Relationship Between Apparent Diffusion Coefficient (ADC) and Glioma Cell Density

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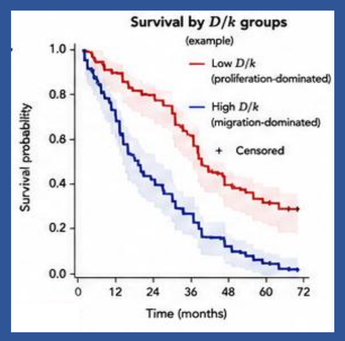
ABSTRACT

Glioma growth and treatment response are strongly influenced by spatial variations in tumor cellularity. Current D/k reaction–diffusion models typically estimate cell density using simplified imaging assumptions, which may not fully capture the underlying tumor biology.



Current D/k models rely on simplified estimates of tumor cell density. MRI-derived estimates of cell density may better represent glioma heterogeneity. Improved cellularity maps could enhance survival prediction and tumor growth modeling.

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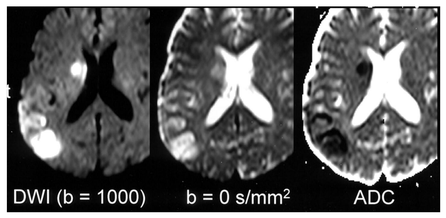
INTRODUCTION

To evaluate the relationship between diffusion MRI-derived ADC and histologically measured glioma cell density using spatially localized biopsy regions.

Diffusion MRI Theory



$$S(b) = S_0 e^{-bADC}$$

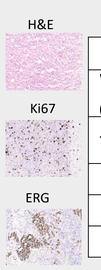
- $S(b)$ is the diffusion weighted signal
- S_0 is the signal without diffusion weighting
- b is the diffusion weighted factor
- ADC is the apparent diffusion coefficient

ADC represents the effective diffusivity of water within tissue under the assumption of Gaussian diffusion behavior at intermediate b-values.

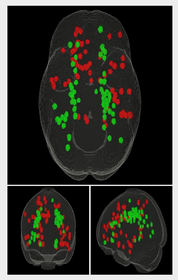
Increased cell density reduces extracellular space and increases membrane barriers, limiting water mobility. This restriction produces steeper signal decay with increasing b-value and results in lower ADC estimates.

DATASET

52 spatially localized biopsies from 23 untreated glioma patients were analyzed, with cell density (nuclei/mm2). To balance tissue representation, 52 contralateral normal-appearing white matter mirror sites were included as virtual biopsies with literature-derived cell density estimates.



Tissue Parameter	Units	Description
World Health Organization (WHO) Grade	N/A	Holistic assessment of malignancy (I-IV) based on tissue features
Tumor Status	N/A	Presence (1) or absence (0) of tumor at a VOI location (Ki67 > 0.2 %, or WHO Grade > 0)
Ki67	% Positive Nuclei	Cellular proliferation marker
ETS-related gene (ERG)	% Positive Area	Vascularity marker
Cell Density (CD)		Number of cellular nuclei per unit area



CELL DENSITY

To evaluate the relationship between diffusion MRI-derived ADC and histologically measured glioma cell density using spatially localized biopsy regions.

$$CD = \left(\frac{T}{V}\right) kN$$

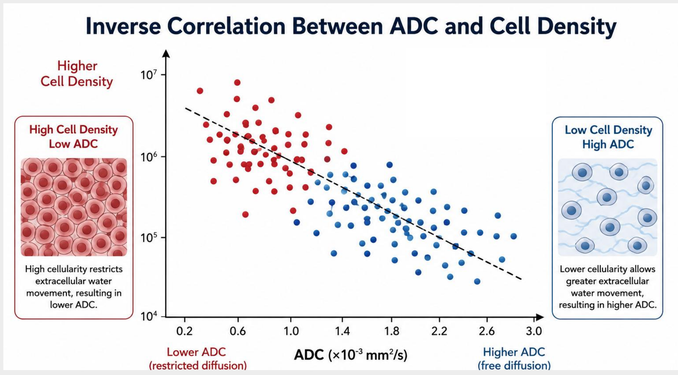
- N is the number of cells
- V is the volume of the voxel
- T is the histology slice thickness
- k is a scaling factor

CELL DENSITY

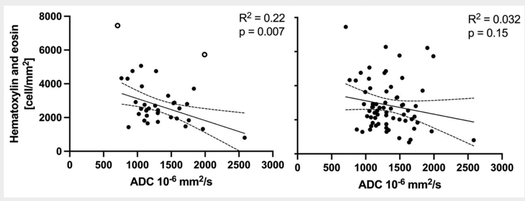
$$N = \left(\frac{\rho V}{V_{avg}}\right)\left(\frac{ADC_w - ADC_{mean}}{ADC_w - ADC_{min}}\right)$$

- ρ is the packing fraction
- V is the volume of the voxel
- V_{avg} is the average volume of a cell
- ADC_w is the ADC value of free water
- ADC_{min} is the minimum ADC, set to zero
- ADC_{mean} is the ADC mean value in our 5 mm spherical VOI

ADC vs CD



Moderate inverse association reported by Nocera, *et al.*[4]



Patient Cohort: 27 patients, 66 image-guided biopsies (13 treatment-naïve, 14 recurrent).

In treatment-naïve gliomas, ADC shows a statistically significant inverse relationship with cellularity.

RESULTS

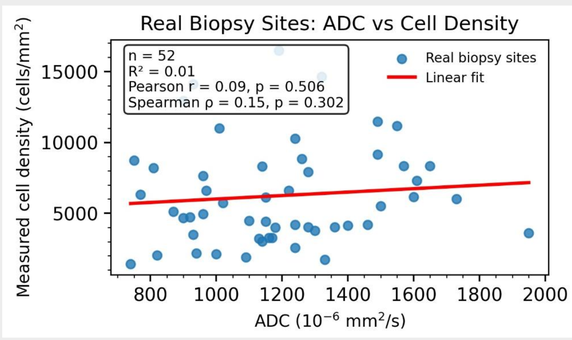


Figure 1: Relationship between ADC and biopsy-derived cell density in treatment-naïve gliomas.

A weak positive trend was observed (slope = 1.211), but the association was not statistically significant (Pearson r = 0.09, p = 0.506; Spearman = 0.15, p = 0.302). The low coefficient of determination (R^2 = 0.01) indicates that ADC explained little of the observed variation in cell density. Unlike Nocera et al., our cohort demonstrated little relationship between ADC and cell density. These findings suggest that ADC alone is insufficient for estimating glioma cellularity and support incorporating additional MRI-derived features into future reaction–diffusion tumor models.

Results

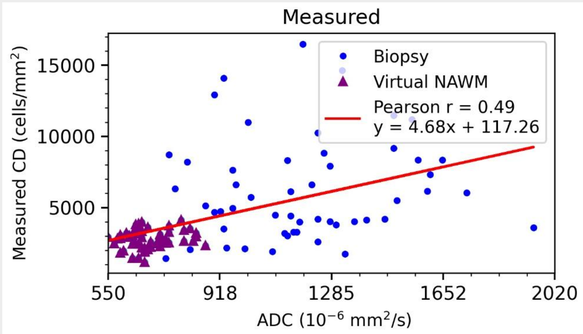


Figure 2: Pretreatment ADC vs cell density at 52 image-guided biopsy sites. Triangles are virtual NAWM and circles are real tumor biopsies.

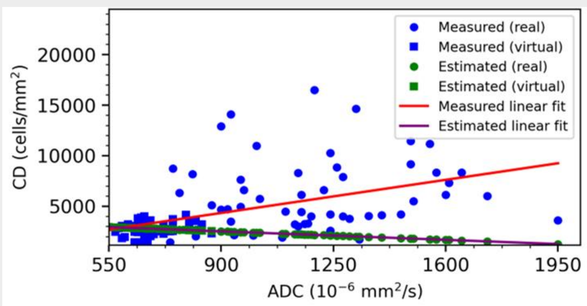


Figure 3: ADC versus measured (blue) and theoretical (green) cell density. Circles denote real tumor biopsies (n = 52) and squares denote virtual NAWM samples. Lines show linear fits.

Contralateral normal-appearing white matter (NAWM) mirror sites were included as virtual biopsy locations. Cell density values were assigned using literature-derived NAWM cellularity estimates. This analysis was performed to explore how inclusion of plausible NAWM values would affect the observed relationship between cell density and ADC.

The theoretical model predicts an inverse relationship between cell density and ADC, corresponding to a slope of -1.72×10^6 cells·s /mm^4. However, when the literature-derived NAWM data were included, the empirical relationship was positive rather than negative, with a slope of $+4.6 \times 10^6$ cells·s /mm^4 (r = 0.48). This finding is inconsistent with the theoretical prediction and suggests that the assumptions underlying the literature-derived NAWM estimates, or the relationship between ADC and cellularity in this dataset, warrant further investigation..

REFERENCES

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