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A Hypercellular Component of Glioblastoma Identified by High b-Value Diffusion Weighted Imaging

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Introduction

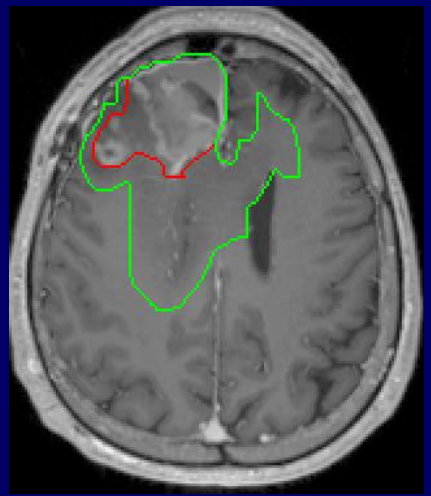
- Standard Tx of GBM is resection, followed by concurrent RT (60 Gy in 30 fx) and TMZ, and 6-12 cycles of TMZ

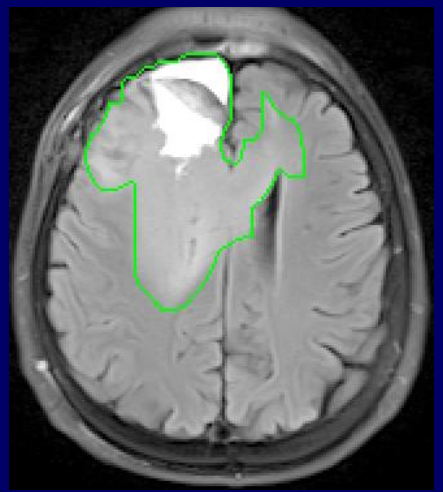
- The majority of the patients fails locally.

Introduction

- NRG BN001 trial aims to determine whether intensified radiation therapy with concurrent TMZ followed by adjuvant TMZ improve OS?
  - ✓ It is important to stratify the patients based upon radiosensitivity using genetic biomarkers
  - ✓ Where to boost is matter
    - ✓ Is the contrast enhanced GTV the effective target to be boosted?

Post Gd T1





T2 FLAIR

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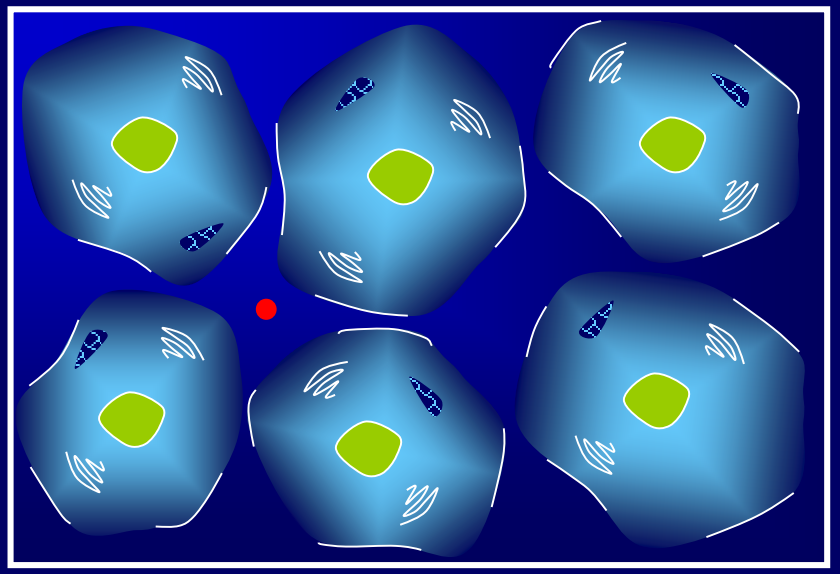
Hypercellularity of GBM Identified by High b-value Diffusion Imaging

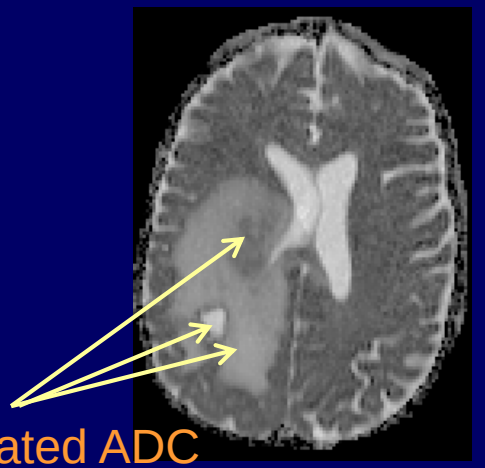
- Microscopic mobility of water in the cellular environment
  - ✓ Sensitive to cellular density, water content and organization of the cellular and extracellular space



- Preclinical studies in 1990s: ADC is inversely correlated with cellularity

- Unpredictable ADC in GBM

A single voxel in GBM is consisted of
tumor cells (low ADC),
edema (high ADC),
micro-necrosis (high ADC),
normal tissue (normal ADC)



Conventional ADC (b≤1000)

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Purpose

- We aim to suppress MR signals from edema, micro-necrosis and even normal tissue to reveal hypercellular (HC) tumor by increasing diffusion weighting (high b-value).

- MR signals decay exponentially with diffusion coefficients and diffusion weighting (b-value).

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Patients

- 44 patients (age: 23-79 years) with GBM
  - ✓ 35 patients with newly diagnosed GBM
    - Received concurrent RT+TMZ, followed by adjuvant TMZ
    - Radiation planning based upon conventional MRI (median dose of 60 Gy in 30 fx)
- MRI scans prior to RT but post-resection on a 3T scanner
  - ✓ Conventional post-Gd T1W and T2 FLAIR images
  - ✓ DWI with b=0, 1000, (2000) and 3000 s/mm^2 (~ 5 min)
- Conventional MRI at routine f/u and recurrence

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Questions

- ✓ Spatial relationship between FLAIR AV and hypercellularity volume (HCV) identified by DW imaging at b=3000
- ✓ Non-enhanced HCV
- ✓ Relationship between HCV and patterns of failure
- ✓ Prognostic values of HCV for PSF and OS

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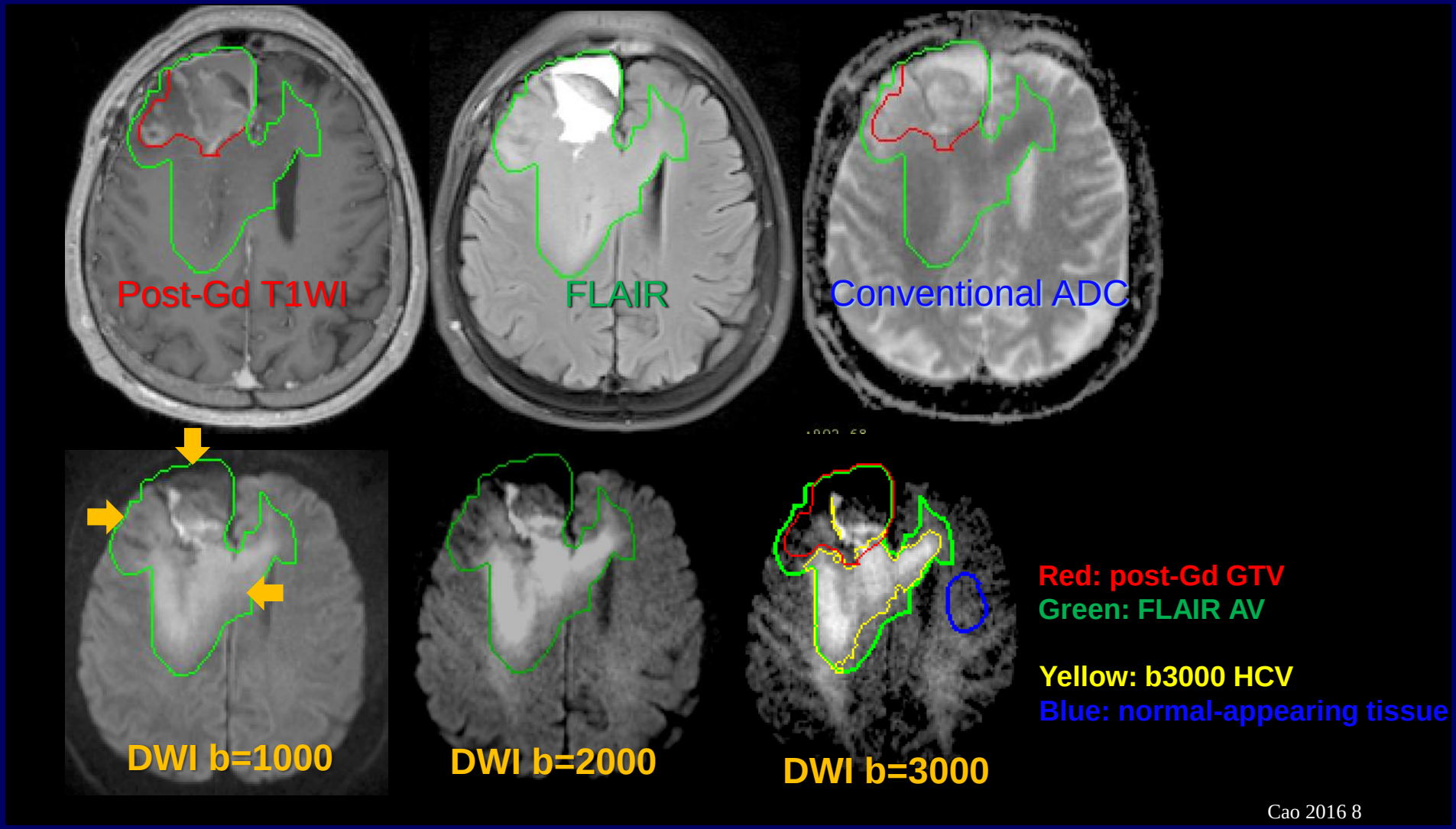
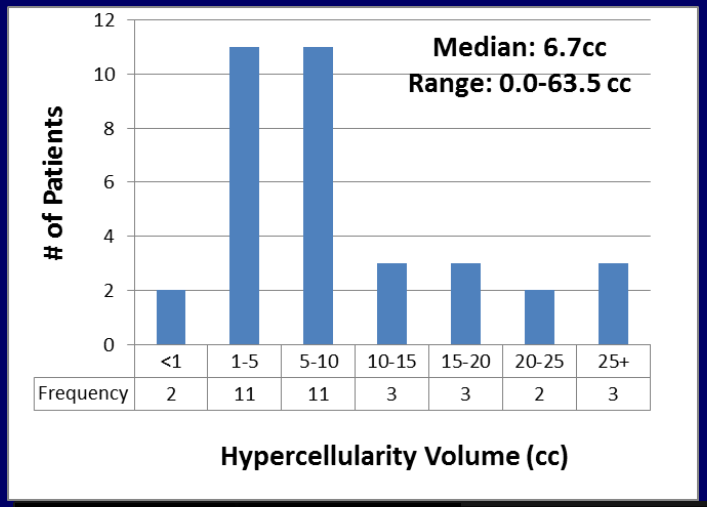
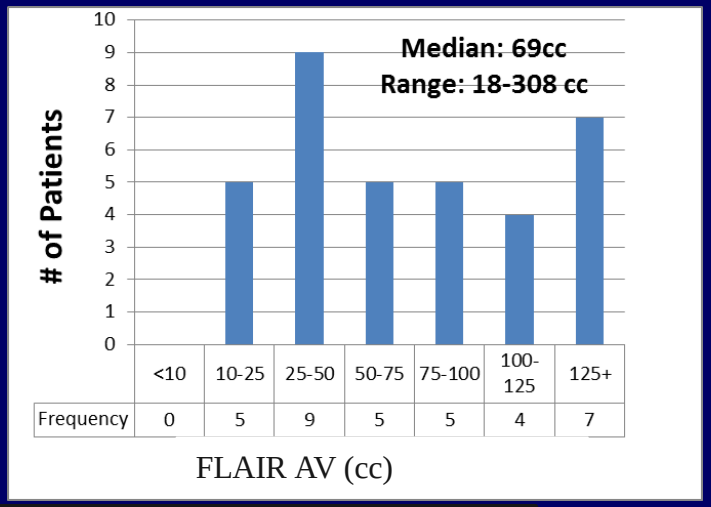
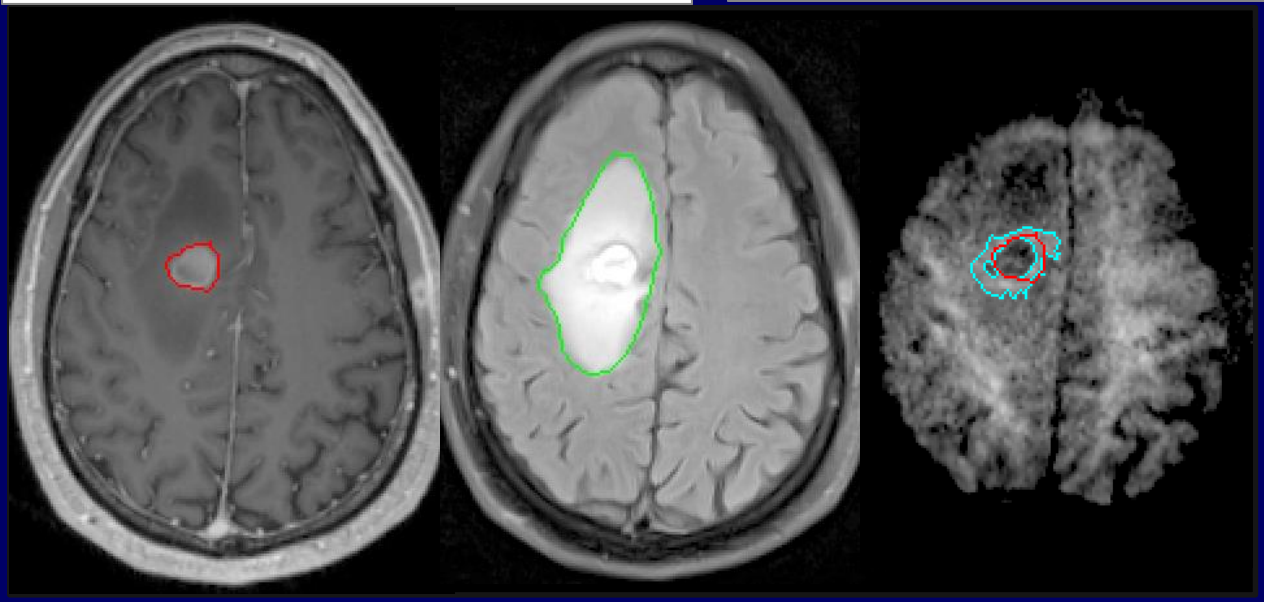
Hypercellularity



HCV is 10 times smaller than FLAIR AV!

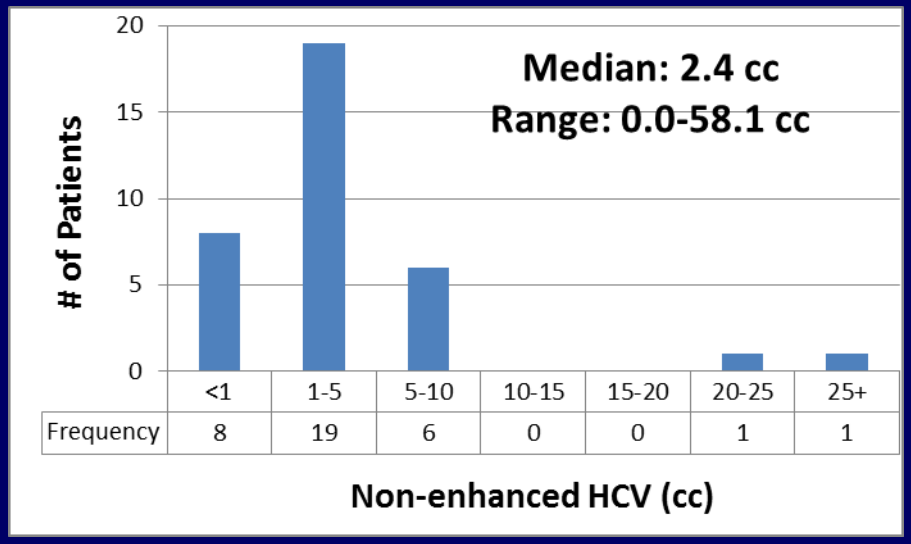


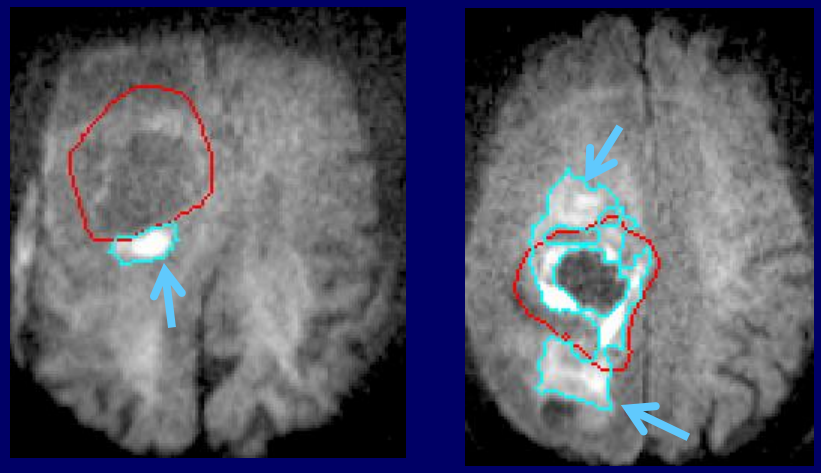




Red: post-Gd GTV
Cyan: b3000 HCV
Green: FLAIR AV

Nonenhanced HCV





Red: post-Gd GTV
Cyan: b3000 HCV

77% (27) patients had non-enhanced HCVs > 1 cc
23% (8) patients had non-enhanced HCVs > 5 cc

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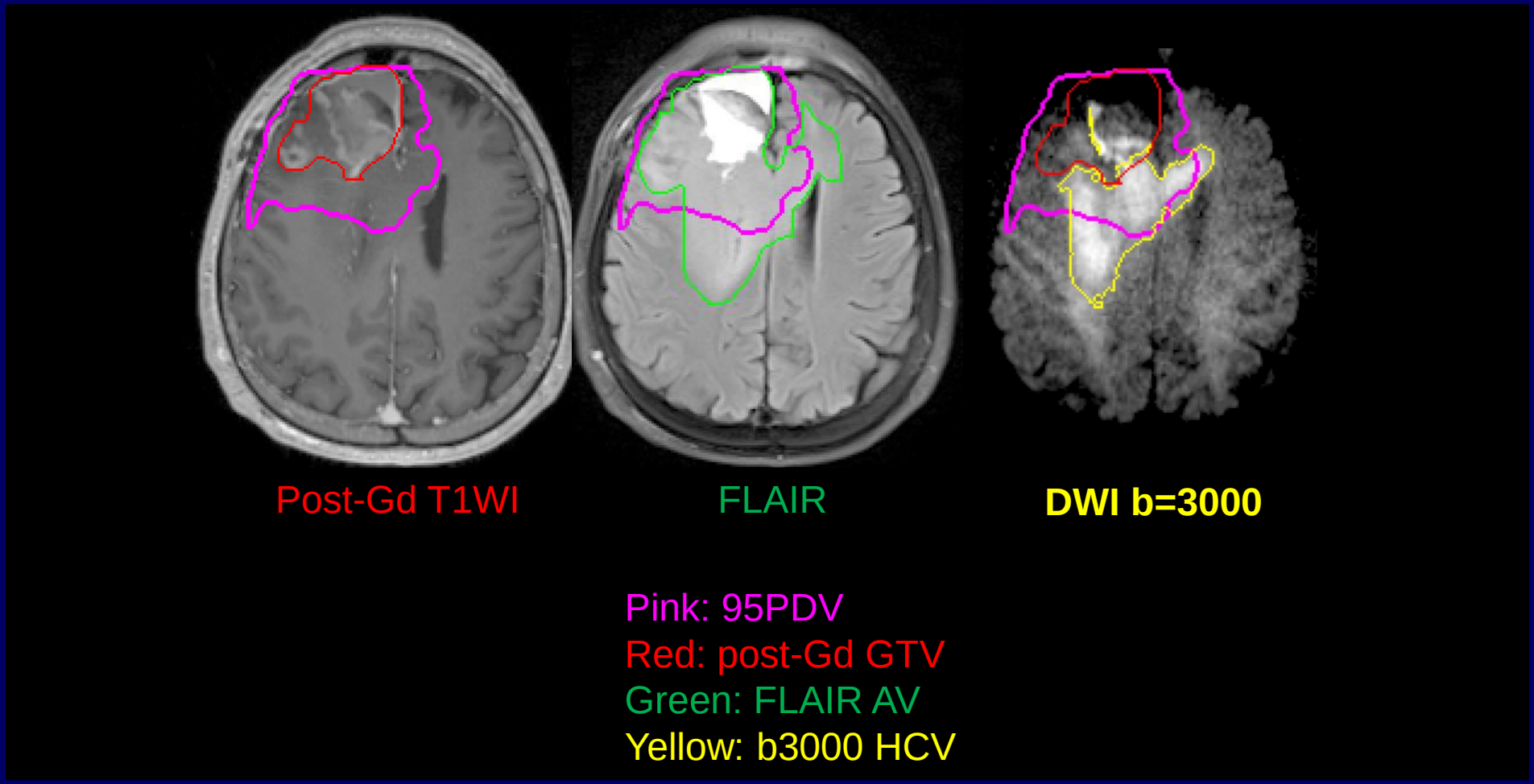
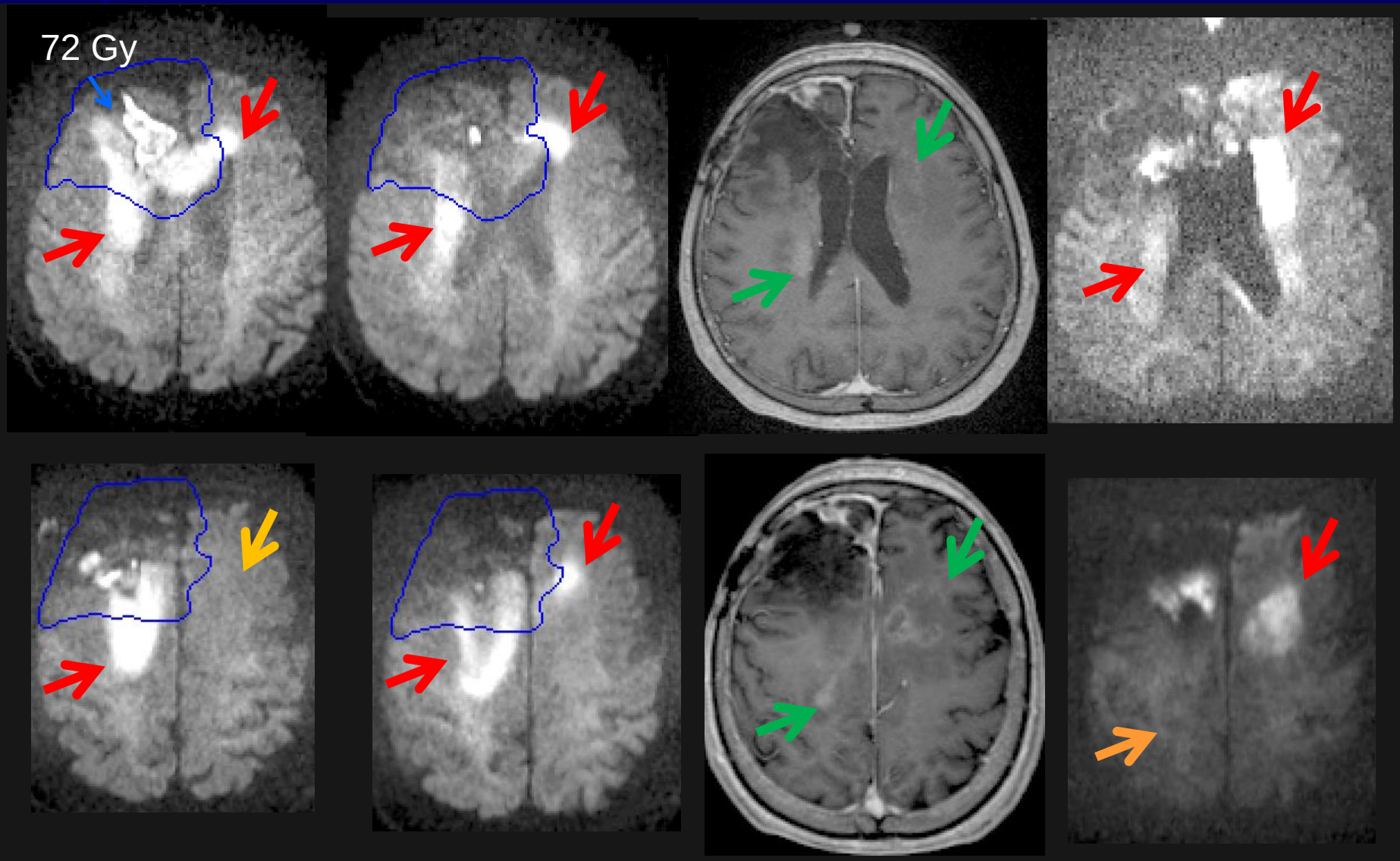
Radiation Dose Coverage



A small number of patients (n=3) had 1 cc or greater HCV that was not covered by 95PDV

Pattern of Failure



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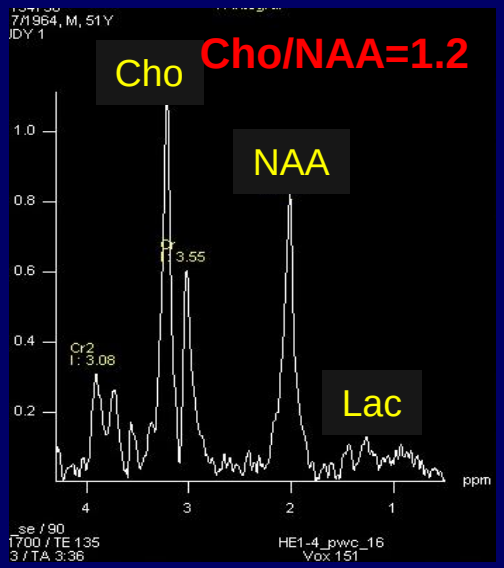
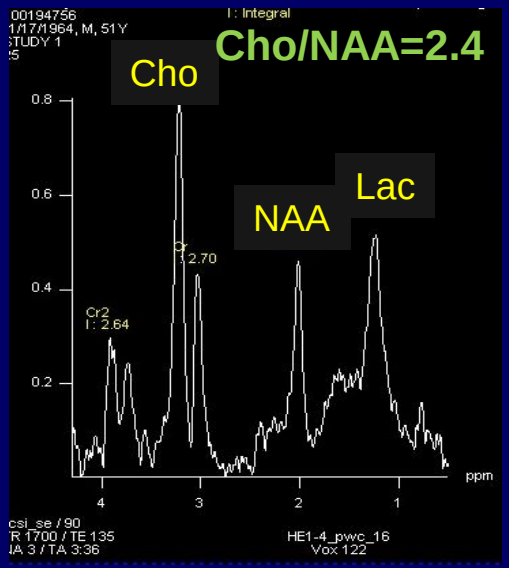
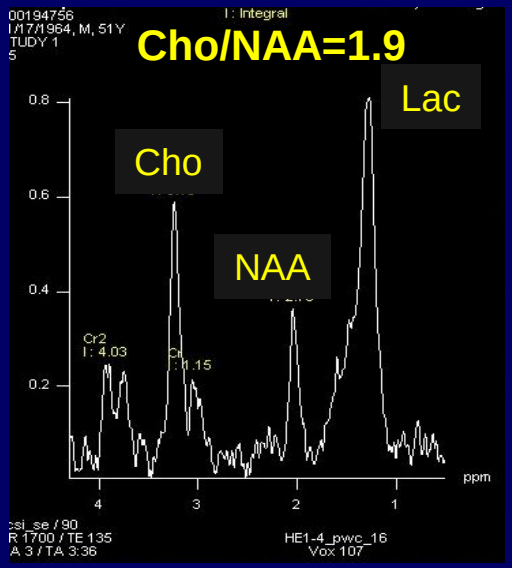
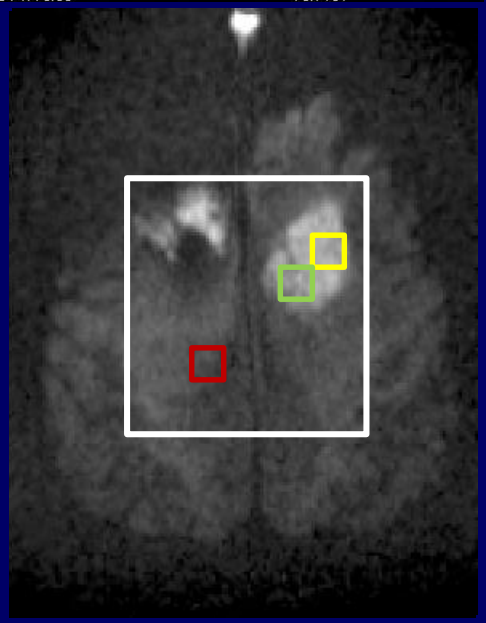
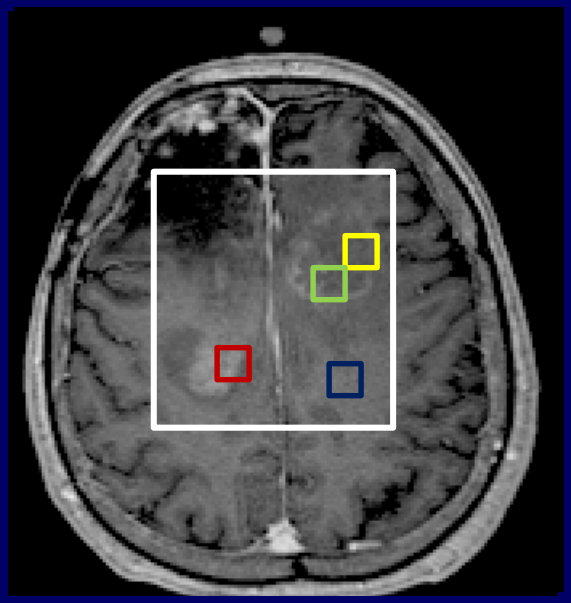
Cross-Comparison

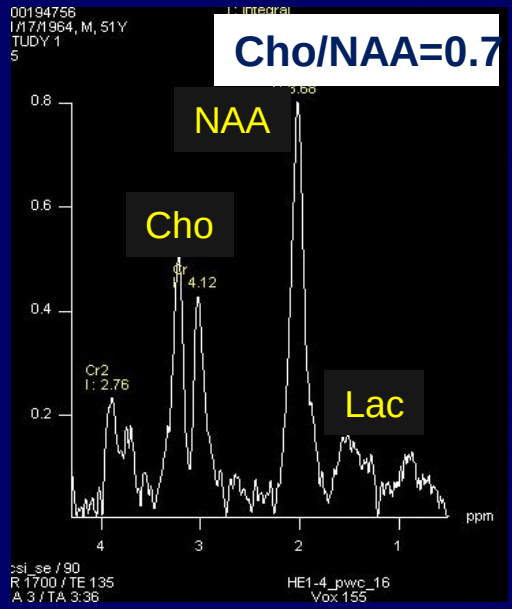












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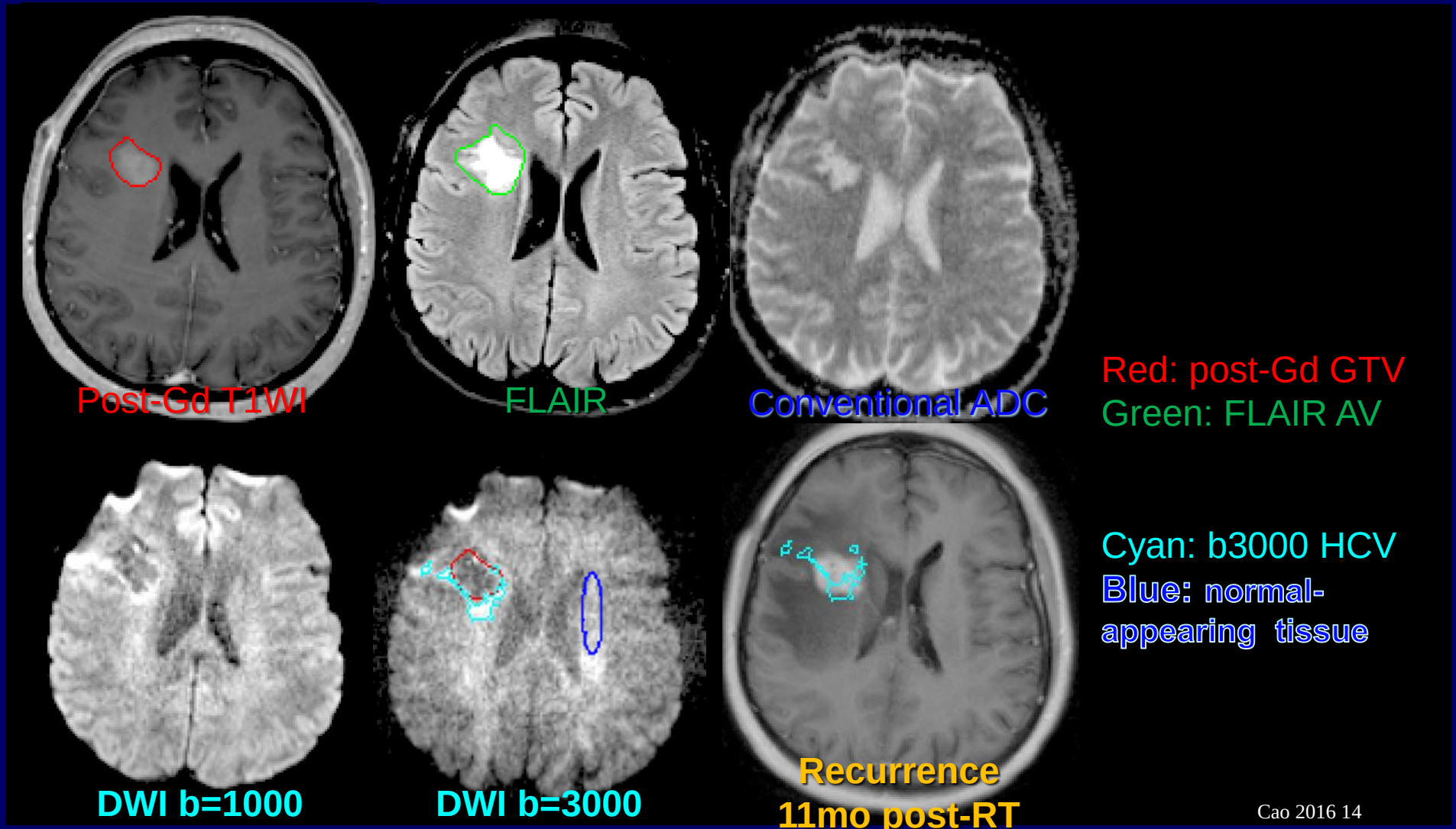
HCV vs Pattern of Failure



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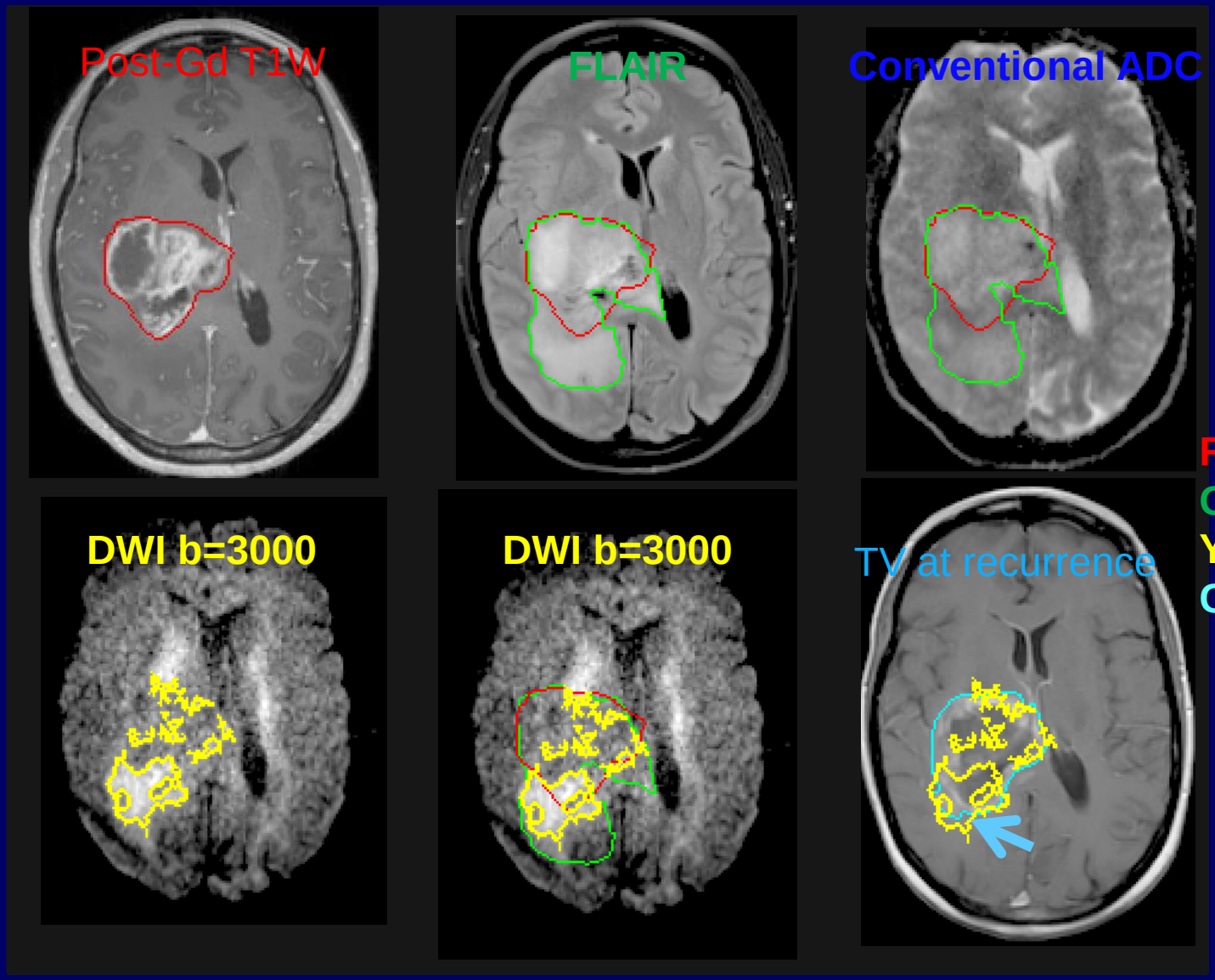
HCV vs Pattern of Failure



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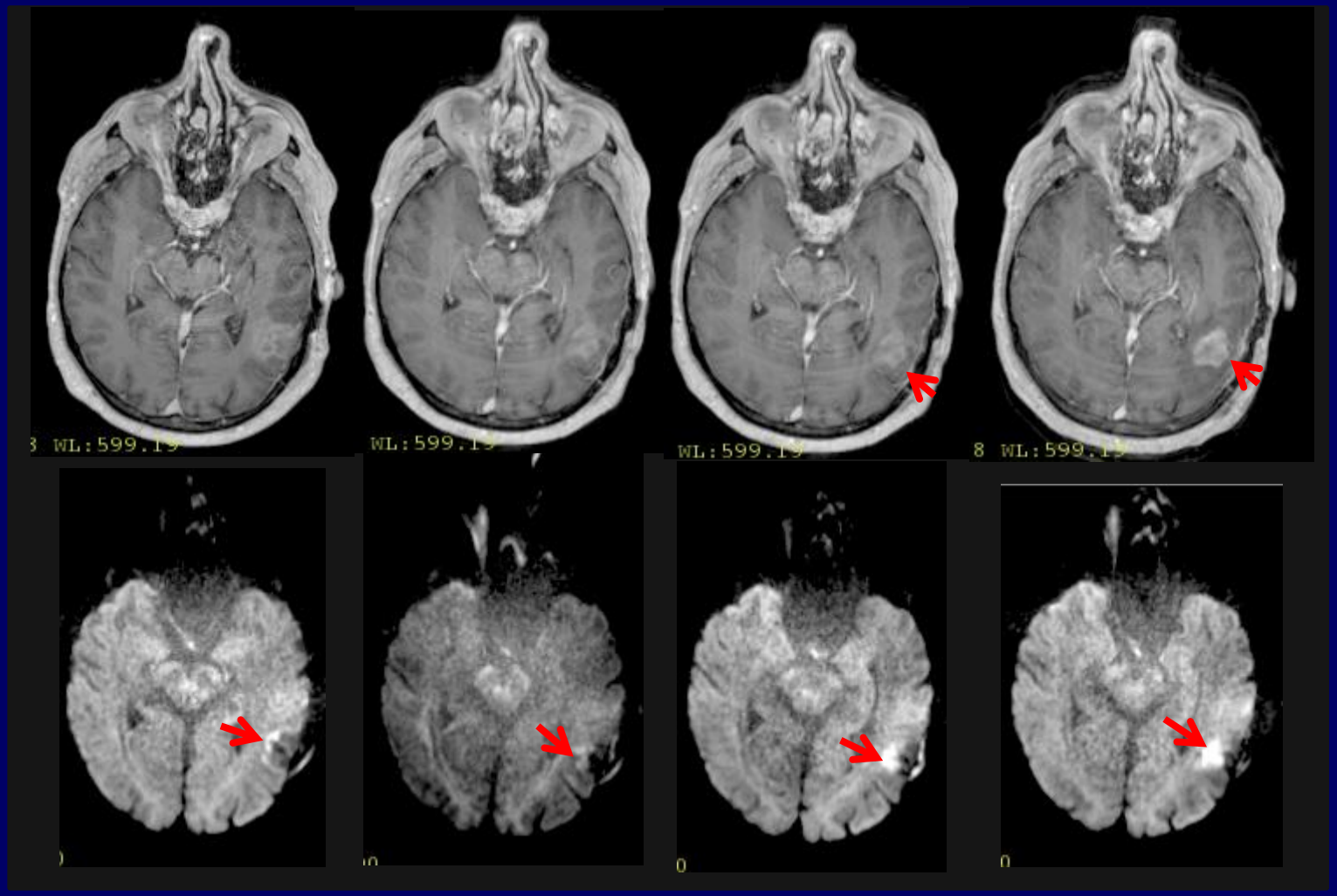
Early Detection of Progression



Pre-RT

Week 3 During RT

Week 6 During RT

1M post RT

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Progression and Survival

- 35 Patients
  - ✓Progression
    - ✓ 28 patients had progression clinically
      - ✓Median PSF of 12 months
    - ✓ 6 had no progression and 1 dead without progression
  - ✓Survival
    - ✓ 22 patients were dead
      - ✓Median OS of 17.5 months
    - ✓ 13 were alive with a median followup of 20 months

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Prediction for PSF and OS

- The HCV pre-RT predicted PSF and ($p<0.003$) and OS ($p<0.05$, univariate Cox regression)
- Considering MGMT status in a multivariate Cox regression model, the HCV pre-RT was still a significant predictor for OS ($p<0.002$)

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Discussions and Conclusion

- The HCV identified by high b-value diffusion imaging is aggressive.
- Using FLAIR AV to define non-enhanced tumor could result in high-risk of radiation toxicity.
- High b-value DW imaging could provide a means to extract hypercellularity components of GB, and define radiation boosting target and assess response.
- A phase II trial is in preparation.

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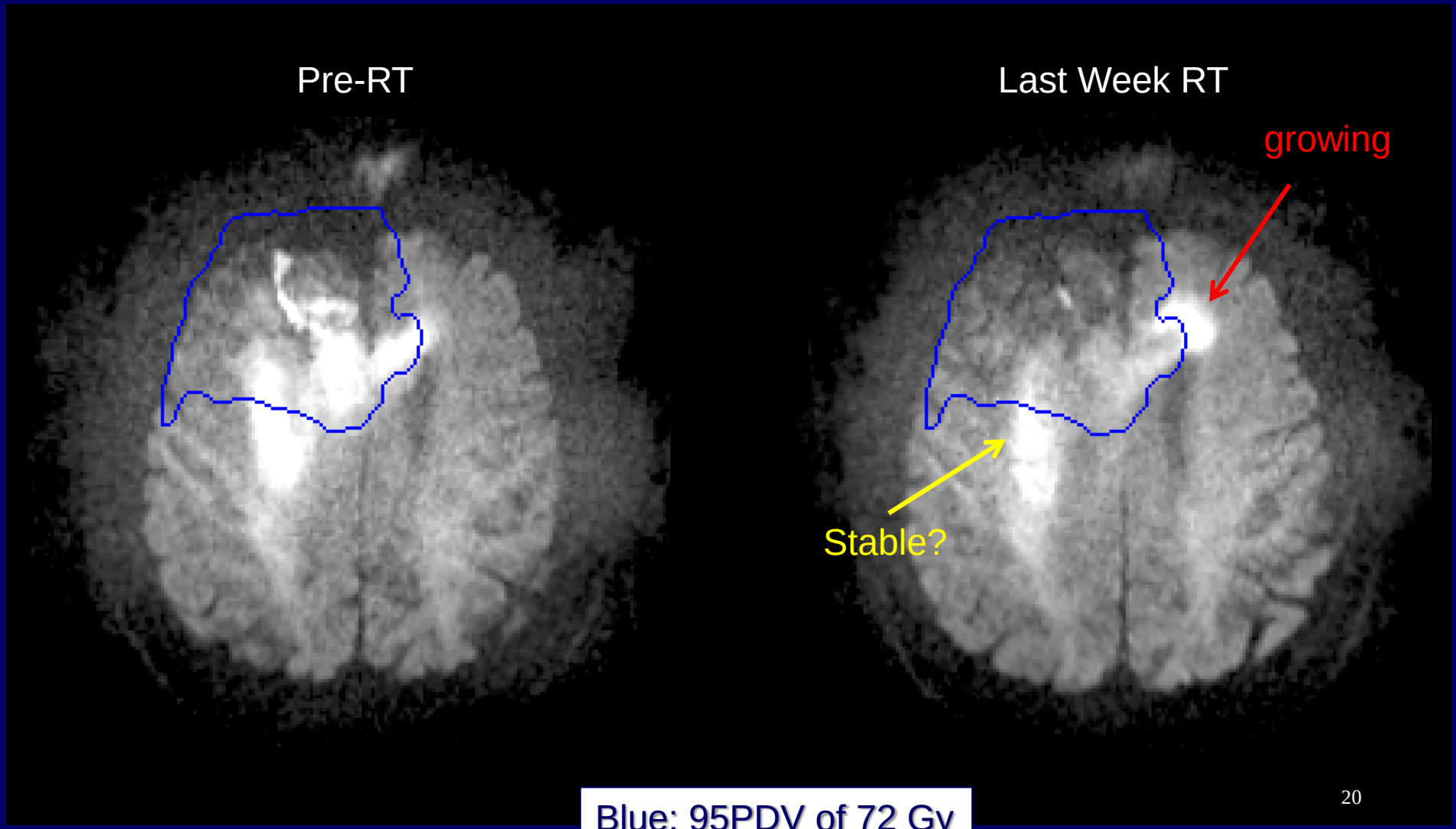
Results: Dose Coverage & HCV Changes



Blue: 95PDV of 72 Gy

MRI Characteristics and Changes

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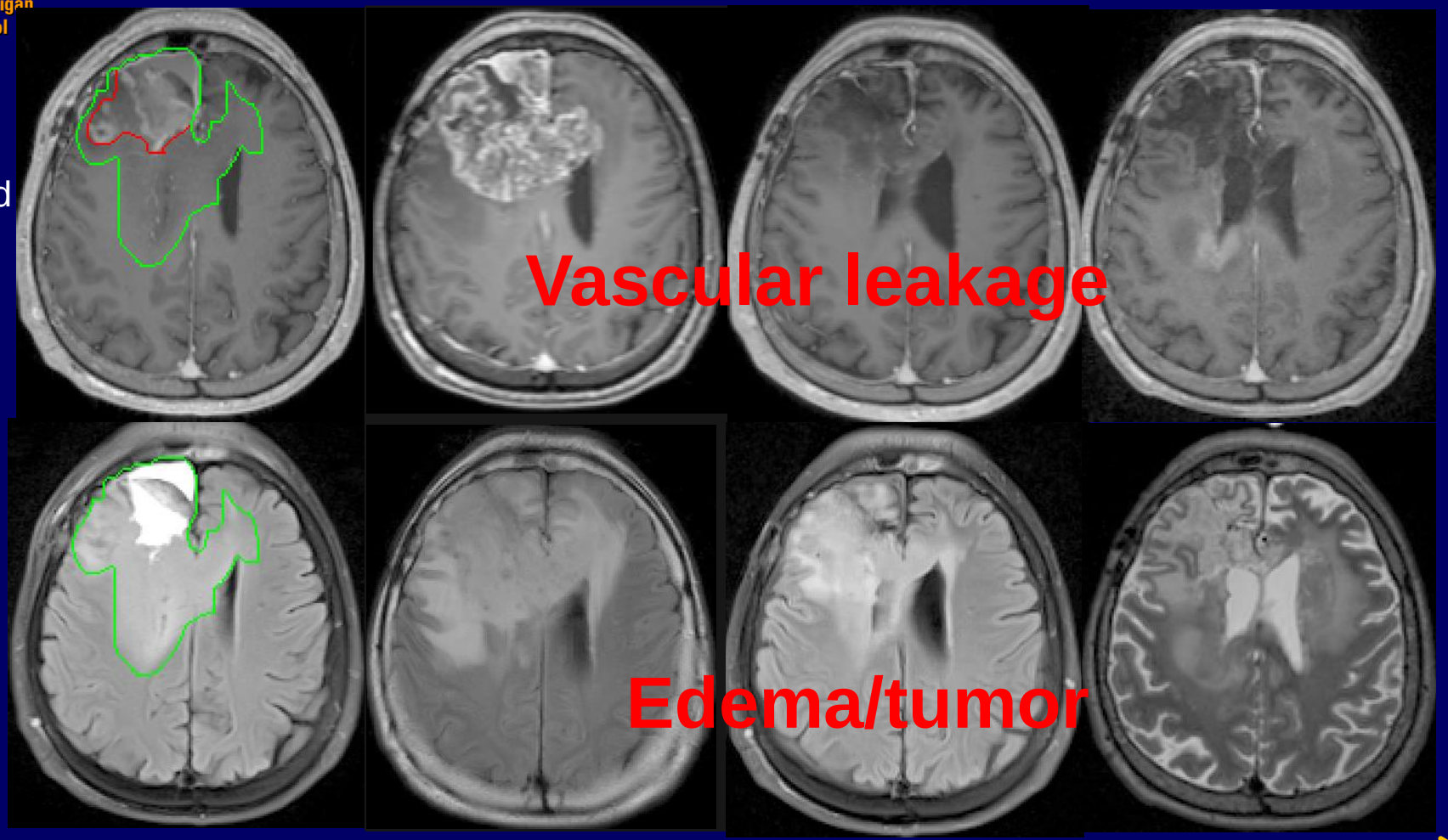

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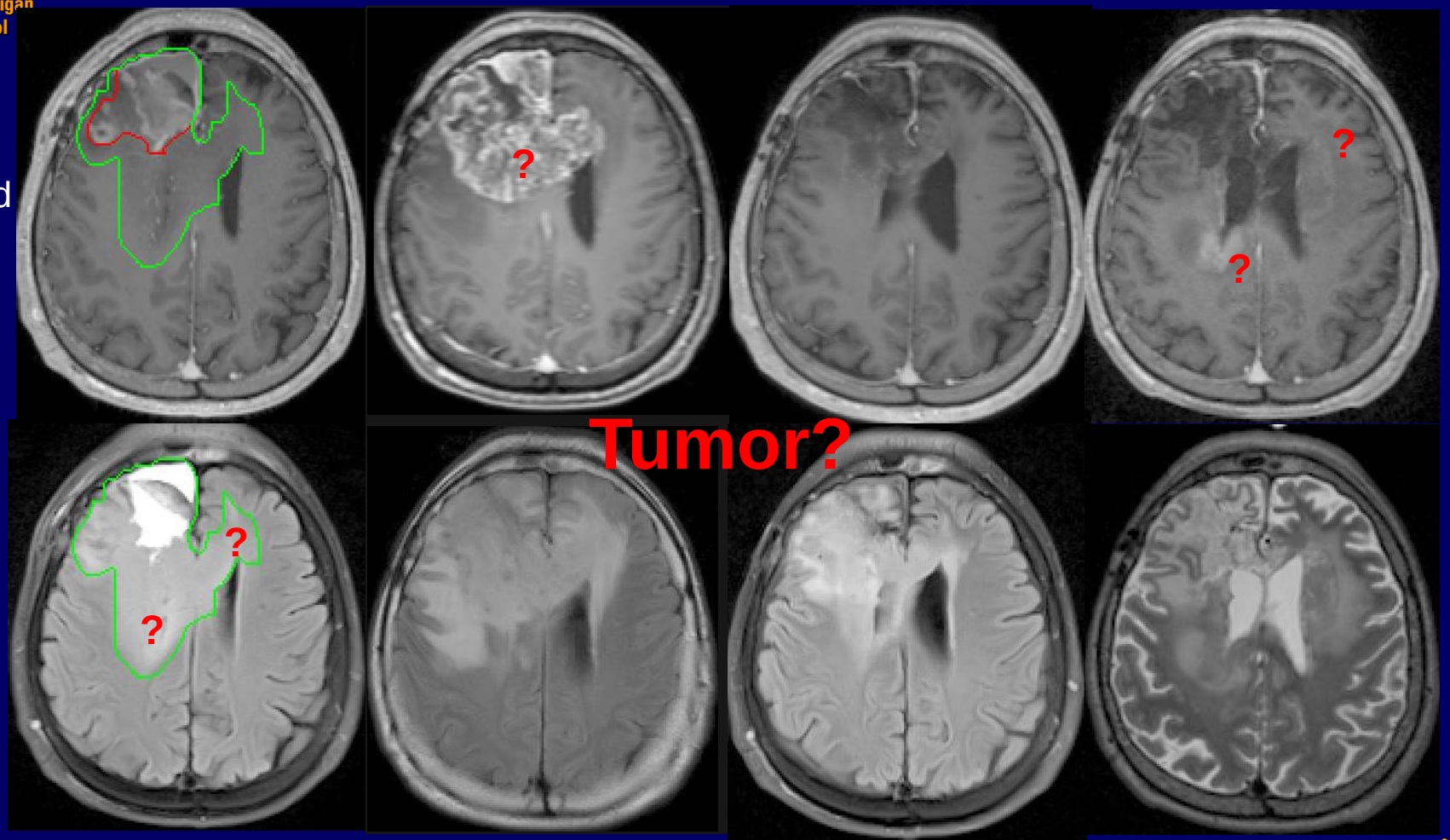
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