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. One of the parameters obtained from DCE-MRI analyses is the fraction of extravascular-extracellular space ($v_e$), 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. 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.

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 mm³, 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. DCE-MRI. Pre-contrast $T_1$ maps were obtained using an IR FLASH gradient echo sequence with eight inversion times with $TR/TE$ of 12100 ms/3.44 ms and $NEX = 4$, $FOV = 35$ mm, and matrix = 128² for fifteen 1 mm slices. The dynamic acquisition employed a SPGR sequence with $TR/TE$ of 100 ms/283 ms 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. DW-MRI. A gated and navigated PGSE sequence was used with the following parameters: $TR/TE/\Delta$ = 2000 ms/42 s/15°, acquisition matrix = 128², $FOV = (35$ mm)², and $NEX = 2$. The diffusion weighted signal at each b-value ($S(b)$) was fit to the following equation to extract the apparent diffusion coefficient (ADC):

\[ S(b) = S_{0}e^{-ADC \cdot b} \]

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 slice.

RESULTS
No direct spatial relationships were evident from the ADC and $v_e$ map data ($r = 0.12 \pm 0.16$). 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.

REFERENCES

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