ALLIANCE A221208:
Phase II Randomized Study of Bevacizumab vs. Steroids (BeSt) for Radionecrosis after Radiosurgery for Brain Mets

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Med Onc Co-Chair:	Glenn Lesser
Community Oncology Co-Chair:	Christopher Goulet
Neurosurgery Co-Chair:	Ian Parney
Neuroradiology Imaging Co-Chair:	Tim Kaufmann
Health Outcomes Co-Chair:	Terri Armstrong
Biomarkers Correlative Co-Chairs:	Erik Sulman
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Statistics:	Rui Qin
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THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®

Radiation Oncology UNIVERSITY OF TORONTO

Background

- ~ 10-30% patients develop brain radionecrosis following SRS[1]
- Incidence of brain radionecrosis ↑ (longer survival, more high-dose RT, SRS, repeat RT)
- Corticosteroids are effective, but not for all patients
- Prolonged corticosteroids can be associated with ++ toxicity

Proposed mechanism:

VEGF ↑ → vascular permeability ↑ → edema,hypoxia ↑ → white matter necrosis

⊤ Bevacizumab

Clinical evidence:

- Small studies of bevacizumab for radionecrosis show radiological and clinical response[2-4]

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[1]Shaw, E – IJROBP 2000 [2]Gonzales J – IJROBP 2007 [3]Wong ET – JCO 2008 [4]Levin – IJROBP 2011

Hypothesis

- Hypothesis: Bevacizumab will provide greater clinical and radiological improvement resulting in greater improvement in the severity of symptoms, neurological and cognitive impairment compared to conservative management with corticosteroids.

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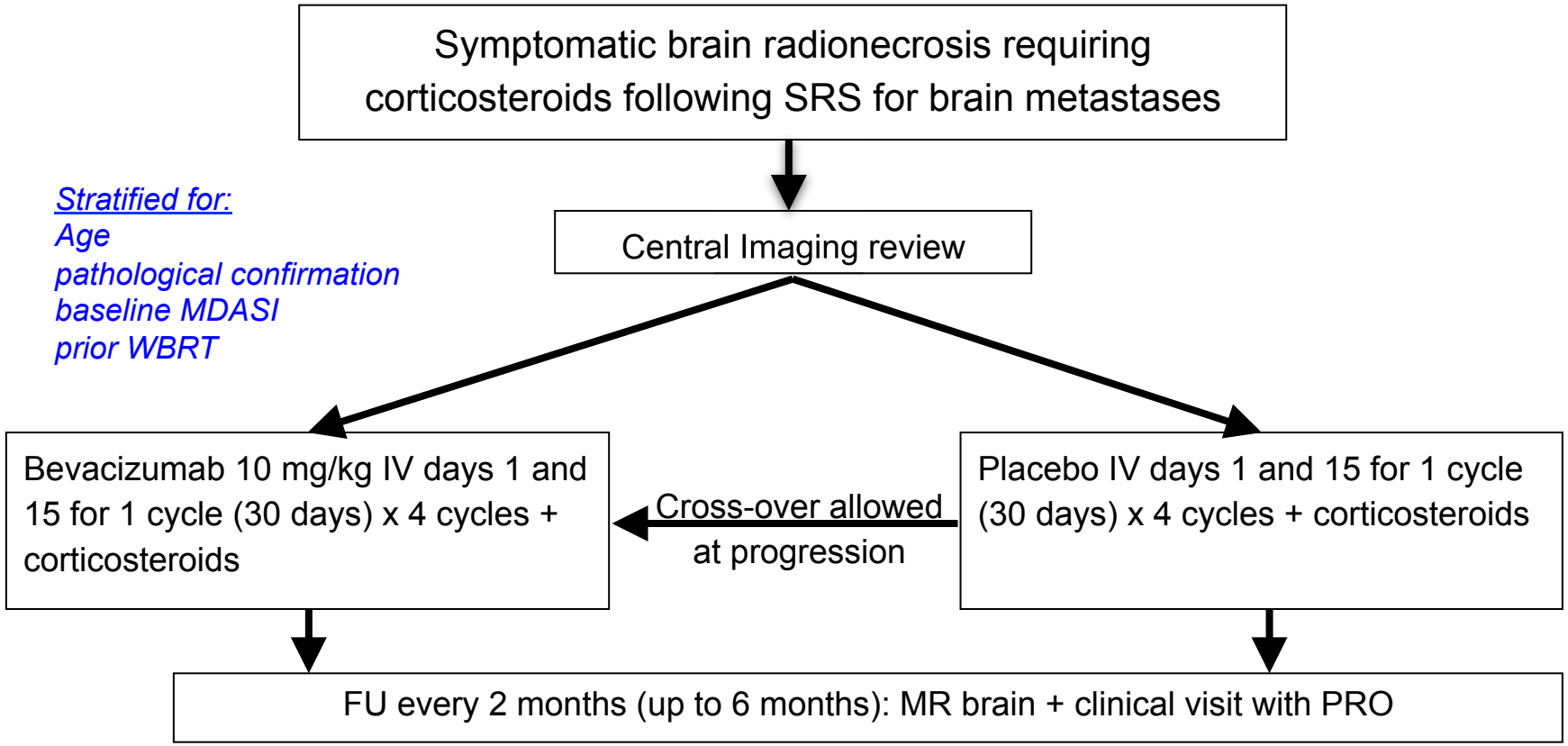
Study Schema

Randomized phase II study of bevacizumab vs. steroid therapy in patients diagnosed with radionecrosis following radiosurgery. **N= 130, 65 per arm**



After 6 months: event monitoring only

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Drug is provided

Eligibility

Inclusion Criteria

- Symptomatic brain radionecrosis defined by onset of symptoms at 3-24 months post-SRS that requires steroid intervention and meets the following radiological criteria:
  - Lesion quotient < 0.3 [1]
  - DSC [2]- At least 1:
    - rCBV <1.5
    - PSR $\geq$ 76%
- Life expectancy $>$ 6 months
- KPS $\geq$ 60%
- Acceptable organ function (bone marrow, renal, liver

Exclusion Criteria

- Acute intracranial/intratumoral hemorrhage
- Glioma or brain mets from melanoma, RCC
- Non-approved systemic therapies (2 wks prior to registration or planned $<$ 1 mo after registration)
- **Except:** Maintenance herceptin or hormonal therapies OR 'Approved systemic' therapies [Appendix]

Standard C/I to bevacizumab:

- Major surgical procedure within 28 days or core biopsy within 7 days
- Pregnant or nursing
- PT INR >1.5
- Bleeding diathesis, coagulopathy, non-healing wound/ ulcer, bowel obstruction/fistula/GI perforation
- Significant cardiovascular disease
- Central lung met with xs active bleeding

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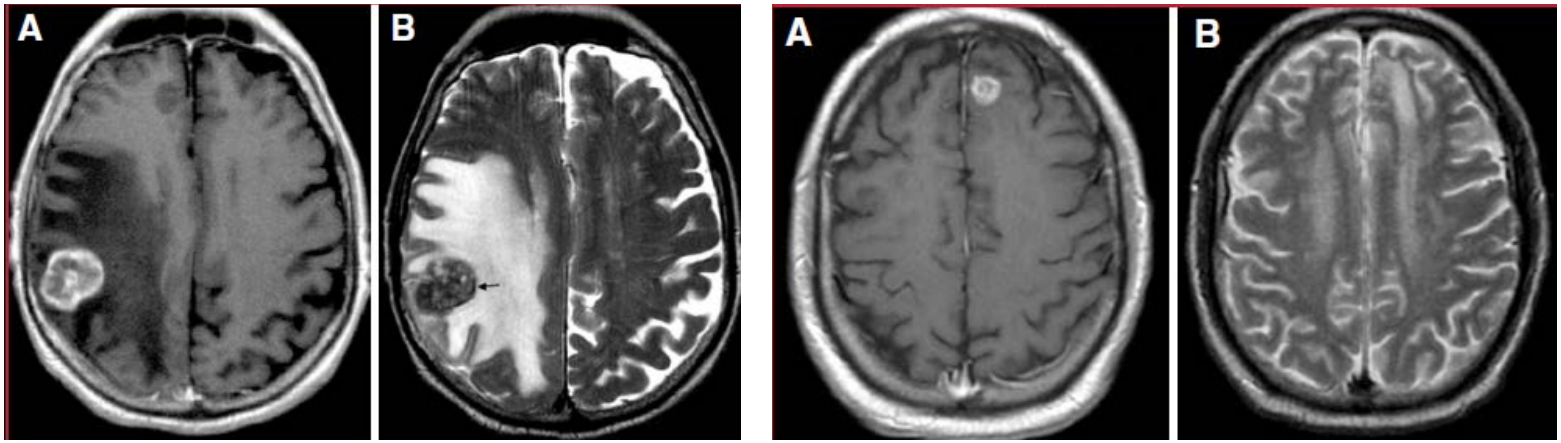
[1] *Kumar – Radiology 2000*
[2] *Barajas – AJNR 2009*

Radiological Diagnosis of Radionecrosis: Conventional Imaging



LESION QUOTIENT = maximal cross-sectional area of T2-w hyperintensity / maximal cross-sectional area of T1-gad enhancement

Stockham et al.
(n = 51 patients)

	Tumor (LQ>0.6)	Radionecrosis (LQ <0.3)
Sensitivity	59%	8%
Specificity	41%	91%
PPV	62%	25%
NPV	39%	73%

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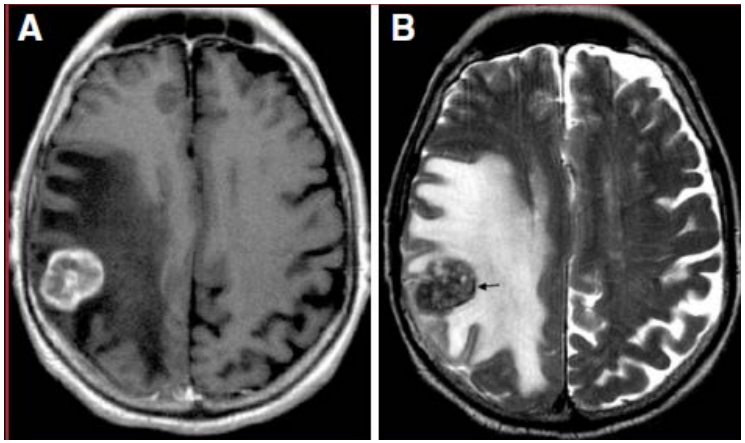
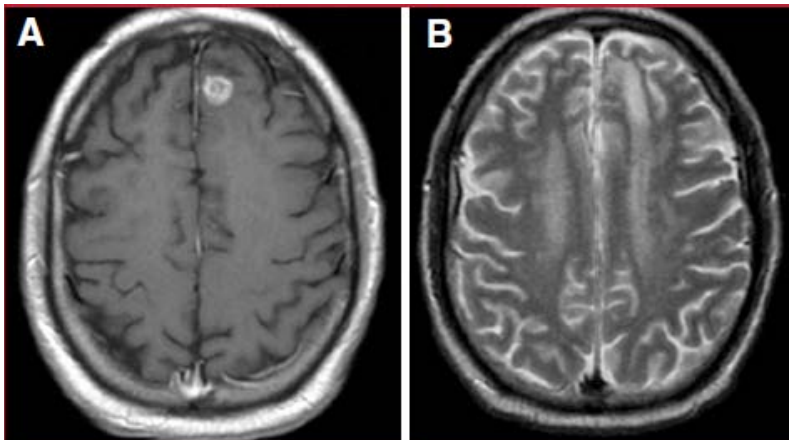
Kumar – Radiology 2000

Radionecrosis & Conventional Imaging: Lesion Quotient



LQ > 0.6 in tumor



LQ < 0.3 in 80% of radionecrosis

LESION QUOTIENT = maximal cross-sectional area of T2-w hyperintensity / maximal cross-sectional area of T1-gad enhancement

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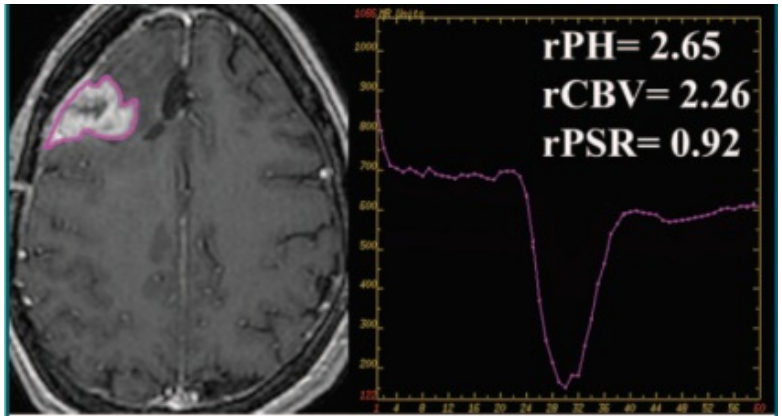
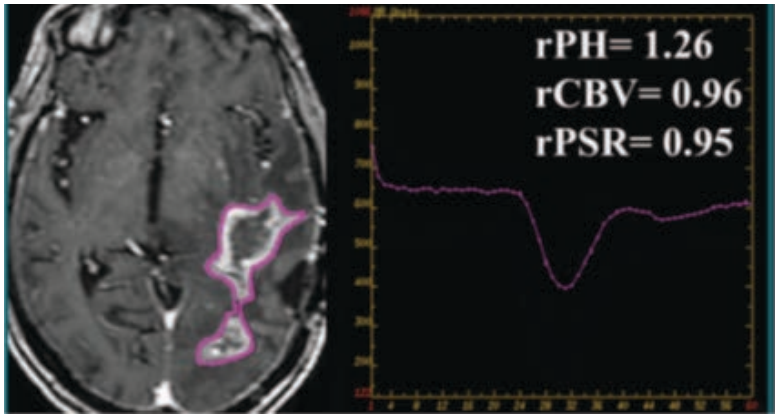
Kumar – Radiology 2000

Radionecrosis & Perfusion Imaging

Eligibility Criteria: **rCBV <1.5**
PSR ≥ 76%



Tumor



Radionecrosis

DSC Perfusion MR Imaging Measurements

Final Diagnosis	rCBV			rPSR		
	Mean*	Maximum*	Minimum*	Mean†	Maximum‡	Minimum§
Recurrent tumor	2.38 ± 0.87 (2.13, 2.63)	8.16 ± 2.92 (7.31, 9.01)	1.61 ± 0.65 (1.42, 1.80)	80.2 ± 10.3 (77.2, 83.2)	92.5 ± 18.8 (87.1, 97.9)	68.8 ± 10.9 (65.6, 72.0)
Radiation necrosis	1.57 ± 0.67 (1.28, 1.86)	4.63 ± 1.98 (3.76, 5.50)	0.94 ± 0.34 (0.79, 1.09)	89.3 ± 12.4 (83.9, 94.7)	100 ± 12.0 (94.7, 105.3)	77.2 ± 15.0 (70.6, 83.8)

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Barajas – AJNR 2009

Endpoints

- ***Primary Endpoint***
  - **Improvement in patient-reported symptoms** measured by MDASI-BT global symptom score (baseline then weeks 2, 4, 6, and 8)
- ***Secondary Endpoint(s)***
  - **Toxicities**: CTCAE version 4.0 & DSQ-C
  - **QoL**: LASA, MDASI-BT symptoms and interference scores
  - **PFS** (progression = restart higher dose steroids or alternative tx)
  - Time to maximum radiographic response
  - Corticosteroid requirements
- ***Correlative Endpoints:***
  - **Biofluid Biomarkers**: angiogenic factors:
    - Angiogenic markers: VEGF-A, B, C, D, angiopoietin-1 and 2, PDGF
    - inflammatory cytokines (TNF-α, TGF-β, IL1, and IL6)
    - genetic markers (Apo E)
  - **Imaging Biomarker Measures**: DWI (ADC), DCE (Ktrans, iAUC)

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Progress Update

- Central study activation April 29, 2016

- Note:
  - Drug is provided for initial randomization & cross-over
  - Correlative biomarker studies are optional

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