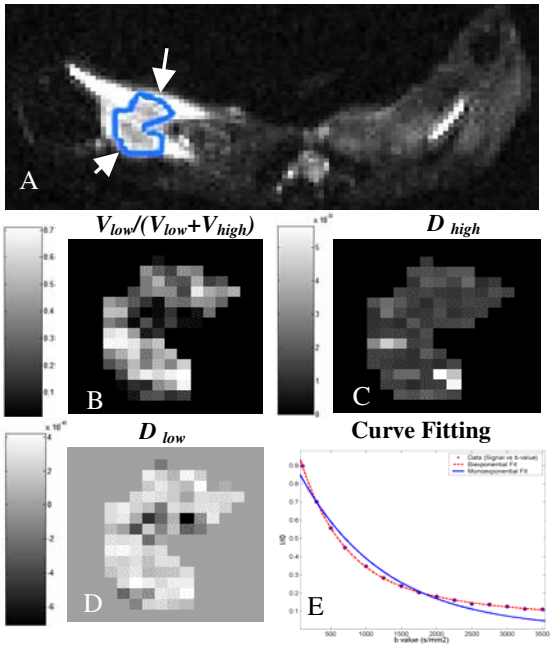

Figure 1. Parametric diffusion maps for low-mobility fraction ratio $V_{low}/(V_{high}+V_{low})$ (B), D_{high} (C) and D_{low} (D) for the two adjacent VX2 tumors outlined in (A, arrows). Bi-exponential (dashed) and mono-exponential (solid) fitting curves of signal decay for a single tumor (E). Notice that the bi-exponential curve clearly provides a better fit to the measured data (solid points).

Table 1. Bi-exponential Two-Compartment, Mono-exponential, and Conventional Diffusion Model Fit Parameters

Tumor	$V_{low}/(V_{low}+V_{high})$	D_{high} (μm^2/ms)	D_{low} (μm^2/ms)	D_{conv} (μm^2/ms)	D_{mono} (μm^2/ms)
1	0.25	1.66	0.25	1.1	0.84
2	0.42	1.23	0.19	0.6	0.47
3	0.23	1.07	0.079	0.7	0.55
4	0.38	1.7	0.28	0.9	0.65
5	0.11	1.8	0.064	1.4	1.15
6	0.17	2.24	0.21	1.5	1.25
7	0.11	2.07	0.1	1.5	1.29
8	0.37	2.79	0.49	1.4	1.05
9	0.12	1.97	0.027	1.4	1.26
10	0.01	2.37	~0	2.4	2.24

Conclusion:

Based upon our preliminary results, rabbit VX2 tumors clearly demonstrate bi-exponential diffusion decay characteristics. These results suggest that the increased parameterization of tissue diffusion properties provided by the multi-component model may permit improved sensitivity for the assessment of response in studies using the rabbit VX2 model for the development of cancer therapies. Further studies are necessary to investigate clinical translation of these techniques as well as to provide direct correlation of bi-exponential tumor diffusion parameters to pathology.

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