Distinct effects of the nuclear volume fraction and cell diameter on diffusion contrast in tumors

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Introduction

Restriction spectrum imaging (RSI) utilizes multiple b-values and gradient directions to separate hindered and restricted water signals along a range (or spectrum) of length scales with spherical and cylindrical geometries [1]. Recently, the apparent restricted water signal in spherical (cellular) compartments (termed "RSI cellularity maps") has been demonstrated to provide improved conspicuity and delineation of high-grade brain tumors along with reduced sensitivity to edema compared with traditional ADC [2]. However, the biological origin of the restricted water signal remains poorly understood. One interesting observation is that despite high-grade (WHO III-IV) tumors demonstrating marked cellularity contrast on RSI [2], low-grade (WHO I-II) tumors often fail to demonstrate any restricted signal at all, despite the obvious presence of tumor cells (Fig 1). The goal of this study was to explore the nature of the apparent restricted water signal using Monte Carlo simulations. Specifically, we explore the role of the nuclear volume fraction and cell diameter on diffusion signal contrast using clinically relevant b-values and diffusion times.

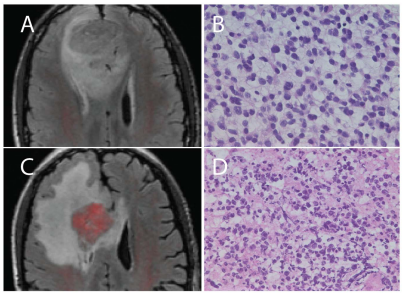

Fig 1. Pre-surgical RSI cellularity maps (red) overlaid on FLAIR along with post-surgical histology for oligoastrocytoma (WHO II, A,B), and lymphoma (C,D).

Materials and Methods

Signal model: For this study, we expand on the restricted isotropic (spherical) signal in RSI (S_{riso}) to include the effects of separable nuclear and cytoplasmic compartments with differential T2 relaxations and intrinsic diffusivities:

$$S_{\text{riso}} = \exp(-AR2 \cdot TE) \cdot \exp(-bADCr); AR2 = f_n R2_n + (1 - f_n) R2_c; f_n = \left(\frac{r_n}{r_c}\right)^3$$

where AR2 is the effective (or "apparent") transverse relaxation rate (1/T2) of the cell, ADCr is the apparent diffusion coefficient for intracellular restricted water, R_{2n} and R_{2c} are the transverse relaxation rates within the nucleus and cytosol, respectively, r_n and r_c are the radii of the nucleus and cell, respectively, and $f_n = (r_n/r_c)^3$ is the nuclear volume fraction, as proportion of the intracellular volume.

Simulation: A simple 3D cell diffusion model was use to simulate intracellular restricted water consisting of separable nuclear and cytoplasmic compartments in exchange (Fig 2). The biological parameters were taken from published experimental results: nuclear membrane permeability (P_{nc}=0.5 μm/ms [3]) nuclear diffusivity (D_n=1.31 μm²/ms [4]), cytoplasmic diffusivity (D_c=0.48 μm²/ms [4]), nuclear transverse relaxation ($T2n=R2n^{-1}$=63.27ms) and cytoplasmic transverse relaxation ($T2c=R2c^{-1}$=23.89ms)[5]. Leakage into the extracellular compartment was considered negligible for this study (P_{ce}=0). The step size of the simulation was 0.001 ms.

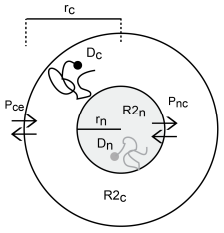

Fig 2. Cell simulation model.

Results and Discussion

The results of the simulation experiments are shown in Fig 3. Our main findings include:

- The AR2 of intracellular restricted water decreases monotonically with increasing nuclear volume fraction (Fig 3A), but does not change with cell diameter (Fig 3B). This relationship is independent of the diffusion time Δ and nucleus to cytoplasm exchange rate (not shown).
- The ADC of intracellular restricted water (ADCr) is relatively insensitive to nuclear volume fraction at clinically relevant diffusion times (Fig 3C), but increases monotonically as a function of cell diameter over a narrow range (Fig 3D).
- In practice, within a clinical setting (long diffusion time, long echo time regime) the main determinant of the apparent restricted water signal magnitude is nuclear volume fraction, while cell diameter plays less of a role. For example, at TE=100ms a more than 10x decrease in signal results from a nuclear volume fraction change from 100% to 0%, while only a 10% reduction in signal going from cell diameter of 6 to 14 μm. The effect of nuclear volume becomes even more pronounced at longer echo times.

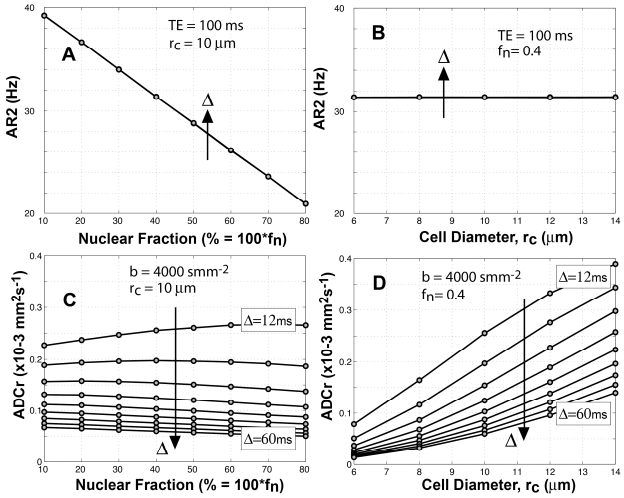

Fig 3. Simulation results. The AR2 and ADCr are plotted as a function of nuclear volume fraction and cell diameter .

Conclusion

The results presented here point to the important role of the nuclear volume fraction on the apparent restricted water signal and may explain in part the lack of RSI signal contrast on low grade tumors with lower nuclear volume fractions compared with high grade tumors. Furthermore, these results suggest that the reduced overall ADC in tumors, as measured with traditional means, may in fact be due to a greater emphasis or weighting on the restricted water fraction for cells with larger nuclei (as a percent of the total cell volume) due to the reduce effective R2 for intracellular water. Conversely, the elevated overall ADC in edema may be caused by a greater weighting on the fast hindered water fraction due to reduced effective R2 for extracellular water. Moreover, these results suggest that combining multi-b-value RSI with multi-echo-time acquisitions may be use to simultaneously estimate the AR2 and ADC of separable hindered and restricted water compartments, which may provide more specific biomarkers for cellular tissue architectures with implications for tumor diagnosis and treatment response monitoring.

References

[1] White et al, HBM 2012. [2] White et al, AJNR *In Press*. [3] Pfeuffer et al, NMR Biom 1998. [4] Grant et al, MRM 2001. [5] Xu et al, MRI 2011.