Toward Patient-Specific Radiotherapy: Biologically Informed Tumor Targeting in Glioblastoma

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Overview

Discuss limitations of conventional imaging for radiation planning and response assessment

Identify key advanced MRI techniques suitable for prognostication and patient treatment

Explain emerging evidence for novel uses of advanced MRI for glioma radiotherapy

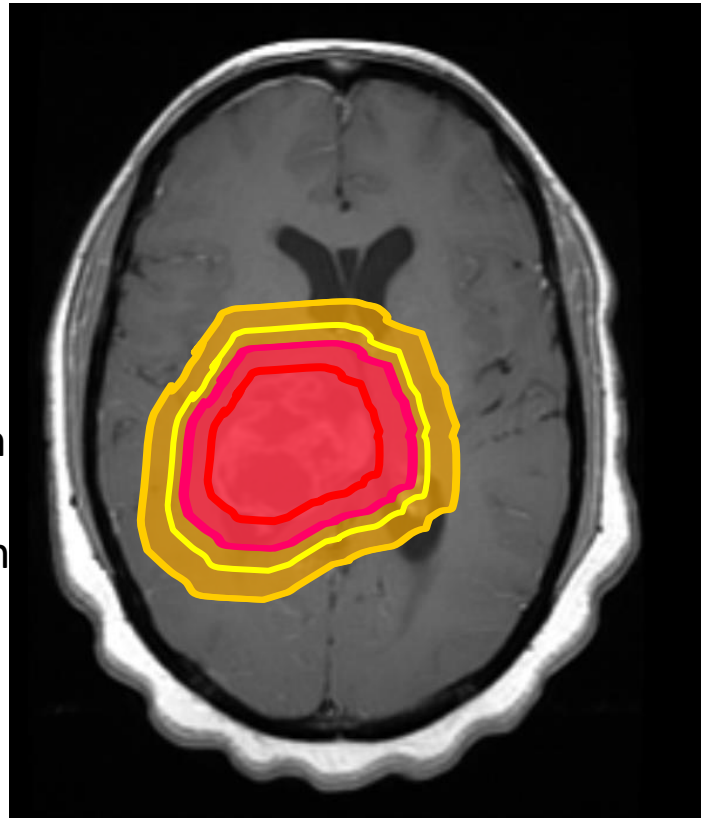
Standard Radiation Treatment Planning = Anatomic tumor extent at a single pre-treatment time point

GTV= T1 post gad enhanced tumor

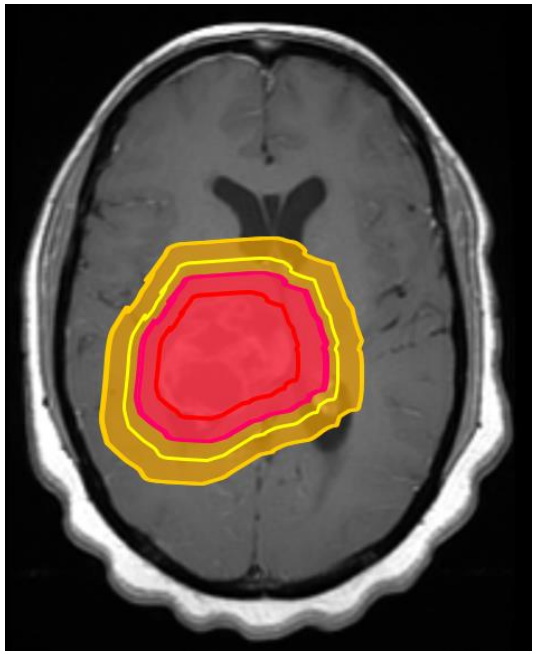
CTV= GTV + 1 cm

PTV1 = CTV + 0.5 cm

PTV2 = GTV + 0.5 cm



Tumor heterogeneity is the underlying basis for treatment resistance



Qazi et al, Ann Oncol 28 (7):1448-56, 2017

Towards patient-specific radiotherapy

To overcome tumor heterogeneity that limits efficacy of targeted drug treatments

To identify biologically aggressive tumor regions missed using anatomic imaging

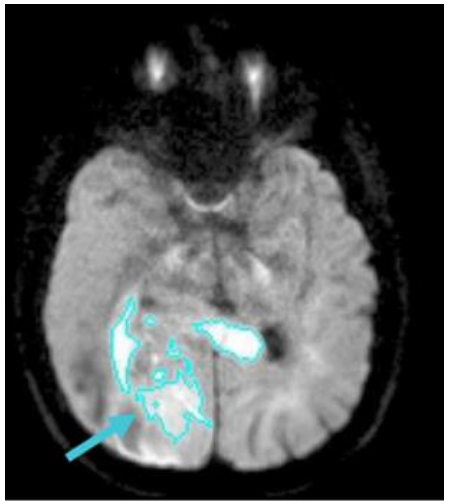
To overcome treatment resistance due to temporal heterogeneity secondary to tumor evolution

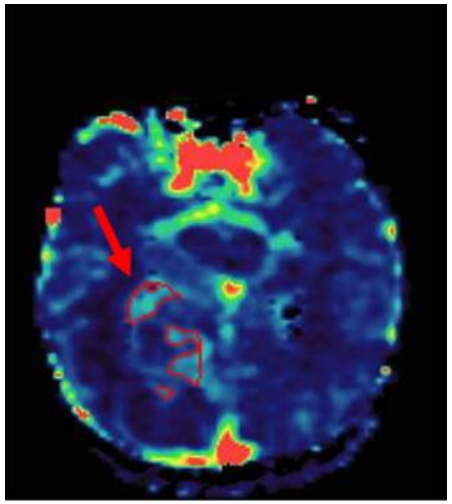
Kim MM et al, Nat Rev Clin Oncol 13(12): 725-39, 2016

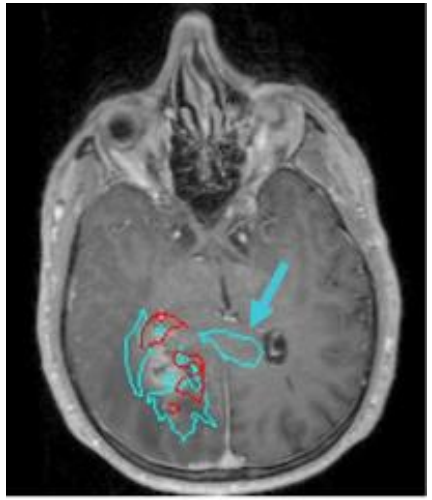
Rationale for multiparametric MRI in GBM

- Both perfusion and diffusion MRI are routinely acquired in brain tumor imaging protocols

- In multiparametric combination, may capture tumor heterogeneity better than single imaging modality alone

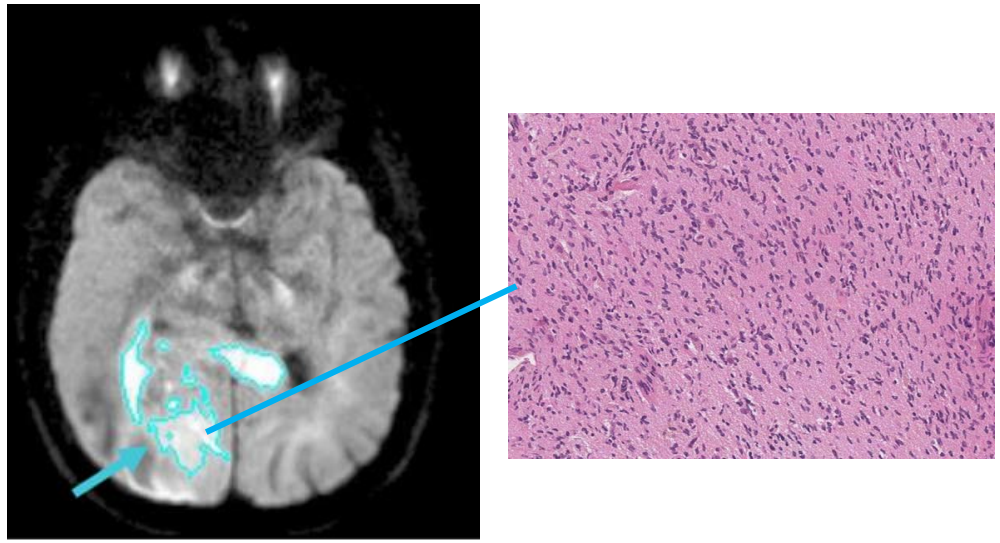






Diffusion-weighted MRI: Tumor cellularity

Hypercellular Tumor Volume (HCV)



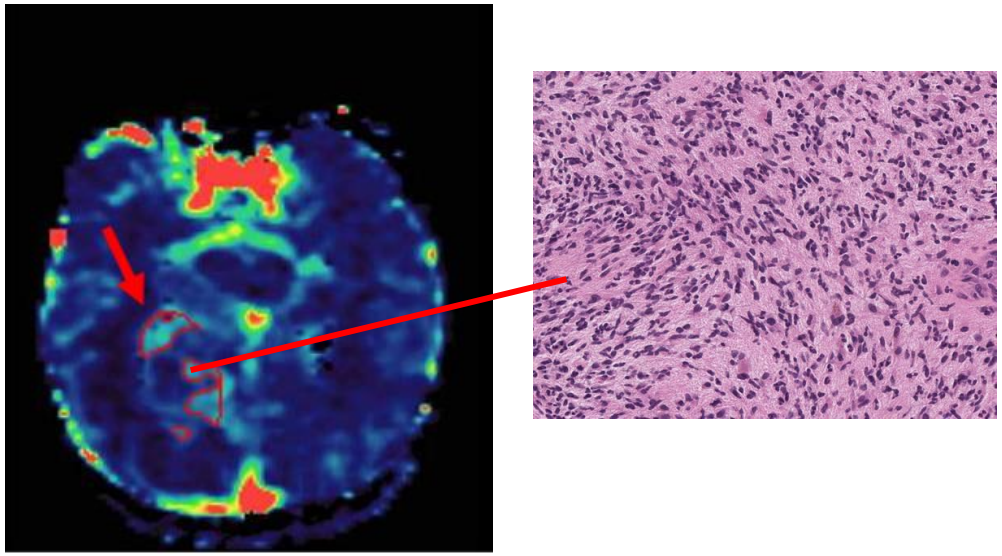
- Conventional DW-MRI (b=0-1000 s/mm2) assesses mobility of water in tissue microenvironment as a surrogate for tumor cellularity, but cannot sistinguish peritumoral edema from cellular tumor

- High b-value DW-MRI (b=3000 s/mm2) allows for specific delineation of tumor cellularity (vs edema) compared with conventional ADC, and identifies aggressive tumor regions that predict recurrence and PFS

Pramanik… Kim MM et al, IJROBP 2015, Aronen CCR 2000, Cao Seminars 2011

DCE-Perfusion MRI: Cerebral blood volume

Hyperperfused tumor volume (hCBV)



- Elevated in growth and neovascularization in GBM, and predicts recurrence and survival beyond clinical factors and anatomic MRI
- Elevated mean relative CBV (rCBV) >1.75 in gliomas is associated with shorter time to progression and predicts OS
- More suitable for precision radiotherapy due to reduced geometric distortion than DSC-MRI

Pramanik… Kim MM et al, IJROBP 2015, Aronen CCR 2000, Cao Seminars 2011

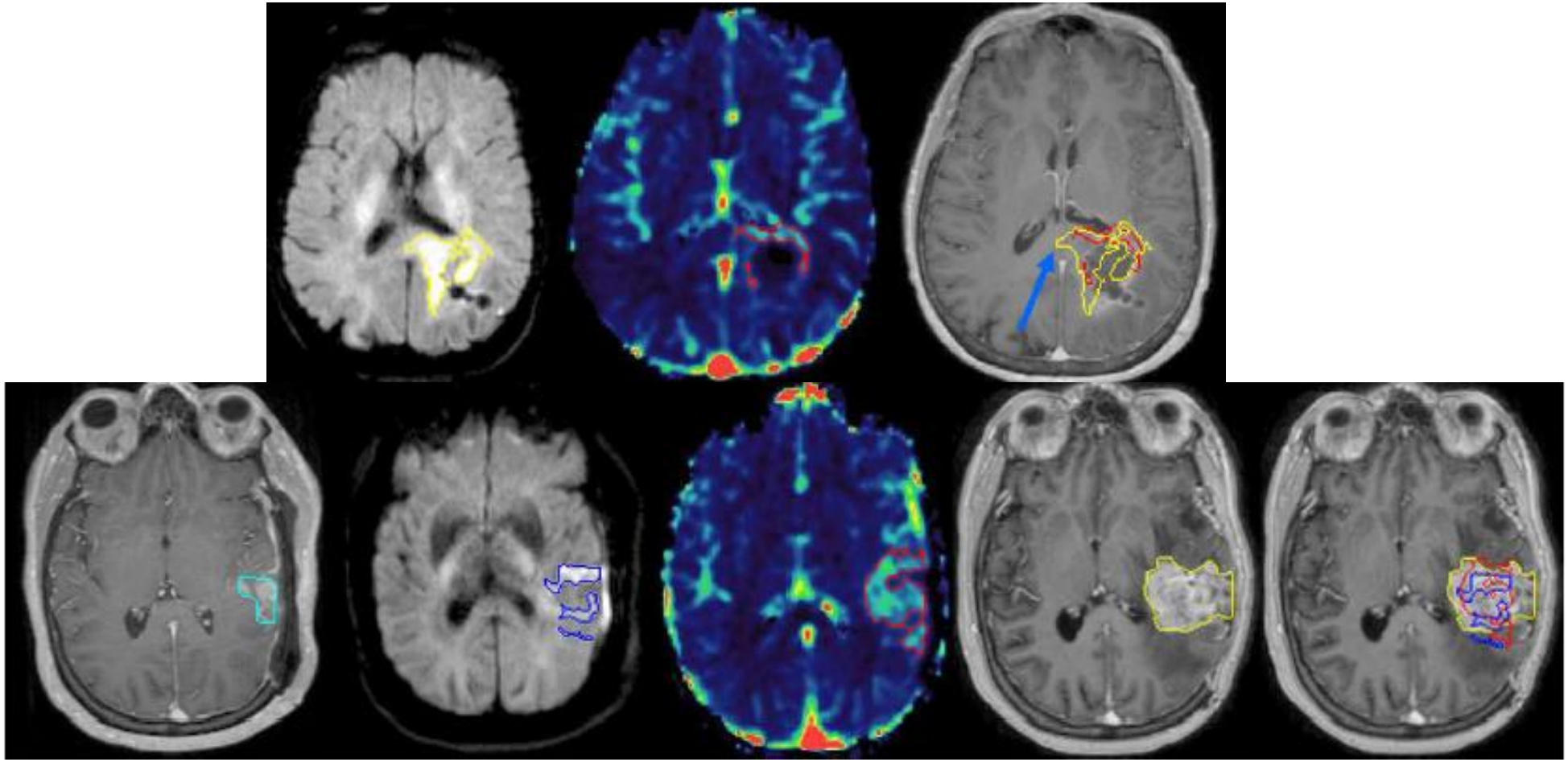
Translational relevance

The combination of both HCV and hCBV in GBM yields

- Highest prediction of survival
- Greatest spatial overlap with eventual tumor recurrence (80% likelihood of progression)
- Identifies tumor outside of enhancement 40% of the time (missed by RT and predictive of worse PFS)
- 1.5-2X smaller than the enhancing tumor

Pramanik… Kim MM et al IJROBP 2015, Wahl, Kim MM et al IJROBP 2018

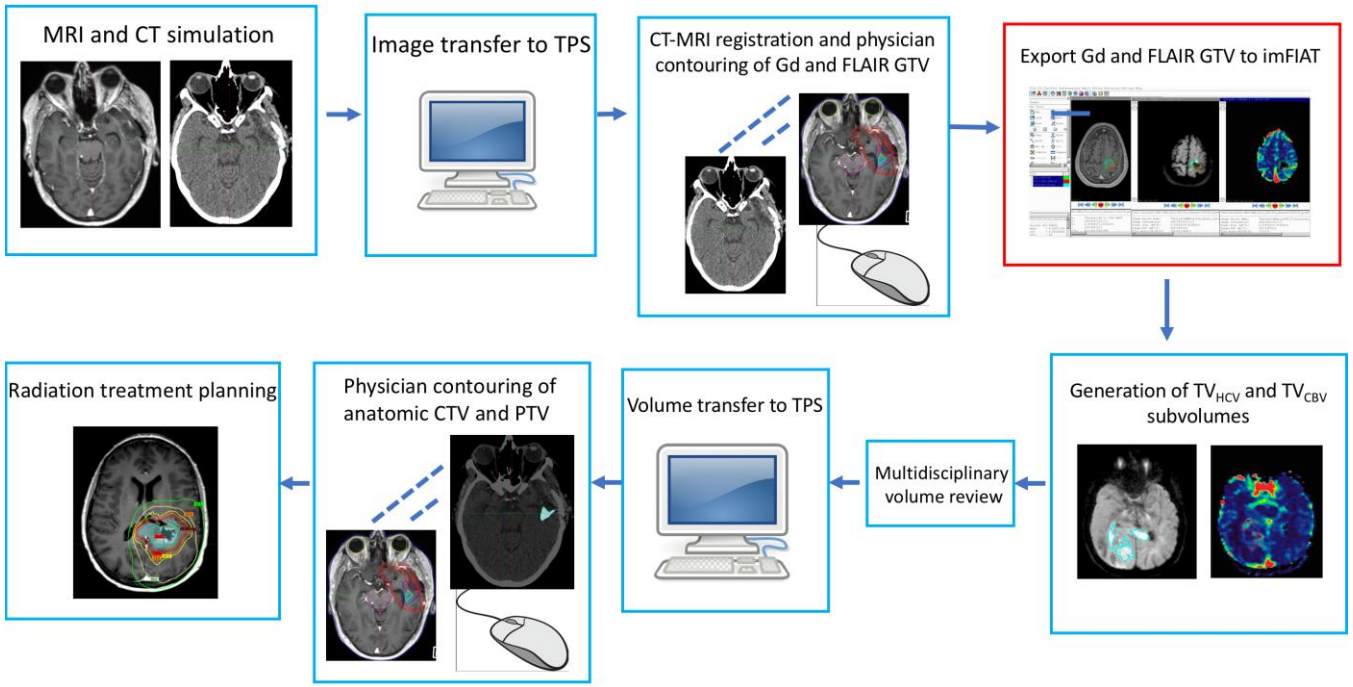
Multiparametric MRI over single-modality



Phase II Study

26 patients with newly diagnosed GBM

75 Gy/30 fractions to HCV/hCBV, 60 Gy to anatomic target



Kim MM et al, Tomography 5(1): 118-26
Kim MM IJROBP 2021, in press

Phase II Study

Hypothesis: Dose-intensified targeting of hyperperfused and hypercellular tumor regions identified with multiparametric MRI improves survival in patients with GBM

Primary endpoint: Improvement in 12 month OS vs historical control (0.65)

Secondary objectives:

- Characterize patterns of recurrence
- Determine incidence of grade 3+ neurologic toxicity (CTCAE v4.03)
- Estimate clinically meaningful change in symptoms, QOL, and neurocognitive function
- Analyze relationship between mid-RT and 3-month hypercellular/hyperperfused tumor and OS

Patient characteristics

Median age 61 (IQR 56-66)

70% male

ECOG 0 (22%) and 1 (74%)

Gross total resection 57%, subtotal resection 30%

22% MGMT methylated, all IDHwt (1 unknown)

Imaging characteristics

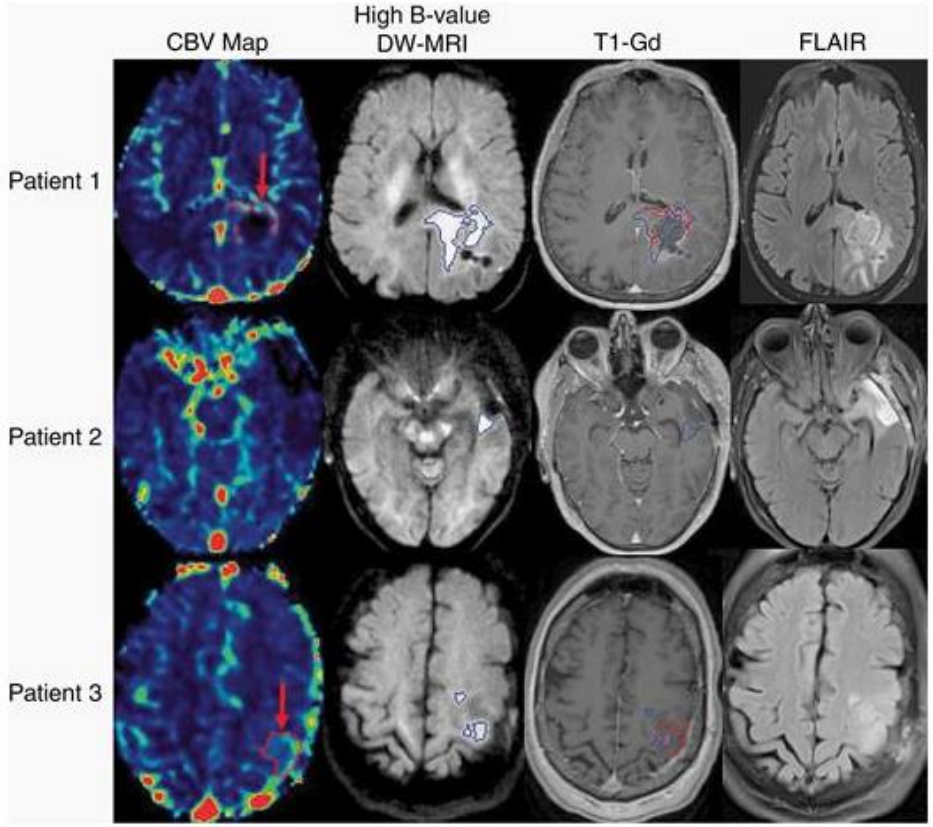
Enhancing tumor volume: 17 cc (11-34)

Combined hypercellular/hyperperfused tumor: 11 cc (7-20)

Overlap: 1 cc (0-1)

Hypercellular tumor volume: 6 cc (4-11)

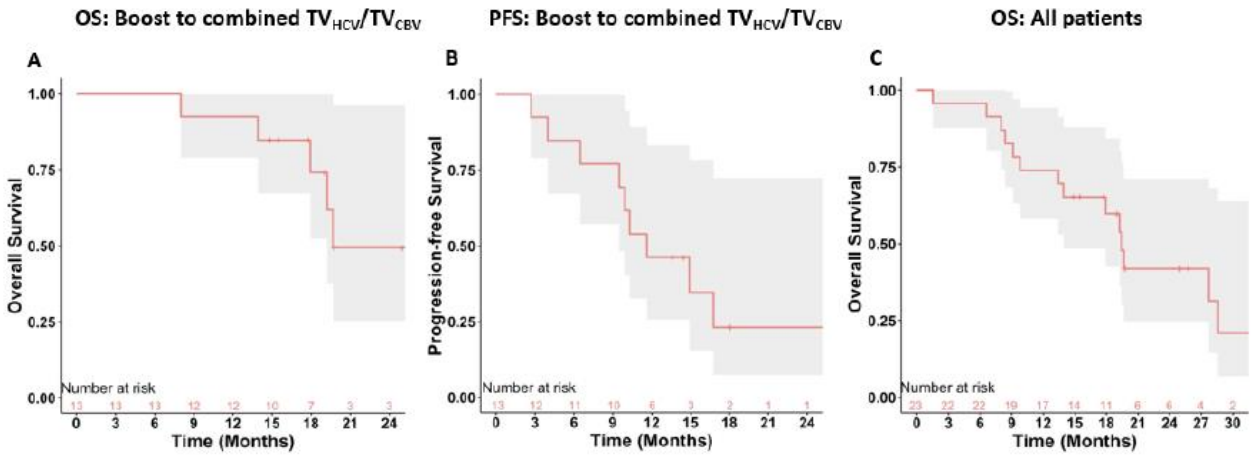
Hyperperfused tumor volume: 5 cc (2-10)



Kim MM IJROBP 2021, in press
Kim MM Neuro-Oncology 2021, in press

Survival and patterns of failure

12-month OS 92% (95%CI 78-100%) (p=0.03)



Pattern of failure:

5/16 (31%) central or in-field

69% outside of boost region, 20% distant failure

Limitations of current response assessment criteria

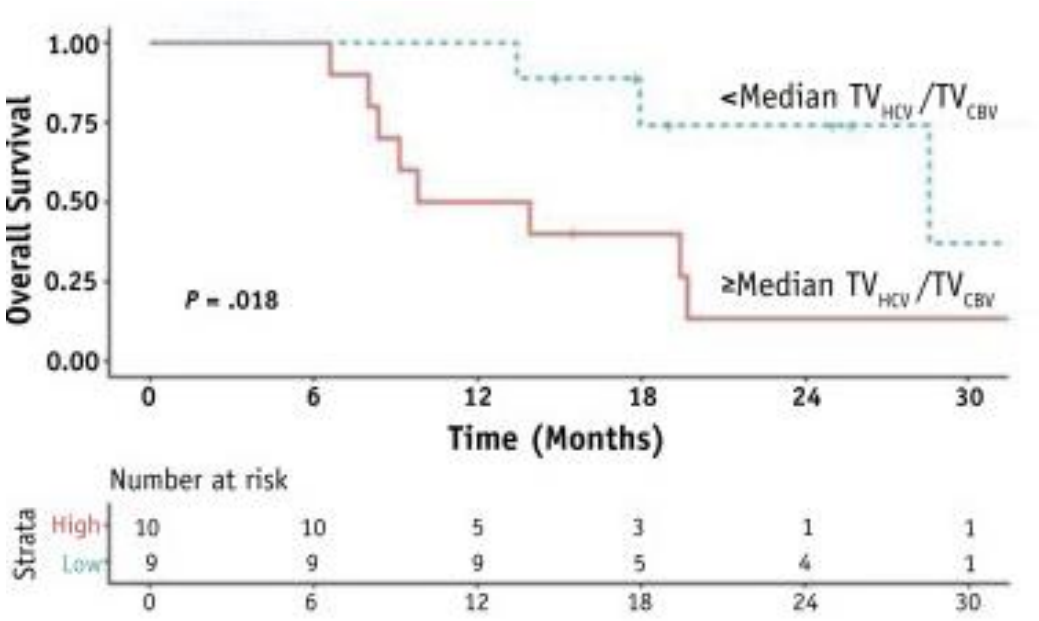
Response **A**ssessment in **N**euro-**O**ncology Criteria (RANO):

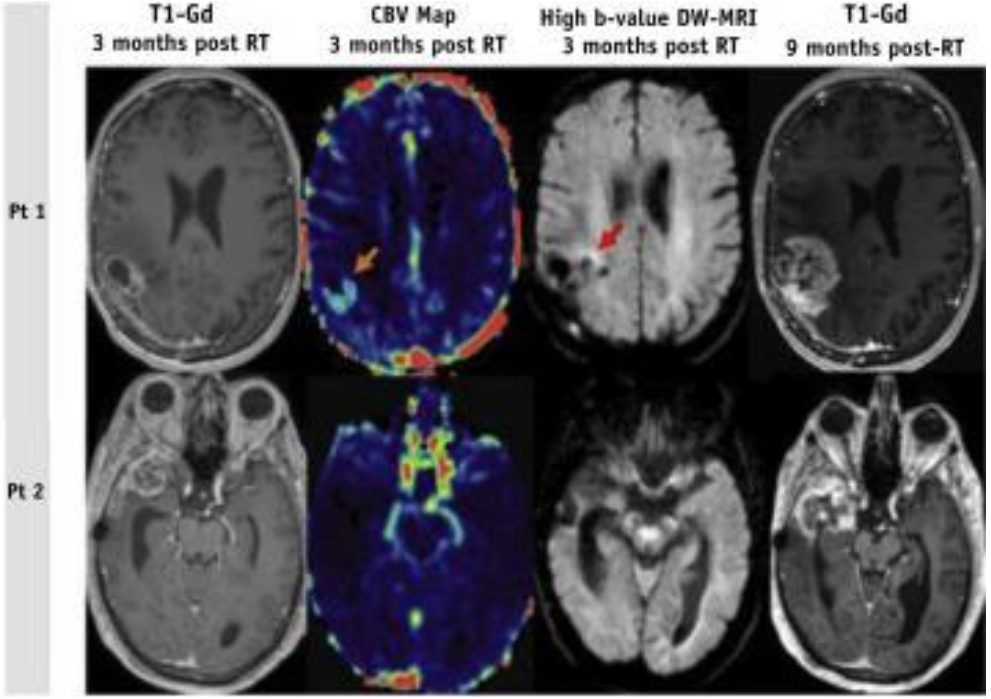
- Constrained by anatomic imaging (T1 gadolininium enhanced, T2 FLAIR MRI)
- Cannot be used to reliably assess tumor status within 3 months post-chemoRT (non-specific treatment-related imaging changes)
- No known role for response assessment during chemoradiotherapy

90% of patients were categorized as having Stable Disease at 3 months

Early patient stratification post-chemoradiation

3-month response in the hypercellular/hyperperfused tumor volume yielded superior OS



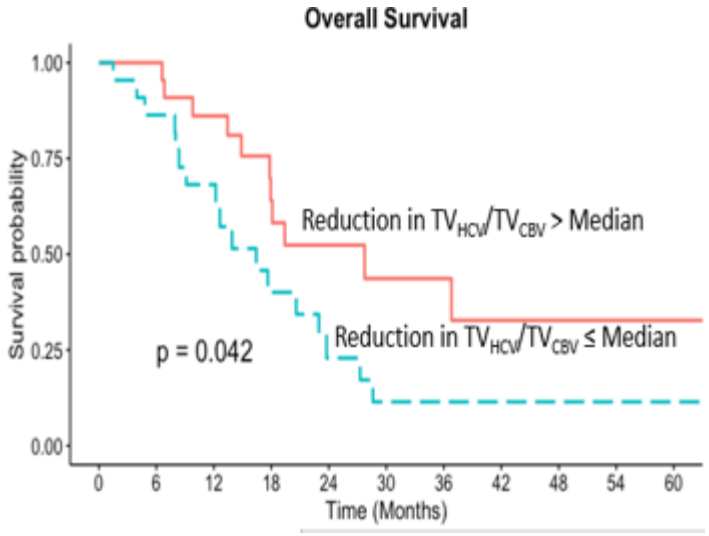


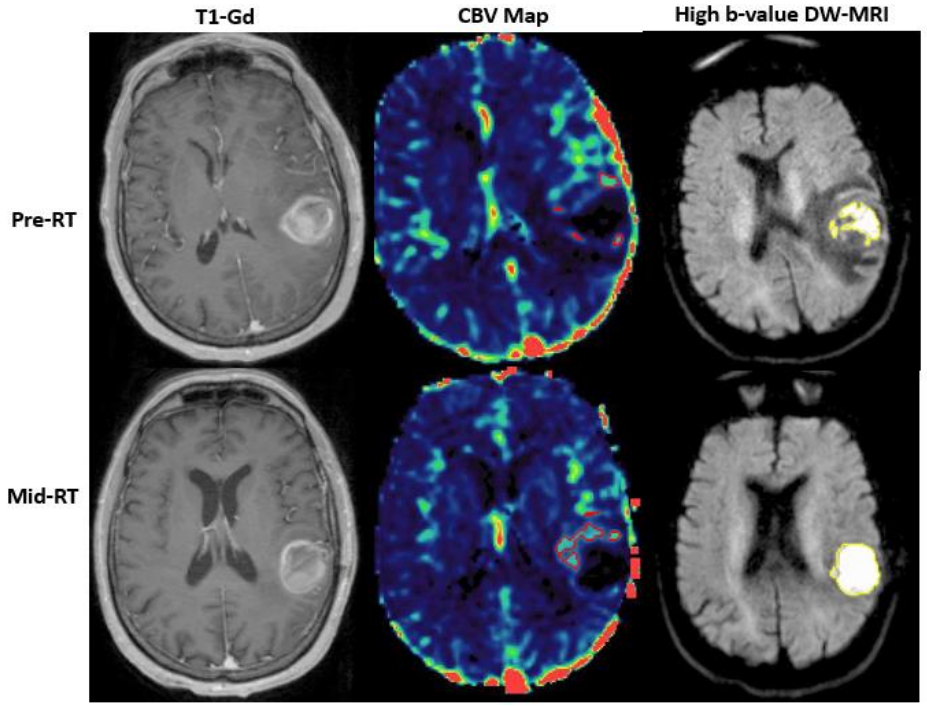
Kim MM IJROBP 2021, in press

Improving the therapeutic ratio: response assessment *during* radiation

Suboptimal response of hypercellular/hyperperfused tumor volume

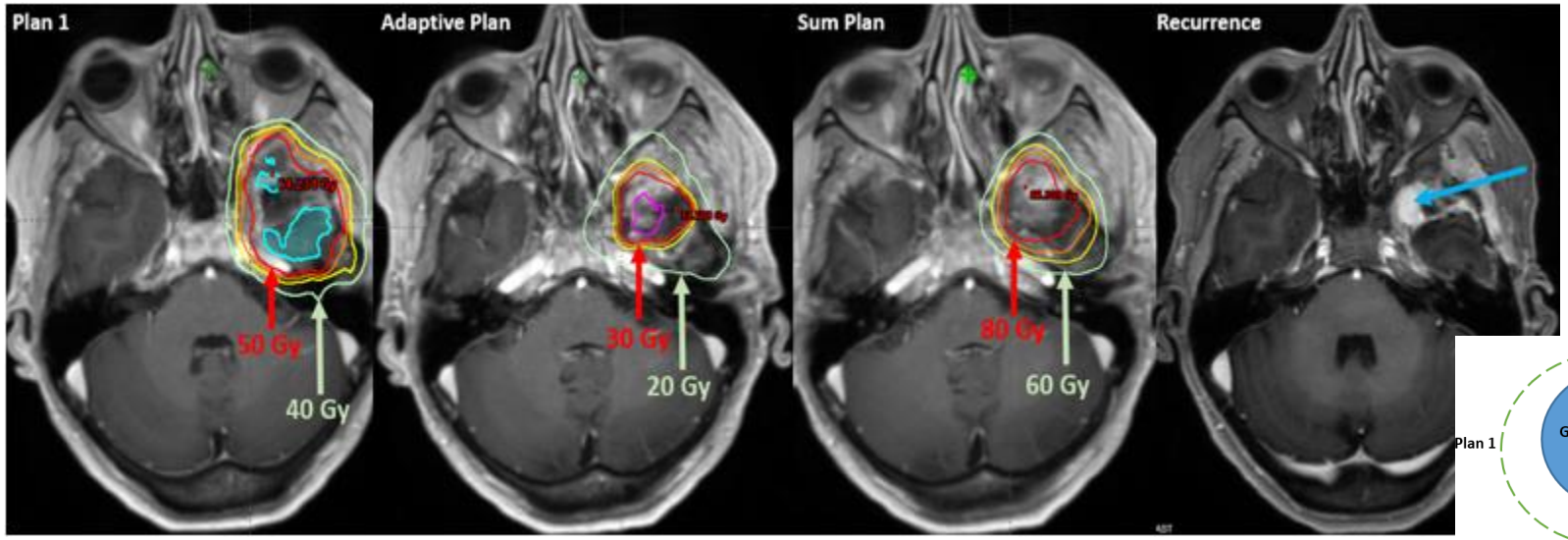
associated with worse PFS and OS, independent of age, extent of residual enhancing tumor, and MGMT methylation status

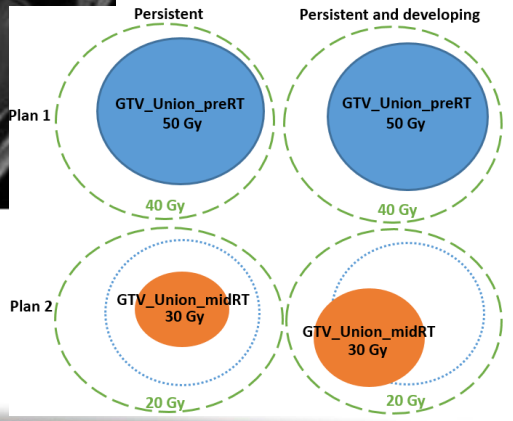




Towards patient-specific radiotherapy

Ongoing Phase II Study of Multiparametric MR-Guided High Dose Adaptive Radiotherapy in Glioblastoma (NCT04574856)





Conclusions

Anatomic MRI is limited in its specificity, biology, definition of tumor extent and characterization of tumor heterogeneity

Advanced MRI techniques are complementary to anatomic MRI, prognostic and spatially predictive of tumor recurrence, and in multiparametric combination may better capture tumor heterogeneity than single imaging techniques

Incorporation of advanced MRI to guide precision radiotherapy and permit early response assessment may enable true individualization of patient treatment before and during therapy