Comparison of tumor microstructure derived NODDI and DTI metrics to histopathology in different grades of brain tumor

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Introduction

✧ Diffusion of water inside a voxel of brain tissue is
  - ✧ Hindered primarily by cell membrane boundaries
  - ✧ Represents the combined water diffusion in a number of compartments

Alexander et al., Nov 2007

Diffusion tensor imaging (DTI):
  - ✧ Assumes single tensor with Gaussian model in each voxel
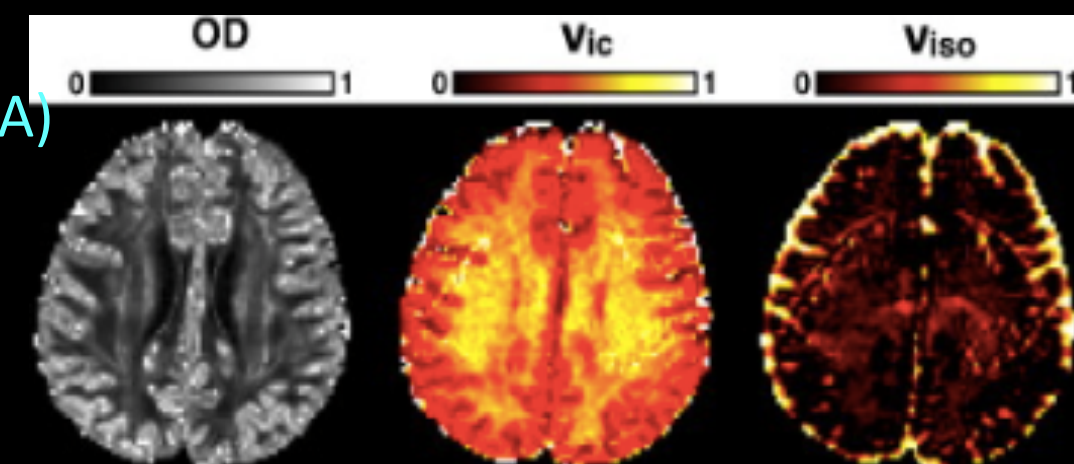 - ✧ Allows data profiling based on white matter tract orientation

T2W (b~0)   MD   FA   Eigenvector
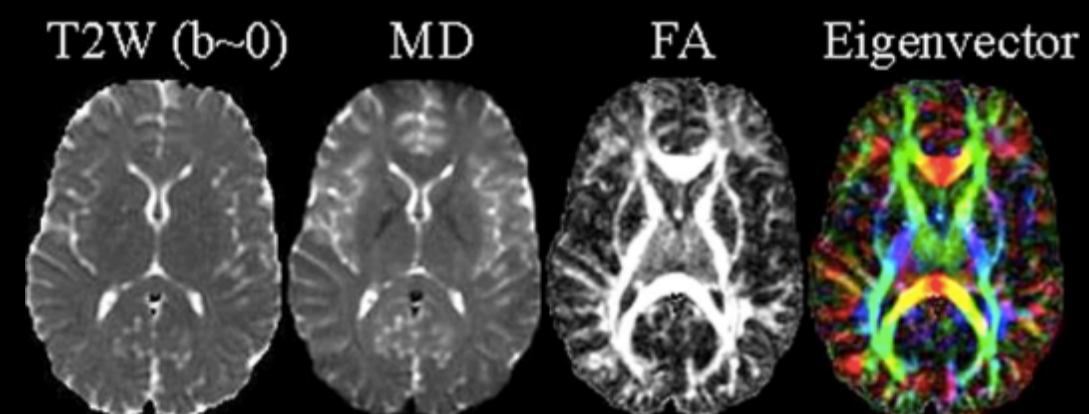
Neurite orientation dispersion and density index (NODDI)
  - ✧ Assumes a non-Gaussian biophysical model that distinguishes three types of microstructural environment: intra-neurite, extra-neurite, and CSF compartments
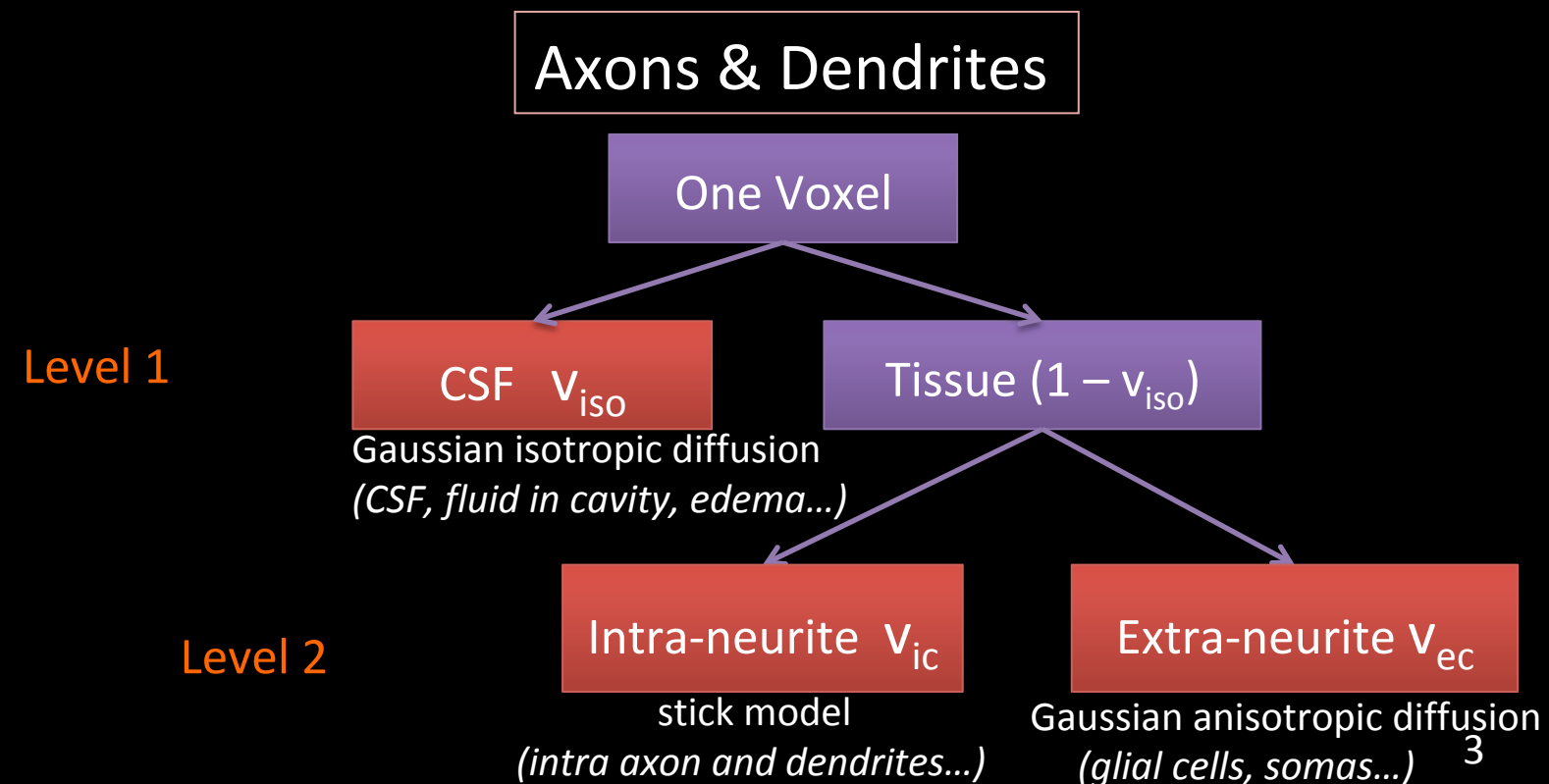
Zhang et al., Jul 2012

  - ✧ Disentangles the key factors contributing to fractional anisotropy (FA)
  - ✧ Provides output maps
    - ✧ V_{ic} – Intraneurite volume fraction
    - ✧ V_{ec} – Extraneurite volume fraction
    - ✧ V_{iso} – Isotropic volume fraction
    - ✧ ODI – Orientation Dispersion Index

OD   Vic   Viso

NODDI Model Details

Axons & Dendrites

One Voxel

Level 1

CSF v_{iso}

Gaussian isotropic diffusion
(CSF, fluid in cavity, edema…)

Tissue $(1 - v_{iso})$

Level 2

Intra-neurite v_{ic}

stick model
(intra axon and dendrites…)

Extra-neurite v_{ec}

Gaussian anisotropic diffusion
(glial cells, somas…) 3

Matrices	Model	Description	Tissue
V_{iso}	Gaussian Isotropic	"Free water" compartment	CSF, fluid in cavity, edema, et al…
V_{ic}	Stick Model	"Spaghetti" Compartment	Axon, dendrites, et al..
V_{ec}	Gaussian Anisotropic	Everything else	Glial cells, Soma, et al…
ODI	Stick Model	High: highly dispersed Low: highly parallel	

Motivation

- In gliomas, tissue structure is very heterogeneous:
  - Including axons, normal cells, tumor cells, vasculature, edema, water-bonded macromolecules etc.
  - DTI is very sensitive to the underlying tissue structure but not specific *(Pierpaoli et al ., 1996)*

- NODDI allows quantification of specific tissue microstructure features and may have the potential to provide meaningful biophysical indices
  - However, NODDI is a model-based approach built on normal brain, that may be limited when used to characterize abnormal tissue structure
  - Recent work has shown the application of NODDI to brain tumors (*Wen et al., Neuroimage Clinical 2015*) to overcome the low specificity of DTI

- In this exploratory study we applied NODDI and DTI to histopathologic features in different tumor grades
  - In order to validate the diagnostic potential of these techniques

Objectives

- To evaluate NODDI and DTI imaging metrics within the T2 lesion and image-guided tissue samples of different grade gliomas by:

  – comparing derived metrics that characterize the T2 lesion with non-enhancing lesion (NEL) and contrast-enhancing lesion (CEL) among different tumor grades

  – investigating the differences in parameters between non-enhancing (NE) and contrast-enhancing (CE) tissue samples in GBMs

  – relating diffusion parameters from acquired tissue samples to histopathological features

Methods: Patient Population

Lesion Data

- 55 patients
- Median Age: 40 (20 –79)
- Gender: 35 Male/20 Female

* Oligoastro with 1p19q not deleted status are considered astro-like and are grouped into Astro group for analysis
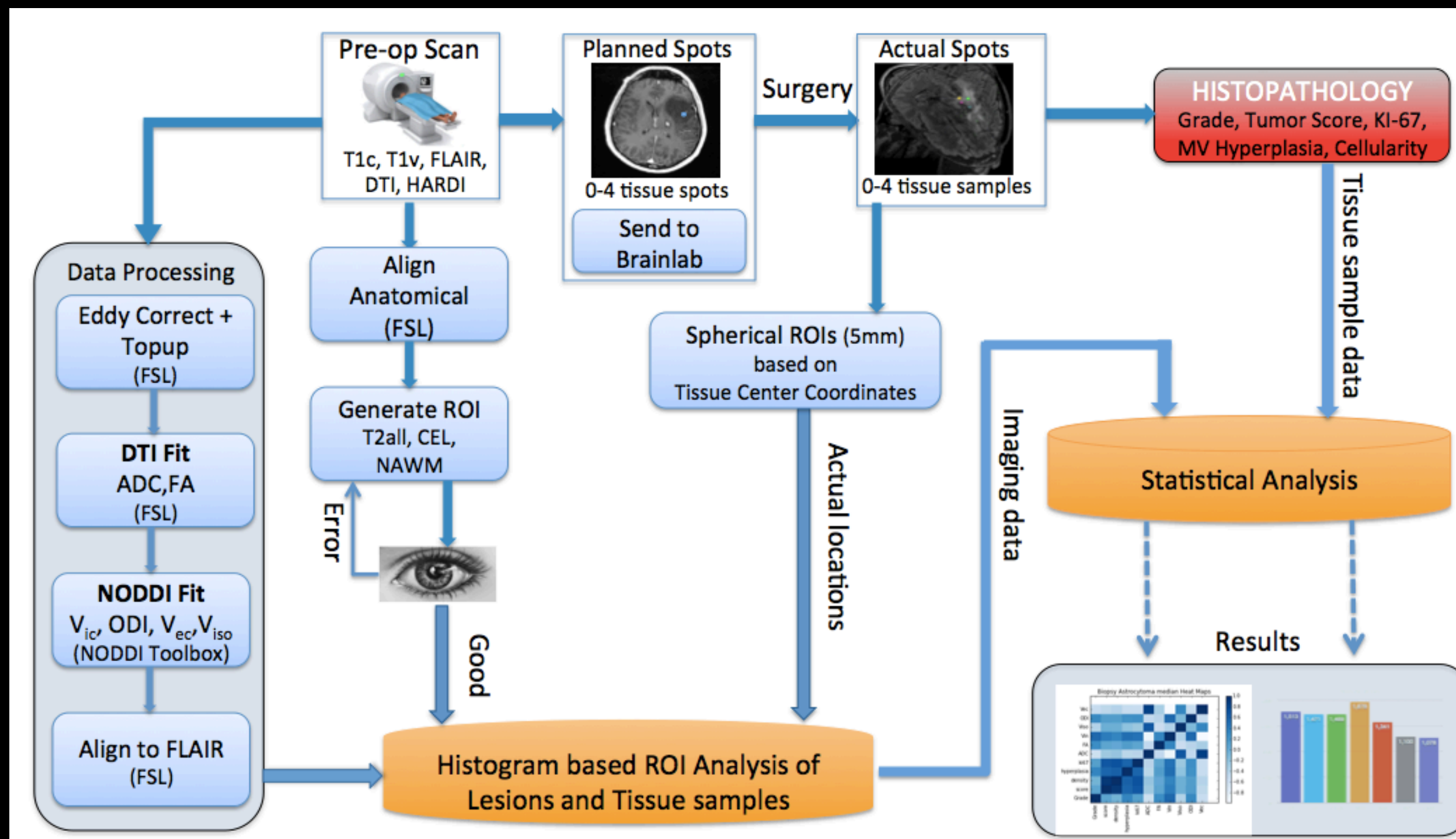
Legend:
- Astro G2
- Oligoastro G2
- Astro G3
- Oligoastro G3
- GBM G4

Pie chart values: 13, 6, 14, 2, 20
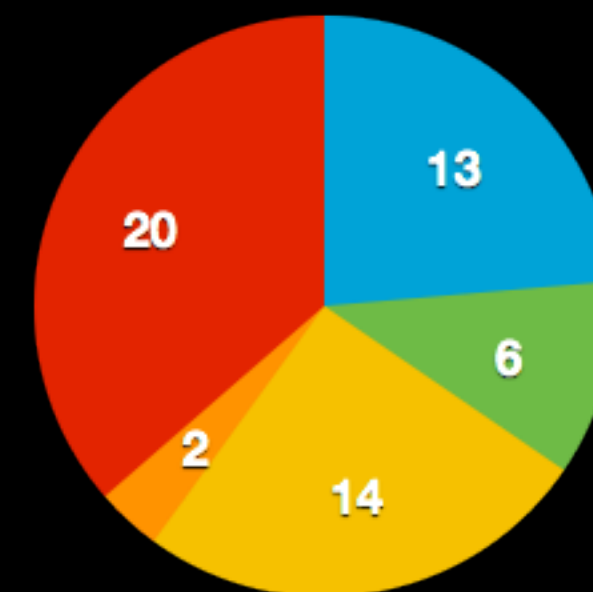
Tissue Data

- 29 patients
- 75 tissue samples
  - 4 necrotic spots, 44 NE, 21 CE, 6 on the border (based on T1 post-gad normalized intensity value)
- Median Age: 48 (24 –79)
- Gender: 17 Male/ 12 Female
- Mean samples/patient: 2.81 (range 1-4)

Legend:
- Astro G2
- OligoAstro G2
- Astro G3
- OligoAstro G3
- GBM G4

Pie chart values: 12 (4), 5 (2), 12 (6), 8 (2), 38 (15)
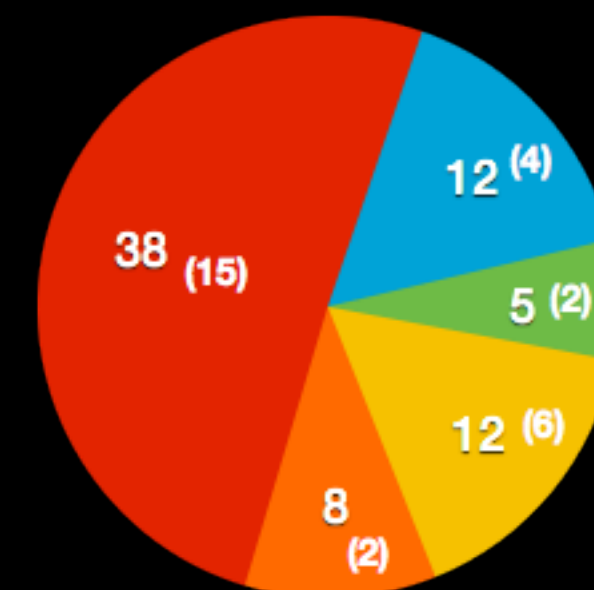
Tissue samples (patients)
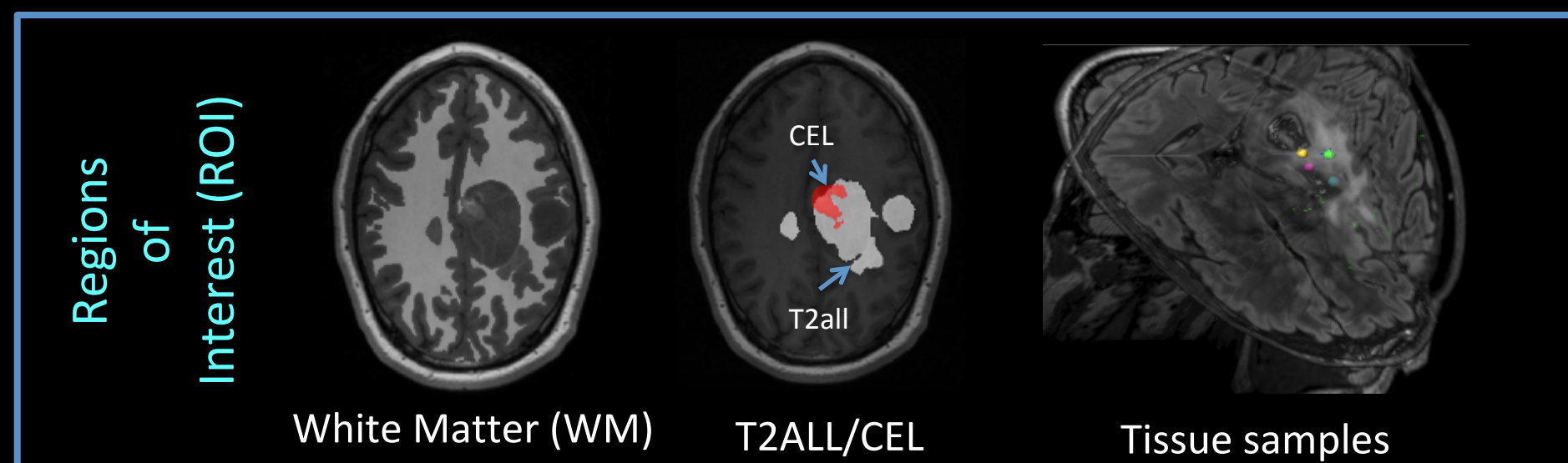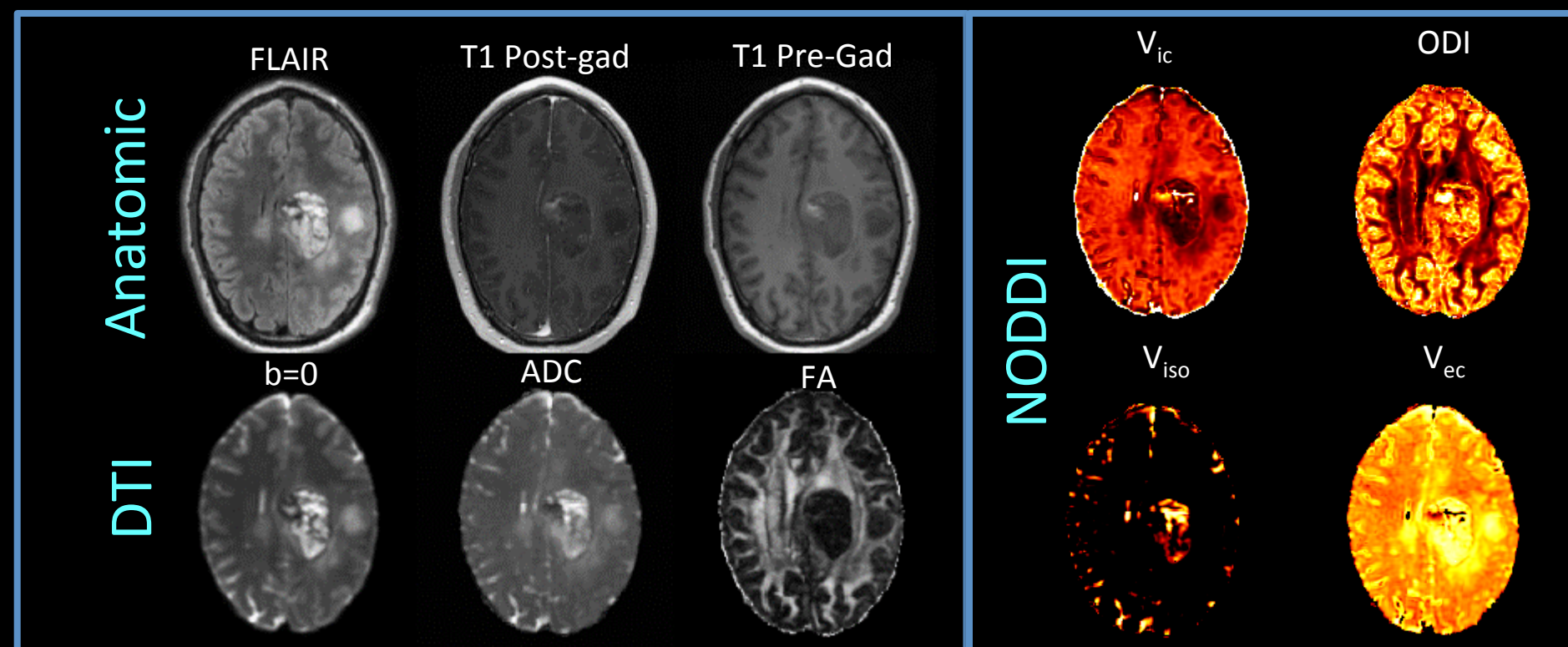
Methods: Data Processing

Methods: MR Imaging Protocol

3T Scan Protocol

(w/8-channel head coil)

- ✧ Calibration/Localization images

- ✧ Anatomical Imaging:
  - ✧ 3D T2 FLAIR (CUBE)
  - ✧ Ax T1 SPGR Pre- & Post-Gad
  - ✧ T1 Spin Echo (clinical)

- ✧ Diffusion-weighted Imaging:
  - ✧ 24 DIR, b=1000
  - ✧ 55 DIR, b=2000
  - ✧ standard SE-EPI sequence
 - ✧ nominal voxel size of 2×2×2 mm
  - ✧ TE/TR/T_{acq} = 99ms/10s/91s

Anatomic: FLAIR, T1 Post-gad, T1 Pre-Gad

DTI: b=0, ADC, FA

NODDI: V_{ic}, ODI, V_{iso}, V_{ec}

Regions of Interest (ROI): White Matter (WM), T2ALL/CEL (CEL, T2all), Tissue samples

Methods: Histopathology Parameters

✧ <u>Cellularity</u>: Mean cell number per 200x-field of view

✧ <u>Tumor Score:</u>
  ✧ 0 = neuropil without tumor
  ✧ 1 = infiltrating margin
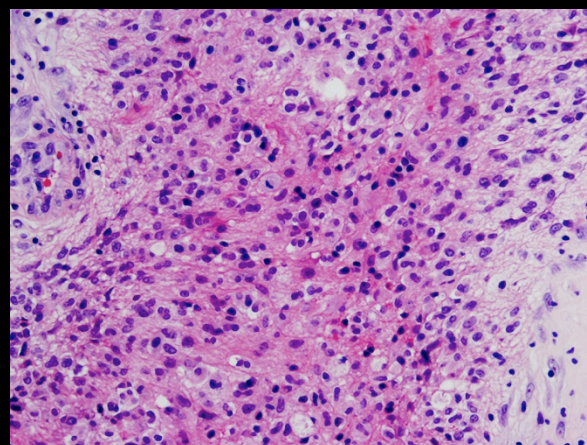 ✧ 2 = infiltrating tumor cells
  ✧ 3 = high percentage of tumor cells

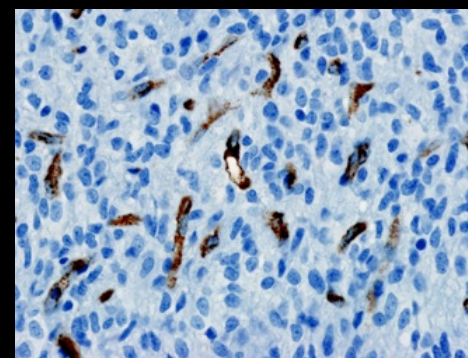✧ % Tumor Nuclei
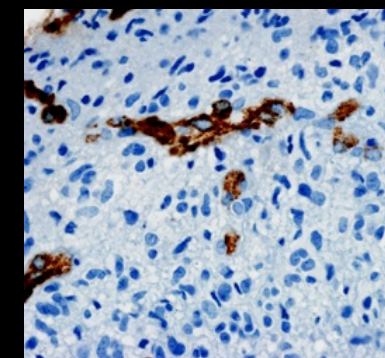
H&E
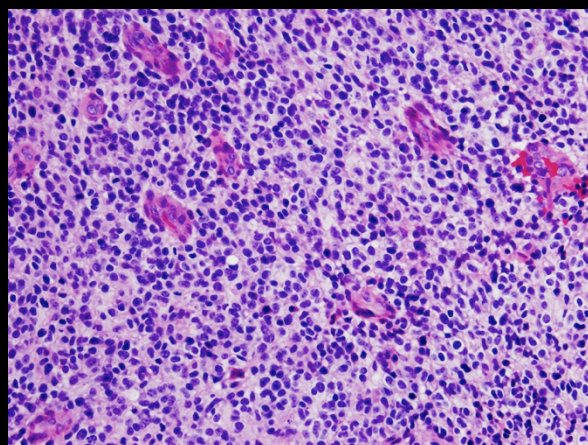
Tumor score = 3
Cellularity* = 254
Estimated tumor nuclei = 90%

Tumor score = 3
Cellularity* = 135
Estimated tumor nuclei = 80%
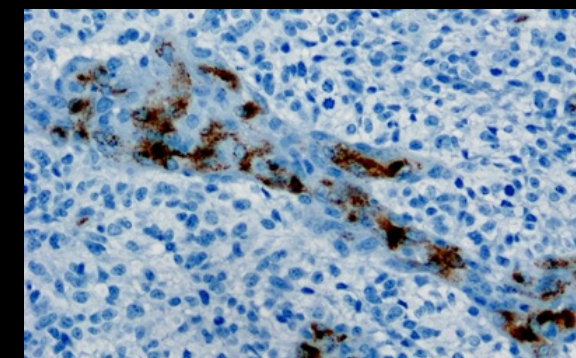
Microvascular (MV) Hyperplasia

(Marker for Angiogenesis)
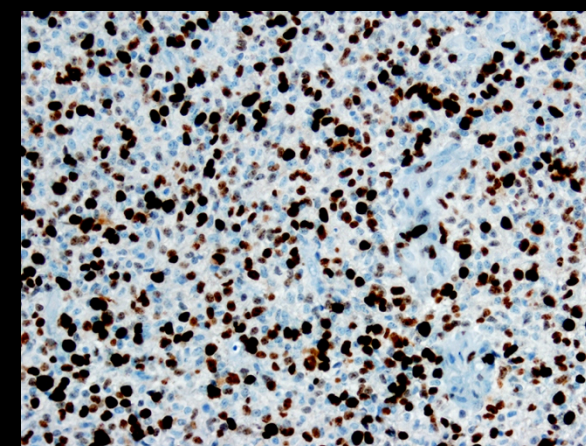
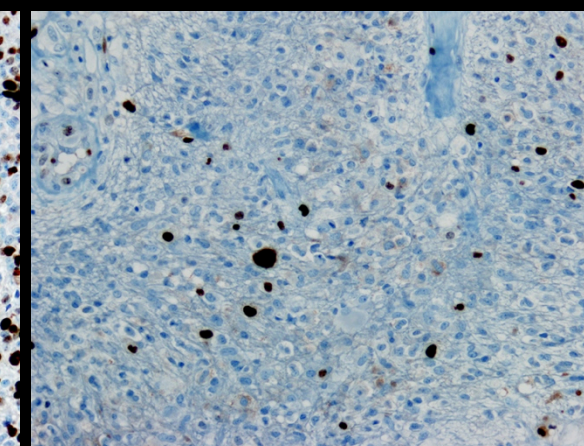0 - Delicate   1 - Simple   2 - Complex

KI-67

(% of all cells positive for MIB-1/Proliferation)

35.5% MIB1+   7.89% MIB1+

Methods: Statistical Analysis

Outcome type	Histopathology parameters	Statistical test	Group differences
Categorical	Tumor score, Tumor grade, MV Hyperplasia	Ordinal logistic regression	Wilcoxon rank-sum test
Continuous	Cellularity, % tumor nuclei, Proliferation	Spearman correlation	N/A

P-values ≤ 0.05 were considered statistically significant in this exploratory analysis

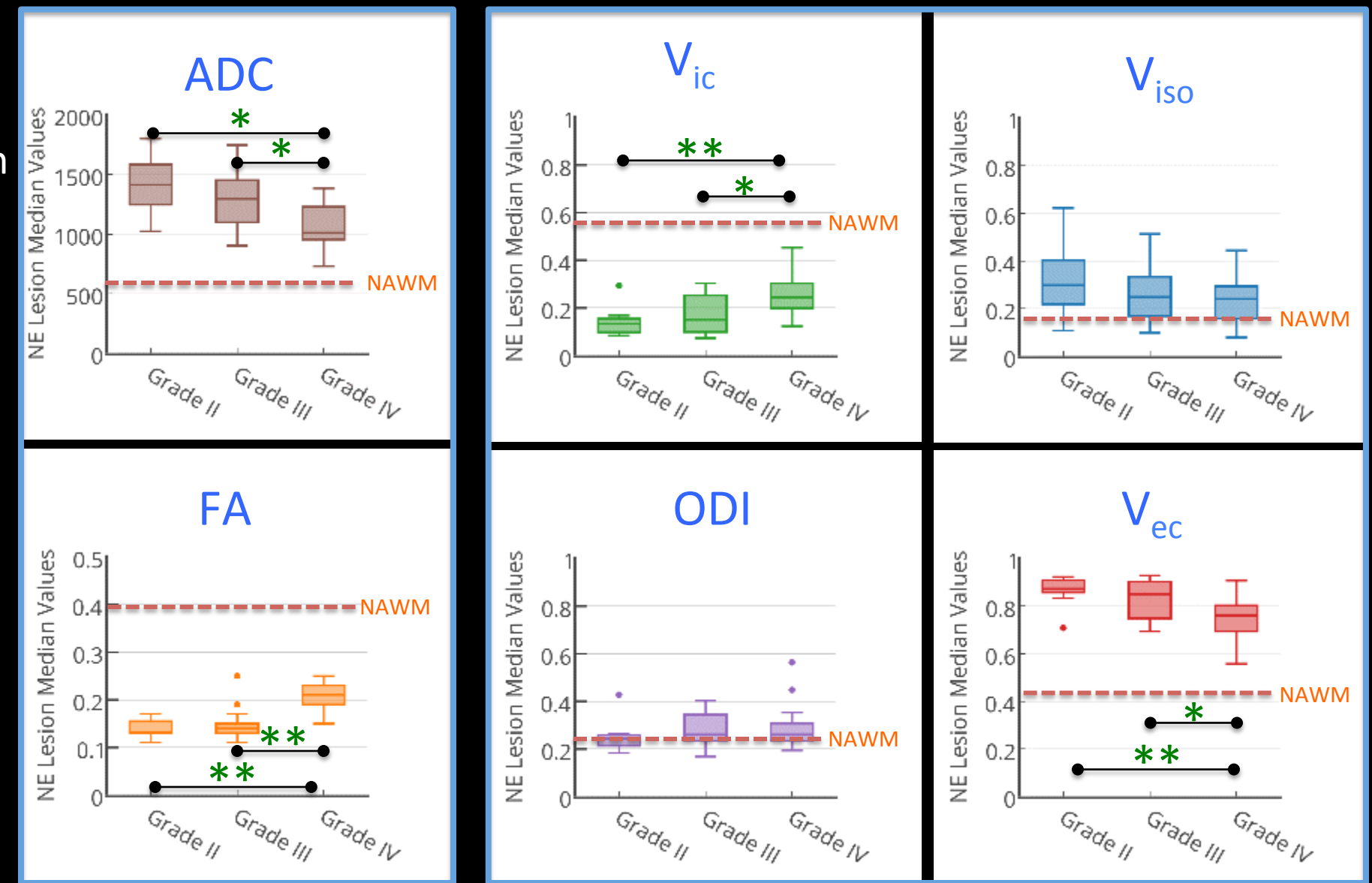# Results: Example DTI/NODDI Maps by Grade
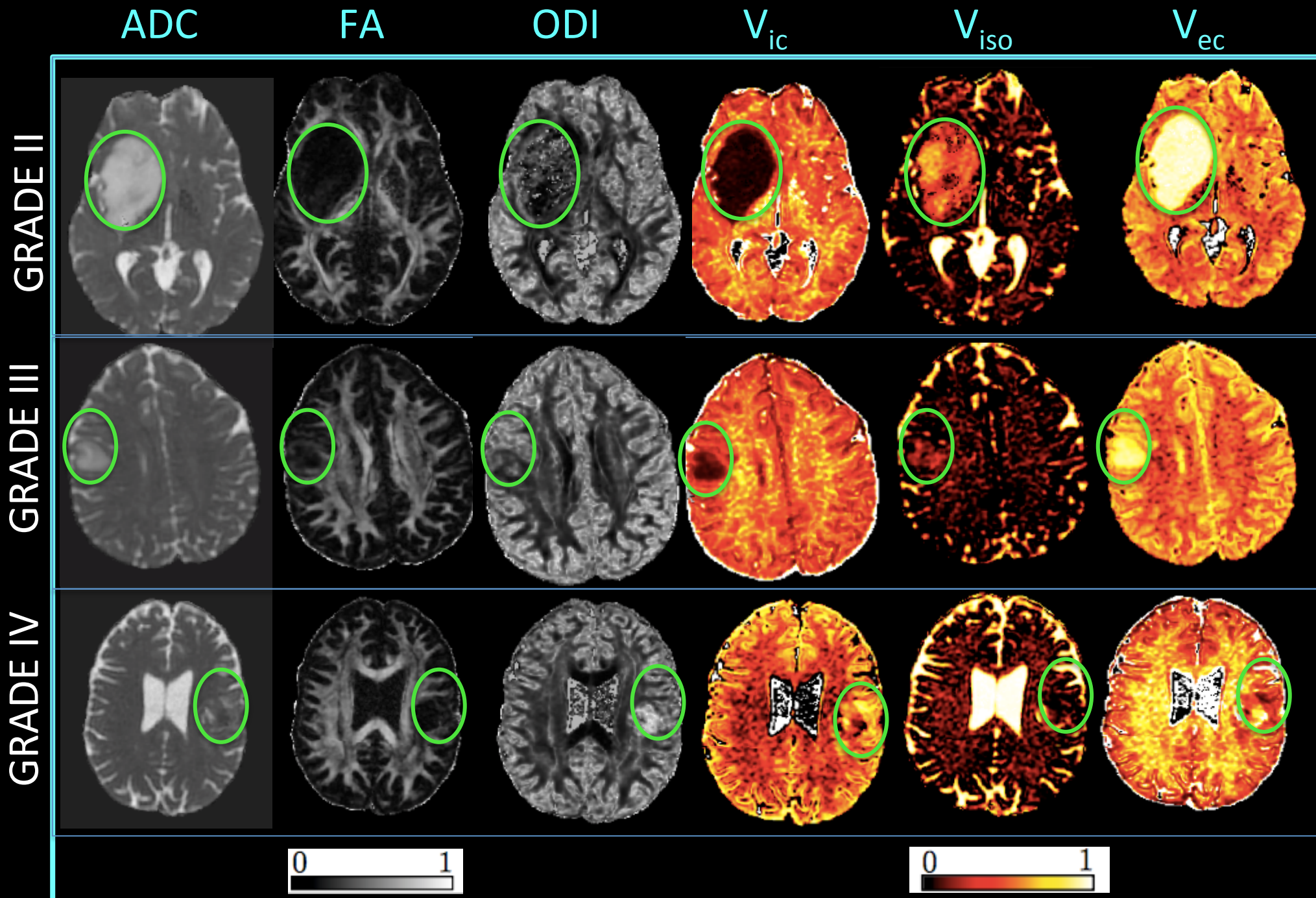
Results: DTI/NODDI Lesion Metrics by Grade

- In all tumor grades, V_{ic} was reduced and V_{ec} elevated compared to NAWM, indicating lower neurite density

- ADC, FA, V_{ic}, & V_{ec} were associated with tumor grade and differentiated GBMs from lower grade tumors

- ODI & V_{iso} were associated with grade, but were not significantly different between grades

Ordinal logistic regression results:

Parameters	χ2	P-value
ADC	22.5	<0.0001
FA	6.6	<0.001
V_{ic}	28.6	<0.0001
ODI	10	<0.005
V_{iso}	6.9	<0.01
V_{ec}	26.3	<0.0001

NAWM = normal appearing white matter

Median NE lesion differences by grade for Astrocytomas
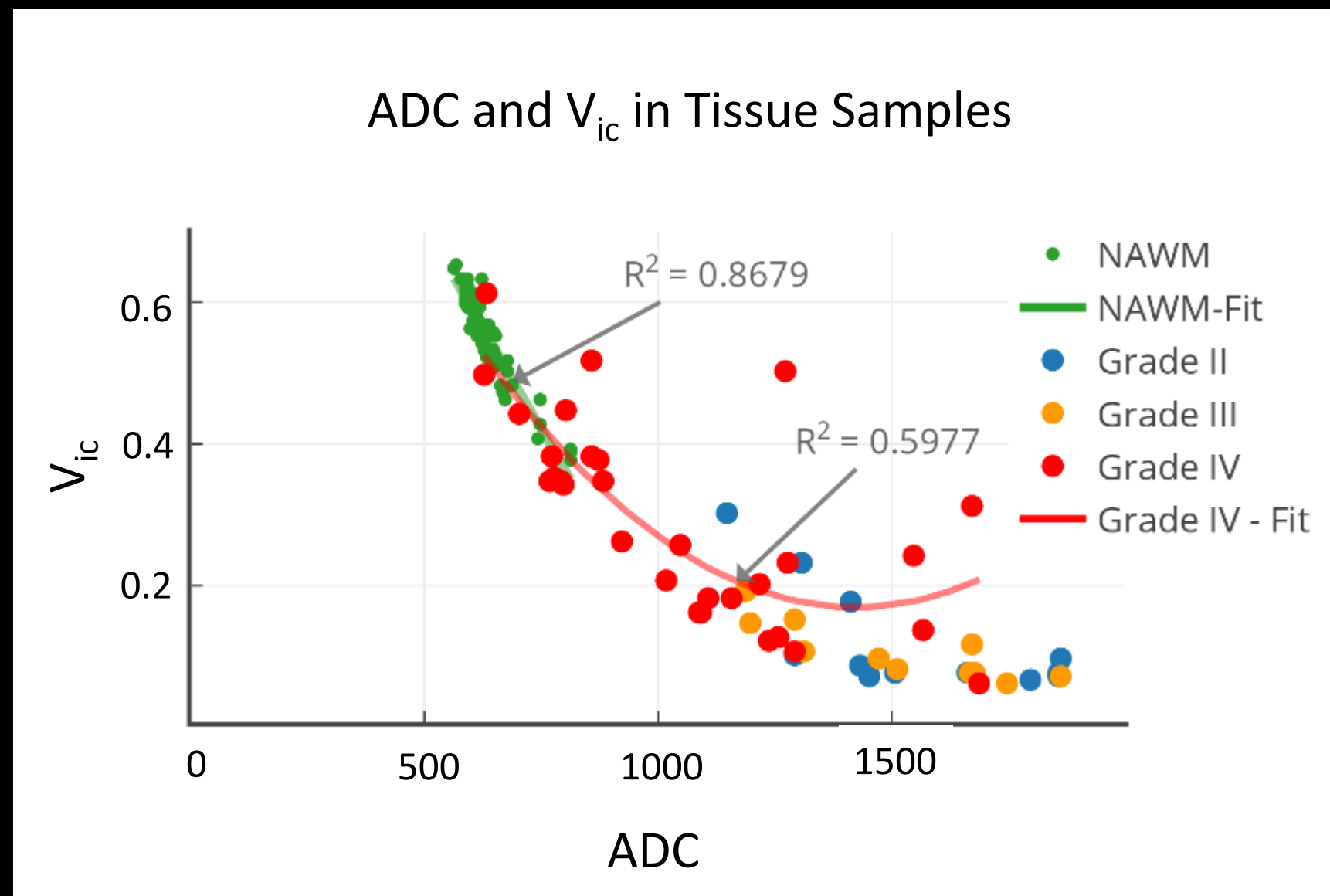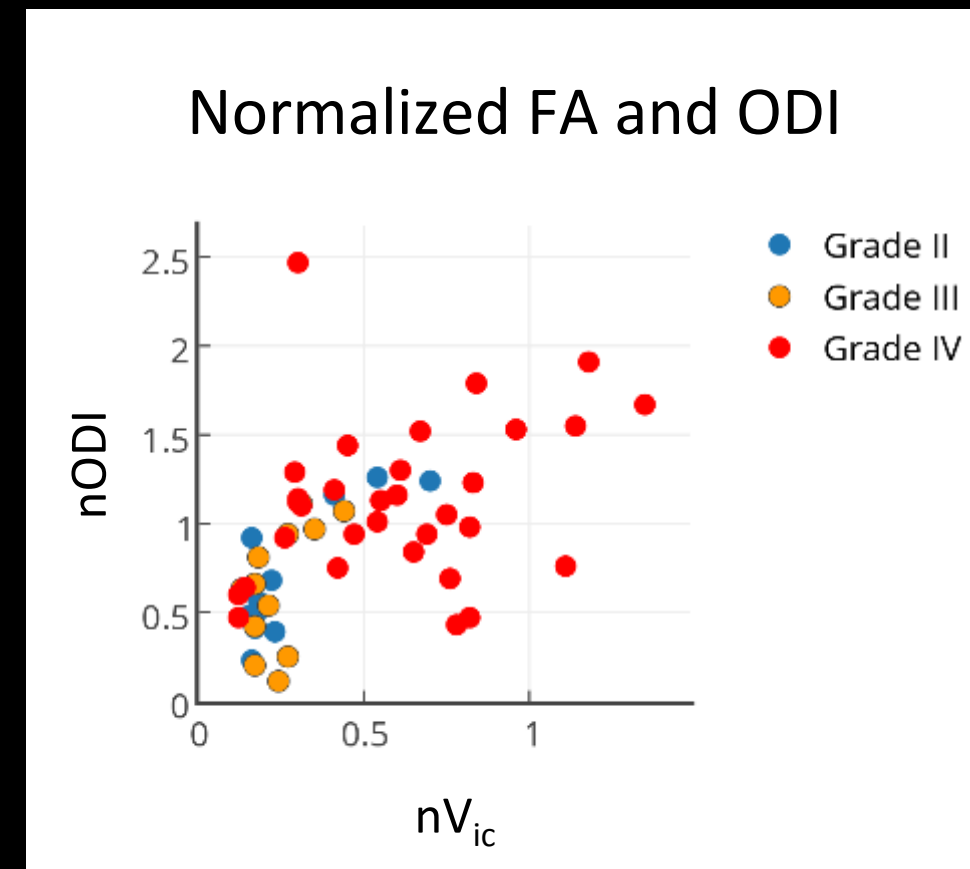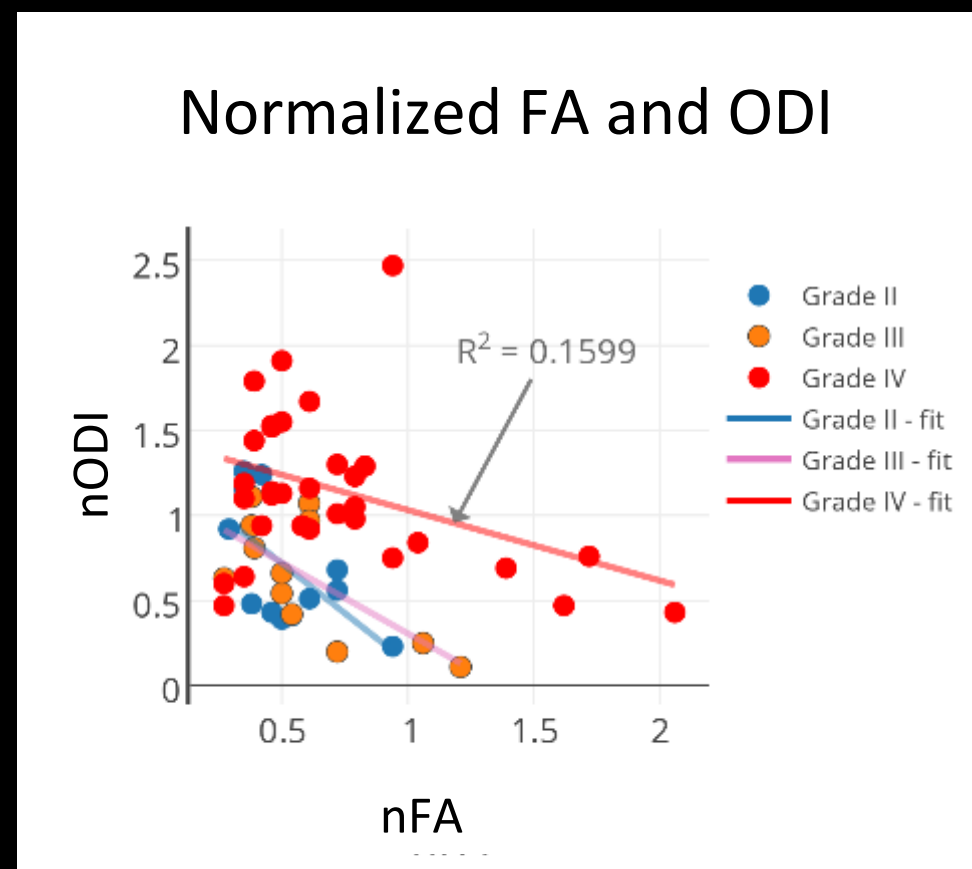

DTI   NODDI   *p<0.05 and ** p<0.005

Results: Relationship Between DTI & NODDI

- ✧ ADC and V_{ic} are inversely correlated
  - ✧ In NAWM relationship is linear
  - ✧ In tumor region, relationship is non-linear

- ✧ Lower grades have low V_{ic} and high ADC

- ✧ GBMs are more heterogeneous, with a wider range of both V_{ic} and ADC values depending on the location sampled

ADC and V_{ic} in Tissue Samples

Results: Relationship Between DTI & NODDI

Normalized FA and ODI

$R^2 = 0.1599$

Legend:
- Grade II
- Grade III
- Grade IV
- Grade II - fit
- Grade III - fit
- Grade IV - fit

nODI vs nFA

Normalized FA and ODI

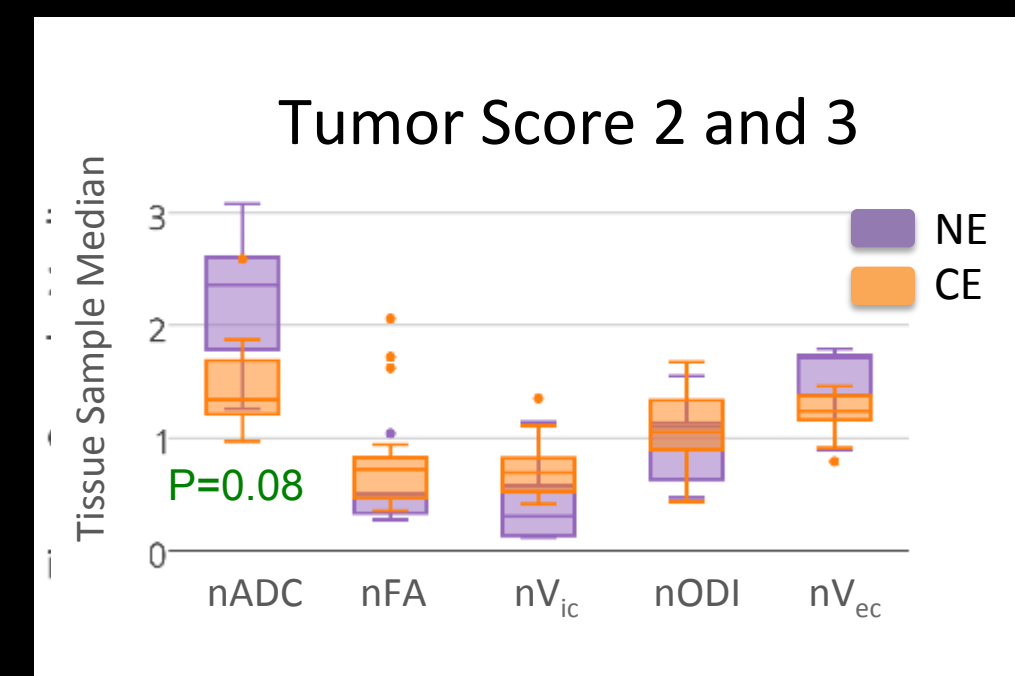Legend:
- Grade II
- Grade III
- Grade IV

nODI vs nV_{ic}

✧ FA and ODI are inversely correlated as expected, with lower FA indicating higher dispersion

✧ V_{ic} and ODI are positively correlated in all grades

Results: NE vs CE Tissue Samples in GBM

Median NE and CE values in DTI and NODDI parameters
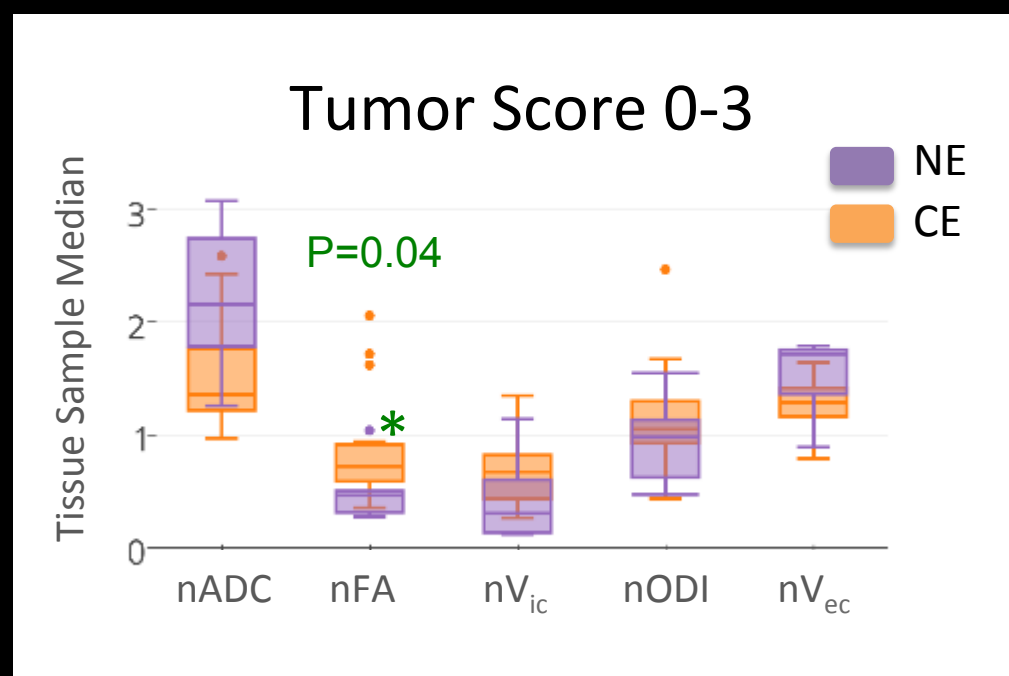
- 8 NE tissue samples
- 19 CE tissue samples

- Difference between NE and CE tissue sample means is only statistically significant for FA when considering tumor score 0-3
- A trend towards lower ADC and elevated FA in CE compared to NE tissue samples could suggest more anisotropy
- Trends toward elevated V_{ic} and ODI in CE compared to NE tissue samples is consistent with lesion analysis in *Wen et al., Neuroimage Clinical 2015* and may suggest more dispersion

Results: DTI/NODDI & MV Cellularity

Significant correlations of CE tissue samples with cellularity in GBM
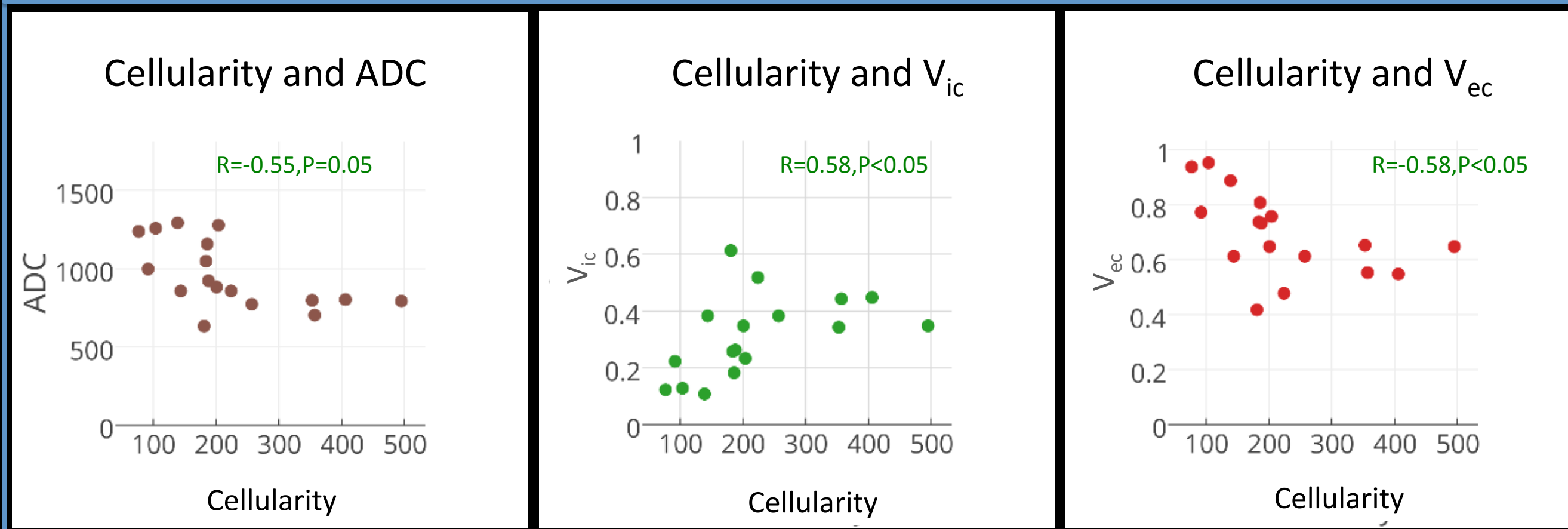
- ADC and V_{ec} are negatively correlated with Cellularity while V_{ic} is positively correlated
- No association with cellularity was found in NE tissue samples or in lower grades of glioma
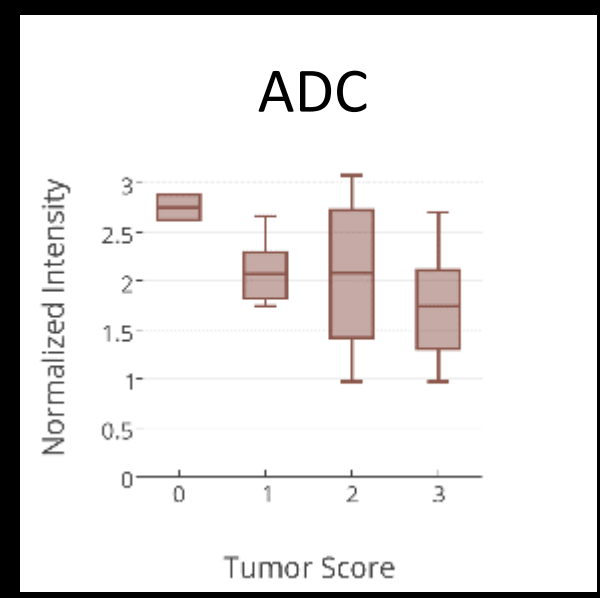
Results: DTI/NODDI & Tumor Score

- Within GBM, tumor score and % tumor nuclei are associated
  - Positively with V_{ic}
  - Negatively with V_{ec}

Tumor score

Parameters	χ2	P-value
V_{ic}	7.7	<0.01
V_{ec}	-8.5	<0.05

%tumor nuclei

| Parameters	χ2	P-value
V_{ic}	.42	<0.01
V_{ec}	.41	<0.01

  - ADC did not show any association

- This suggests that NODDI parameters may be more sensitive to malignant tumor cells than ADC

- However, across all grades of astrocytoma, ADC, V_{ic} and V_{ec} are associated with tumor score

Astrocytomas, all grades

- 0 -neuropil
- 1 - Infiltrating
- 2 -less tumor cells
- 3 – high % tumor cells

Parameters	χ2	P-value
ADC	4.6	~0.03
V_{ic}	14.2	~0.002
V_{ec}	16	<0.001
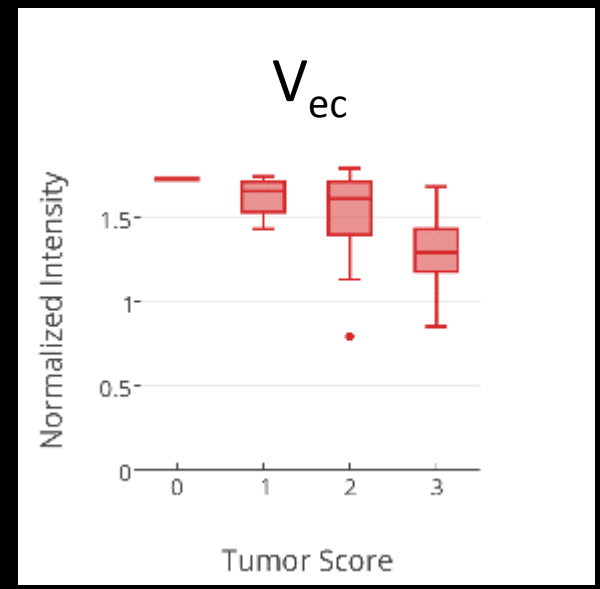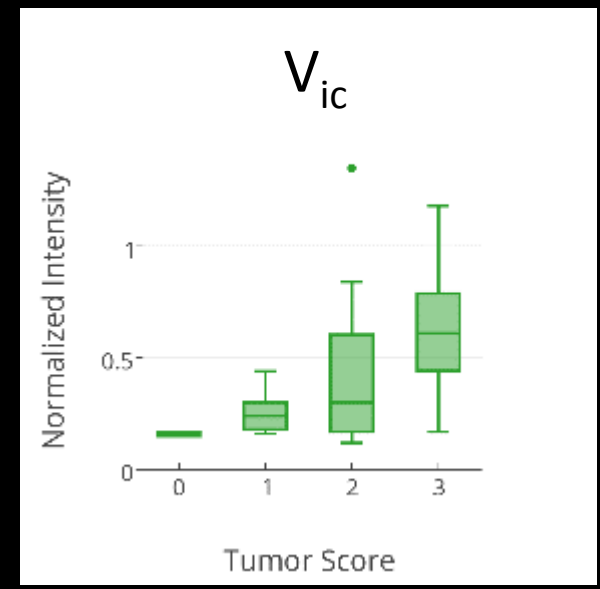
Results: DTI/NODDI & MV Hyperplasia

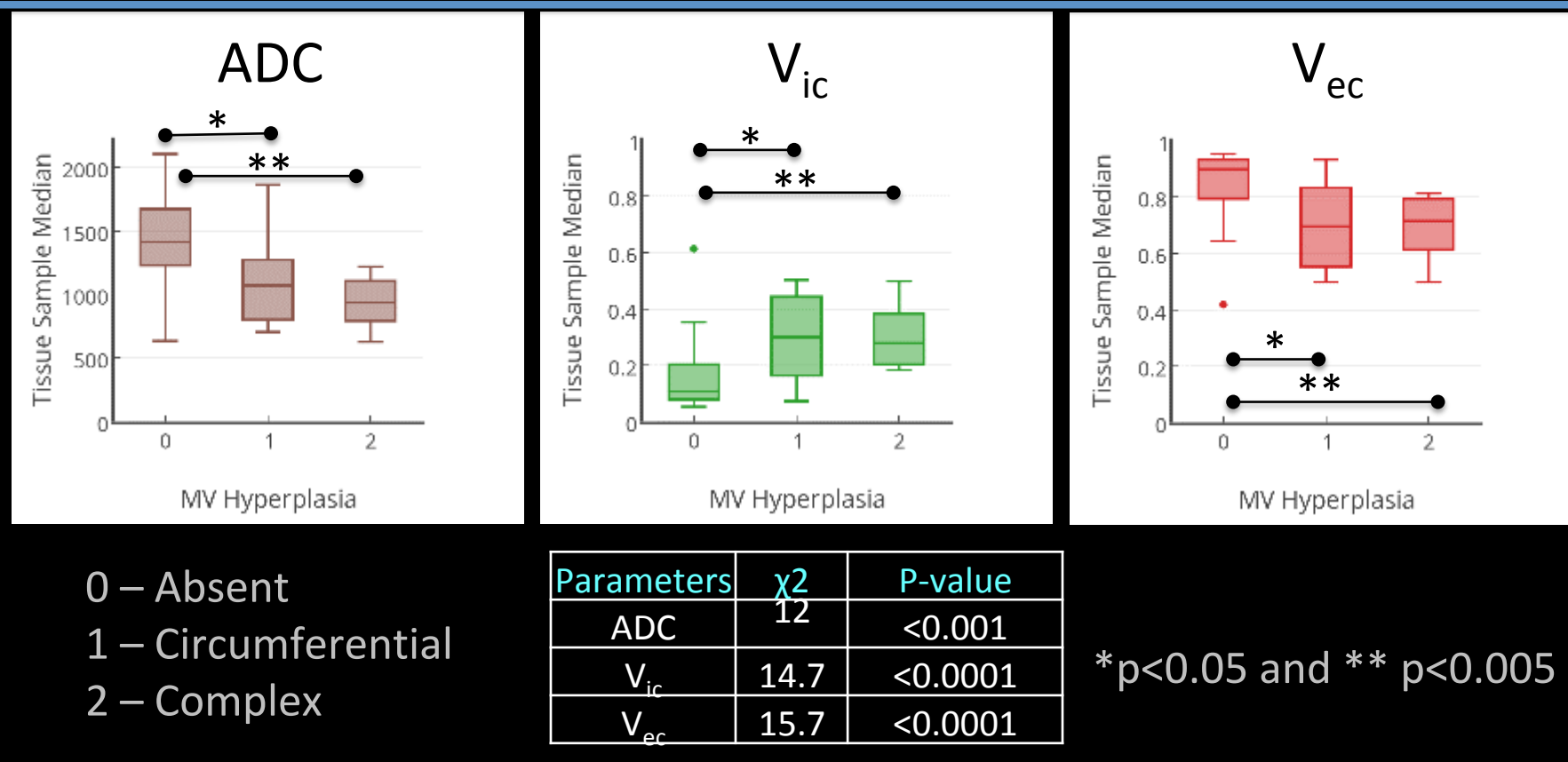- In Astrocytoma across all grades:

  - ADC, V_{ic} and V_{ec} are associated with MV Hyperplasia

  - Significant differences were found in ADC, V_{ic} and V_{ec} between normal (0) and abnormal (1&2) vessels

Astrocytomas all grades

ADC

V_{ic}

V_{ec}

0 – Absent
1 – Circumferential
2 – Complex

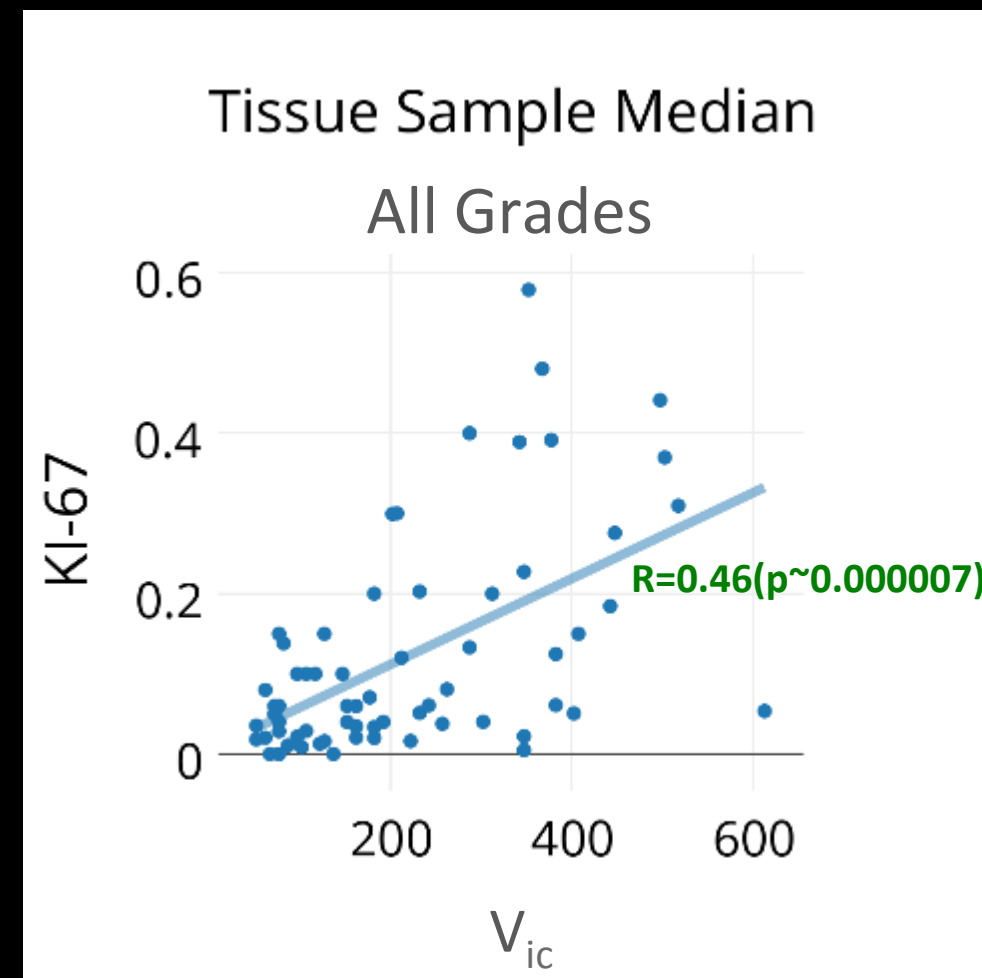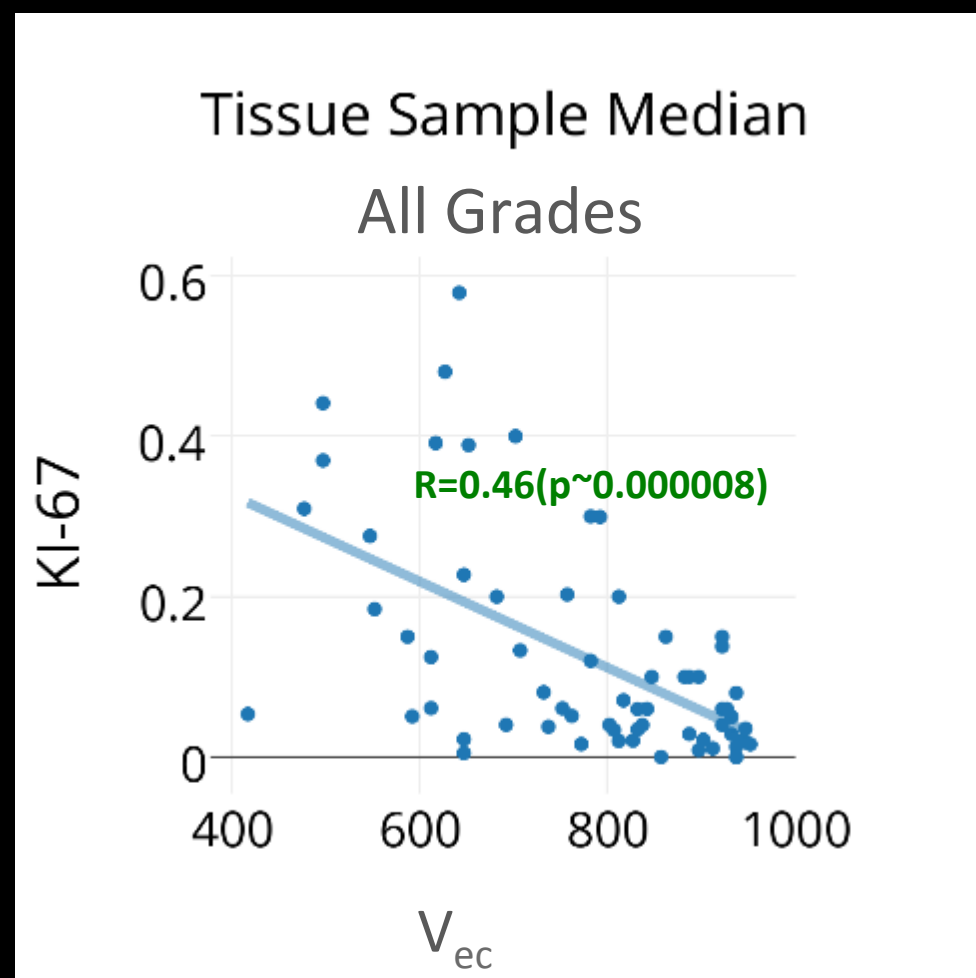| Parameters	χ^2	P-value
ADC	12	<0.001
V_{ic}	14.7	<0.0001
V_{ec}	15.7	<0.0001

*p<0.05 and ** p<0.005

**Double check Vic and Vec graphs with data

- In GBM only, none of the parameters showed significant association with MV Hyperplasia

Results: DTI/NODDI & KI-67/Proliferation

Tissue Sample Median — All Grades (V_{ec} vs KI-67): R=0.46(p~0.000008)

Tissue Sample Median — All Grades (V_{ic} vs KI-67): R=0.46(p~0.000007)

All Grades

Parameters	R	P-value
ADC	-0.38	<0.005
V_{ic}	0.5	<0.00001
V_{ec}	-0.54	<0.00001
ODI	0.28	<0.05

GBM

Parameters	R	P-value
ADC	-0.33	<0.05
V_{ic}	0.5	<0.005
V_{ec}	-0.5	<0.005

- Considering all astrocytic tumor grades:
  - V_{ic} and ODI are positively correlated
  - ADC and V_{ec} are negatively correlated
- Within GBM:
  - no correlation with ODI
  - ADC, V_{ic} and V_{ec} correlated

Conclusions

- NODDI parameters are sensitive to tumor cellularity and complement the conventional DTI model metrics, although the NODDI model was not directly derived for tumor.

- 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.

- ADC and NODDI parameters V_{ic} and V_{ec} were significantly correlated with brain tumor histopathology.

- Although FA and ODI were very highly correlated, their association with histopathology features varied, indicating that each of these provide distinct information about the underlying tissue structure.

- Although ADC and V_{ic} were highly correlated, only V_{ic} was associated with tumor score in GBM suggesting that it may be more specific to heterogeneous tumor microstructure.

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