Application of an advanced diffusion-weighted MRI technique to characterize glioma microstructure and relationship to histopathology

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Introduction

Background

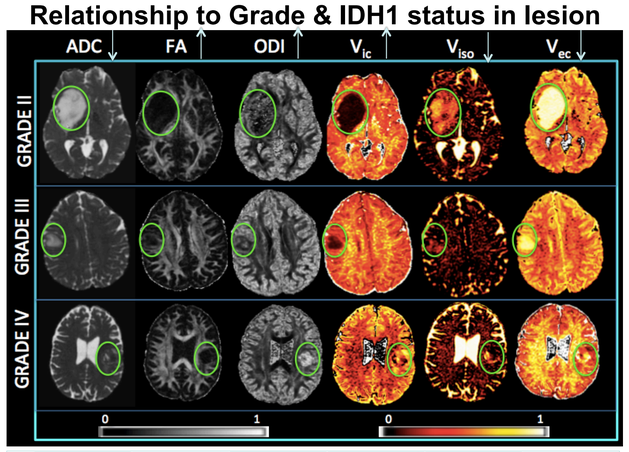
- Diffusion Tensor Imaging (DTI) techniques have shown great potential in evaluating tumor cellularity and response to therapy.
- Although DTI is very sensitive to underlying tissue structure, it is not specific.
- Recent advances in diffusion models such as Neurite orientation dispersion and density imaging (NODDI) that probe underlying tissue microstructure in normal brain[1] have shown potential new contrast within both T2- and contrast enhancing lesions[2].
- NODDI assumes a biophysical model that distinguishes three types of microstructural environments: intra-neurite(V_{ic}), extra-neurite(V_{ec}), and CSF(V_{iso}) compartments expressed in volume fractions as well as an orientation dispersion index (ODI).

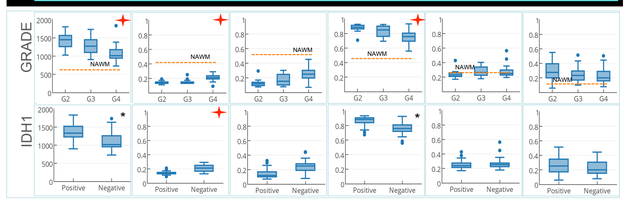
Objective

The goal of this study was to evaluate the relationship between NODDI derived parameters and histopathological features of glioma compared to that of the Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) metrics calculated from DTI.

Results

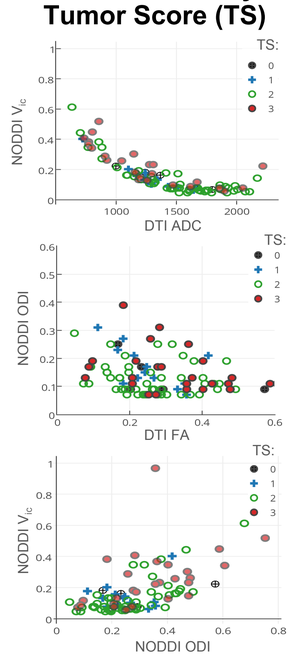
Relationship to Grade & IDH1 status in lesion





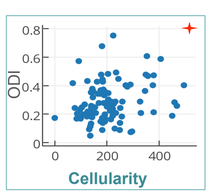
- Median values within non-enhancing lesion

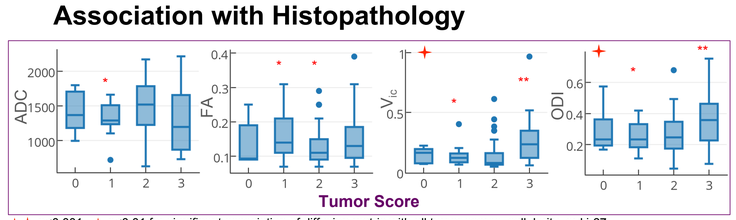
NODDI vs DTI by Tumor Score (TS)



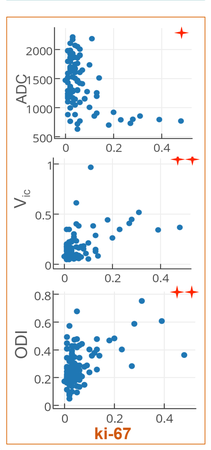
+ p<0.0001, * p<0.001

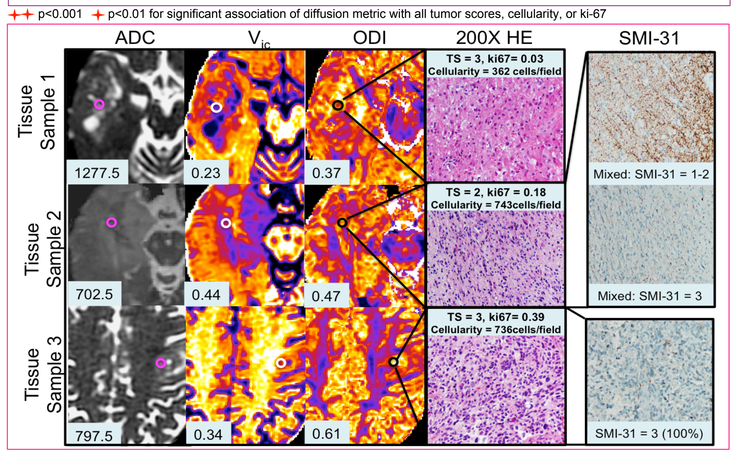
Association with Histopathology





++ p<0.001 + p<0.01 for significant association of diffusion metric with all tumor scores, cellularity, or ki-67





Methods

Patient Population

- Newly-diagnosed astrocytic gliomas, grade 2-4

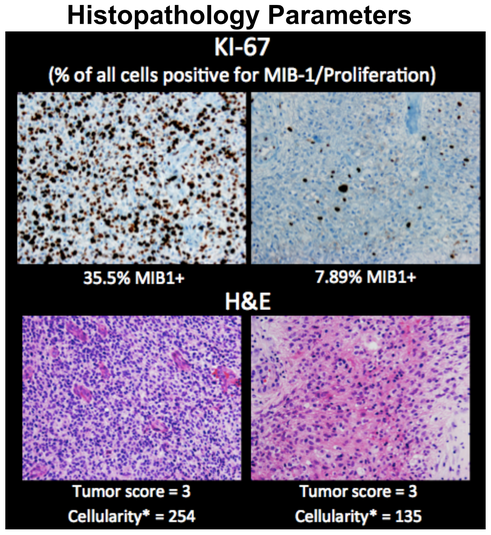
Lesion Data
- 60 patients
- Median Age: 40
- Age Range: 20 –79
- Gender: 39M / 21F

Tissue Data
- 101 tissue samples from 36 patients
- Mean samples/patient: 2.81 (range 1-4)

Grade Classification	Tumor Type	Lesion Data # patients	Tissue Sample Data # patients	Tissue Sample Data # samples
Grade II	Astrocytoma	15	14	40
	Oligo Astrocytoma	5	2	5
Grade III	Astrocytoma	13	9	22
	Oligo Astrocytoma	2	1	4
Grade IV	Glioblastoma	25	11	31
Total		60	36	102

* Oligoastrocytomas with 1p19q intact were grouped with Astrocytomas

Histopathology Parameters



Cellularity : Mean cell number per 200x-field of view
Tumor score:
0 = neuropil without tumor
1 = infiltrating margin
2 = infiltrating tumor cells
3 = high % of tumor cells

Statistical Analyses

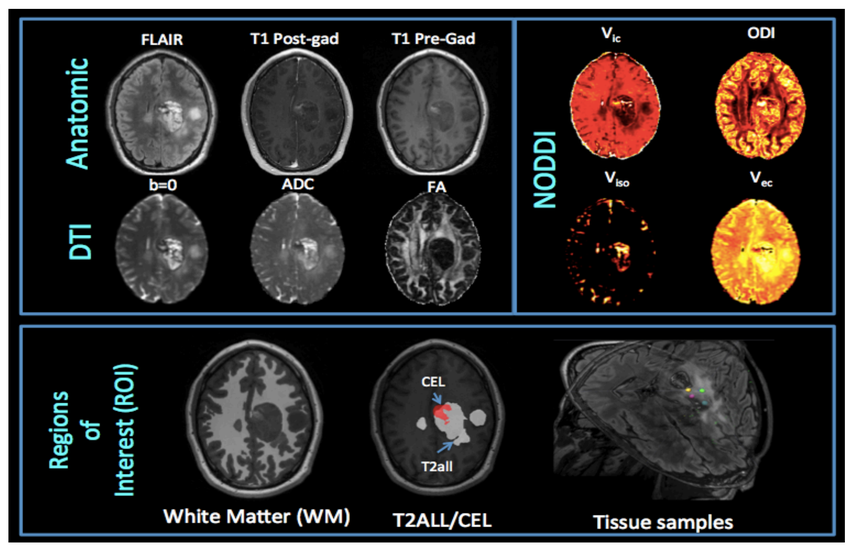
Outcome type	Histopathology variable	Statistical test
Categorical, ordinal	Tumor grade, IDH1 *(lesion level)*	Ordinal logistic regression
Categorical, ordinal	Tumor score *(tissue sample based)*	Generalized Estimating Equations
Continuous	Cellularity, Proliferation (ki-67)	Univariate mixed effects model

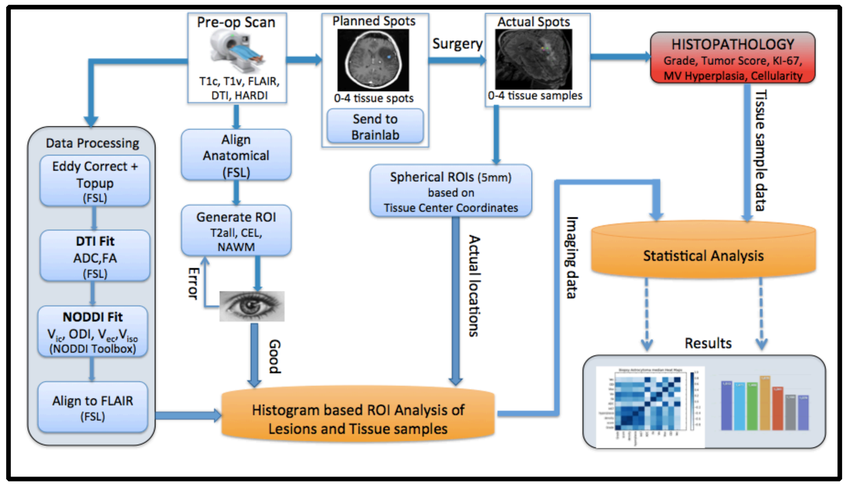
MR Imaging Protocol & Processing

3T GE Scanner (w/8-channel head coil)

Anatomical Imaging: 3D T2-weighted FLAIR, 3D T1-weighted SPGR Pre- & Post-Gad

Diffusion-weighted Imaging: 24 DIR, b=1000; 55 DIR, b=2000; standard SE-EPI sequence ,2×2×2 mm, 4 b0 images, and SENSE w/R=2 & TOPUP to minimize distortion





Summary / Conclusions

Summary of Results

- In all tumor grades, V_{ic} was reduced and V_{ec} elevated compared to NAWM, indicating lower neurite density.
- ADC, FA, V_{ic}, and V_{ec}, were associated with tumor grade and differentiated GBMs from lower grade tumors.
- In both the lesion and individual tissue samples, V_{ic} was correlated with both ADC and ODI.
- Although DTI metrics (ADC & FA) can distinguish low and high tumor scores, only NODDI parameters V_{ic} & ODI were associated with the entire range of tumor scores.
- When limiting the comparison to tumor score 2 and 3, only V_{ic} was significantly associated (p=0.01) with tumor score.
- Although ADC, V_{ic}, and ODI were associated with ki-67, only ODI was associated with cellularity.
- The 3 example tissue samples illustrate how V_{ic} is more specific to tumor score than ADC while ODI values might be a marker of axonal disruption as indicated by a high SMI-31 score of 3 in addition to increased cellularity, TS, and Ki-67 .

Conclusions

- V_{ic} and ADC have distinct variations within CE and NE regions that when combined can offer additional insight into the heterogeneity of tissue microstructure among brain tumors.
- NODDI parameters are sensitive to tumor score and cellularity and can complement the conventional DTI model metrics, even though the NODDI model was not directly derived for tumor.
- Although ADC and NODDI metrics V_{ic} & ODI were significantly associated with brain tumor histopathology, only V_{ic} was associated with tumor score in astrocytomas, suggesting that it may be more specific to malignant tumor microstructure.
- Future studies will aim to elucidate the relationship of these metrics with tumor type, molecular phenotype, and outcome.

References:
1. Zhang, H., et al., NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage, 2012. 61(4): p. 1000-1016.
2. Wen, Q., et al., *Clinically feasible NODDI characterization of glioma using multiband EPI at 7 T.* Neuroimage Clin, 2015. **9**: p. 291-9

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