Correlation of Quantitative Tissue Characteristics Derived from DCE-MRI, DW-MRI and Histology in Murine Tumors

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INTRODUCTION

Apparent diffusion coefficient (*ADC*) maps obtained from DW-MRI have been shown to be a metric of cellularity in tumors[1]. One of the parameters obtained from DCE-MRI analyses is the fraction of extravascular-extracellular space (v_e)[2], so maps of *ADC* and v_e should in principle be directly related to each other because they both depend strongly on cell density. However, previous literature suggests that the relationship between these parameters may be more complex, especially in tumors in response to treatment[3,4]. The goal of this study is to assess the quantitative relationship between these parameters in a mouse tumor model using two treatment regimens, cediranib (AZD2171) which acts as an anti-angiogenic therapy and AZD1480, which inhibits Jak 1/2 receptors to suppress tumor growth[5].

MATERIALS and METHODS

Thirty athymic nude mice were injected with Calu-6 lung cancer cells in the hind limb; once the tumor reached approximately 200 mm^3, the mice were randomly assigned to the following treatment groups: AZD1480 (50 mg/kg, *p.o. q.d.*), cediranib (6 mg/kg *p.o. q.d.*), and vehicle control. All animals were imaged at 9.4T at baseline, day 3 and day 5 post-treatment time points. <u>DCE-MRI.</u> Pre-contrast T_1 maps were obtained using an IR FLASH gradient echo sequence with eight inversion times with $TR\backslash TE\backslash\alpha$= 12100 ms\ 3.44 ms\15° and NEX = 4, FOV = 35 mm^2, and matrix = 128^2 for fifteen 1 mm slices. The dynamic acquisition employed a SPGR sequence with $TR\backslash TE\backslash\alpha$ = 100 ms\2.83 ms\10°, and NEX = 4. A bolus of 0.1 mmol/kg Gd-DTPA was delivered *via* a jugular catheter using an automated syringe pump. A population derived VIF (C_p) was used to fit the tissue signal data (C_t) for the central slice for each mouse at each time point using a standard model[6]. <u>DW-MRI.</u> A gated and navigated PGSE sequence was used with the following parameters: $TR\backslash TE\backslash\alpha$ = 2000 ms\42 s\15˚, acquisition matrix = 128^2, FOV = (35 mm)^2, and NEX = 2 with Δ = 35.00 ms and δ =5.00 ms for b-values of 150.88, 500.2, and 800.22 mm^2/s. The diffusion weighted signal at each *b* (*S(b)*) was fit to the following equation to extract the apparent diffusion coefficient (*ADC*)[7]

$$S(b) = S_0 e^{-ADC \cdot b} \text{ .}$$

Eight baseline data sets were used to examine the spatial correlation between *ADC* and v_e maps; linear regression was performed on single voxel data and the Pearson correlation coefficient was found. Additionally, day 5 imaging data were aligned to histology slices (n = 18 for *ADC* and n = 15 for v_e). The percent of extracellular space (*EC(%)*) was determined using the H&E results by determining the area of stained (purple, orange and white color in Fig **b.**) and subtracting it from the area of the entire slide.
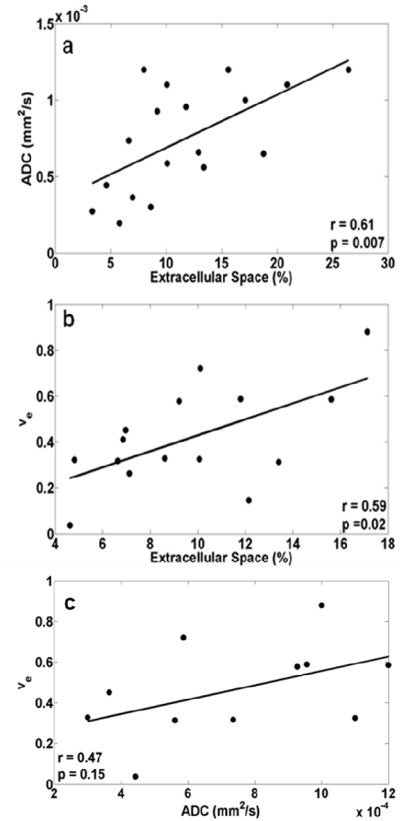
Fig 1. Plots demonstrating the relationship between *ADC* and *EC* (%) (**a**), v_e and *EC* (%) (**b**), and *ADC* and v_e (**c**).
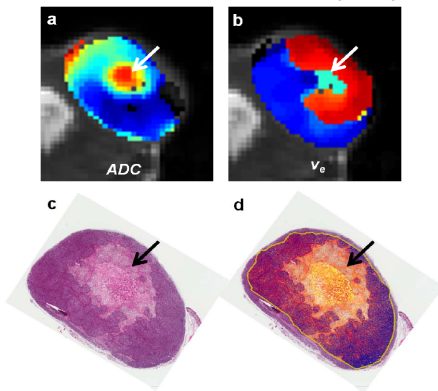
Fig 2. *ADC* (**a**) and v_e (**b**) maps with corresponding histology (**c**) and thresholded histology slice. The arrows indicate a high *EC (%)* area.

RESULTS

No direct spatial relationships were evident from the *ADC* and v_e map data (r = 0.12 ± 0.16). However, a significant positive correlation was found between both *ADC* and *EC(%)* and v_e and *EC(%)*, as shown in **Fig. 1a** and **1b**. Upon plotting *ADC* and v_e against each other from the day 5 data, a positive trend is evident but was not statistically significant (**1c**). Upon closer inspection in **Fig. 2**, both *ADC* and v_e maps correlate with areas of low cell density (arrows) in the H&E data but v_e maps maintain more heterogeneity and overestimation than *ADC* maps.

DISCUSSION

This study shows that both *ADC* and v_e have a statistically significant positive correlation with the amount of extracellular space within the tumor. However, v_e from DCE-MRI is hugely overestimated compared to its histological counterpart. Thus, it seems that while both v_e and *ADC* correlate with cell density, there are other factors that influence these estimates, specifically v_e. The derivation of v_e is based on the indirect method of quantifying the pharmacokinetics of a contrast agent (CA) in tissue, so factors that affect the flow and/or distribution of the CA (*e.g.*, passive diffusion or active delivery of the CA) may inherently confound the v_e measurement. The results of this study suggest that incorporating spatially dependent diffusion into the two compartment model is required to rigorously evaluate the relationship between different imaging parameters[8].

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