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

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

Study Co-Chairs:	Caroline Chung
	Warren Mason
Symptom Intervention Committee Chair:	Charles Loprinzi
Rad Onc Co-chairs:	Paul Brown
	Normand Laperriere
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
	David Grosshans

Alliance for Clinical Trials in Oncology

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Making Cancer History®

Background

- ~ 10-30% patients develop brain radionecrosis following SRS[1]
- Incidence of brain radionecrosis is rising
  - Longer survival
  - Rising cumulative RT dose with higher dose initial RT and increased reirradiation
  - Rising use of SRS
- Corticosteroids are effective, but not for all patients
- Prolonged corticosteroids can be associated with ++ toxicity

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

RTOG 90-05: Dose-Escalation Study

156 adults with solitary recurrent non-brainstem tumors with max diameter 4cm

36% primary (median prior dose 60 Gy)

64% brain mets (median prior dose 30 Gy)

Maximum Tolerated Dose	Maximum Tumor Diameter
24 Gy	<20 mm
18 Gy	21-30 mm
15 Gy	31-40 mm

Increased risk of grade 3-5 neurotoxicity (MVA) associated with:

- Tumor size: 21-40 mm 7.3 – 16X risk vs. <20 mm
- Tumor dose
- Karnofsky Performance Status

Actuarial incidence of radionecrosis:

5% (6mo), 8% (12 mo), 9% (18mo), and 11% (24mo)

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Shaw E et al. Int J Radiat Oncol Biol Phys. 2000;47(2):291.

Risk Factor: Volume of SRS

Study	N	Incidence	Risk Factor	Risk %
Minniti (2011)	206 pts 310 lesions	14% S-RN 10% A-RN	V10 Gy > 12.6cm^3 V12 Gy>10.9cm^3	47% 47%
Blonigen (2010)	63 pts 173 lesions LINAC	10% S-RN 4% A-RN	V10 Gy 2.2-6.3 cm^3 6.4-14.5 cm^3 V12 Gy 1.6-4.7 cm^3 4.8-10.8 cm^3	11.9% 34/6% 11.9% 34.6%
Korytko (2006)	129 pts 198 lesions		V12 Gy 0-5cc V12 Gy 5-10 cc V 12 Gy > 15cc	23% 20% 54%
Ohtakara (2012)	57 pts 131 lesions LINAC	8.4% S-RN 6.9% A-RN	V12 Gy V 22 Gy (no prior WBRT)	

Minniti - Radiation Oncology 2011, 6:48
Blonigen-IJROBP 77(4):996-1001, 2010
Korytko-IJROBP 64(2):419-424,2006
Ohtakara-JNeurooncol 108:201-209,2012

Diagnostic Dilemma

Limitations of Radiological Evaluation

- Radiological appearance of brain tumours and brain radionecrosis can be very similar

Limitations of Pathological Confirmation

- Fails to have 100% sensitivity or specificity
  - Spatial heterogeneity
  - Presence of both tumor cells (which may or may not be viable) and necrosis
- Invasive procedure with additional risks to the patient

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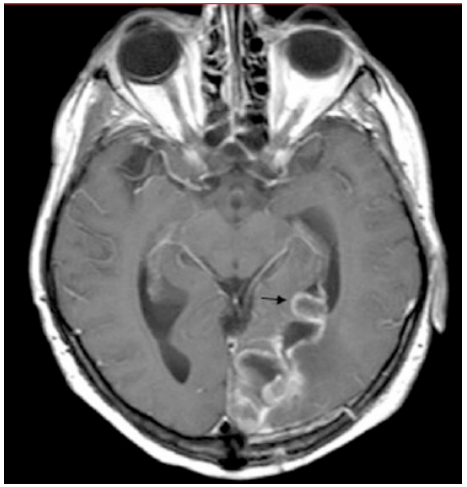
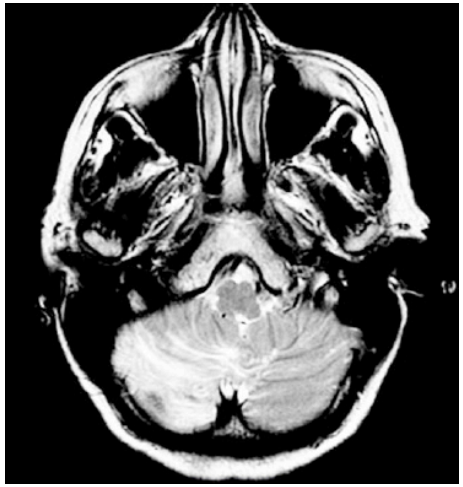
Conventional MRI

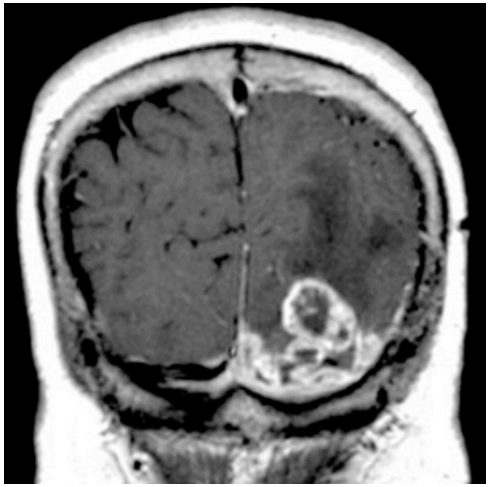
Conventional radiographic features achieved ≥ 80% predictive value but low sensitivity/specificity:



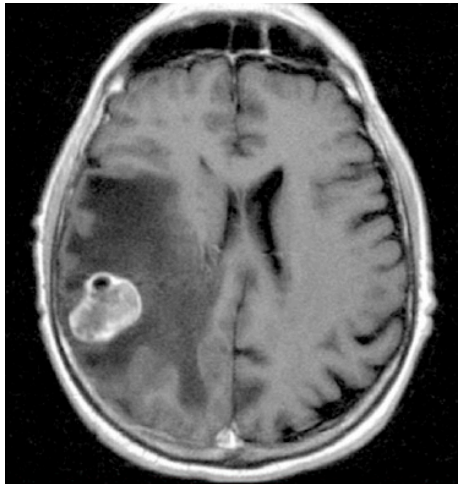
AV shunting



Gyriform lesion/edema

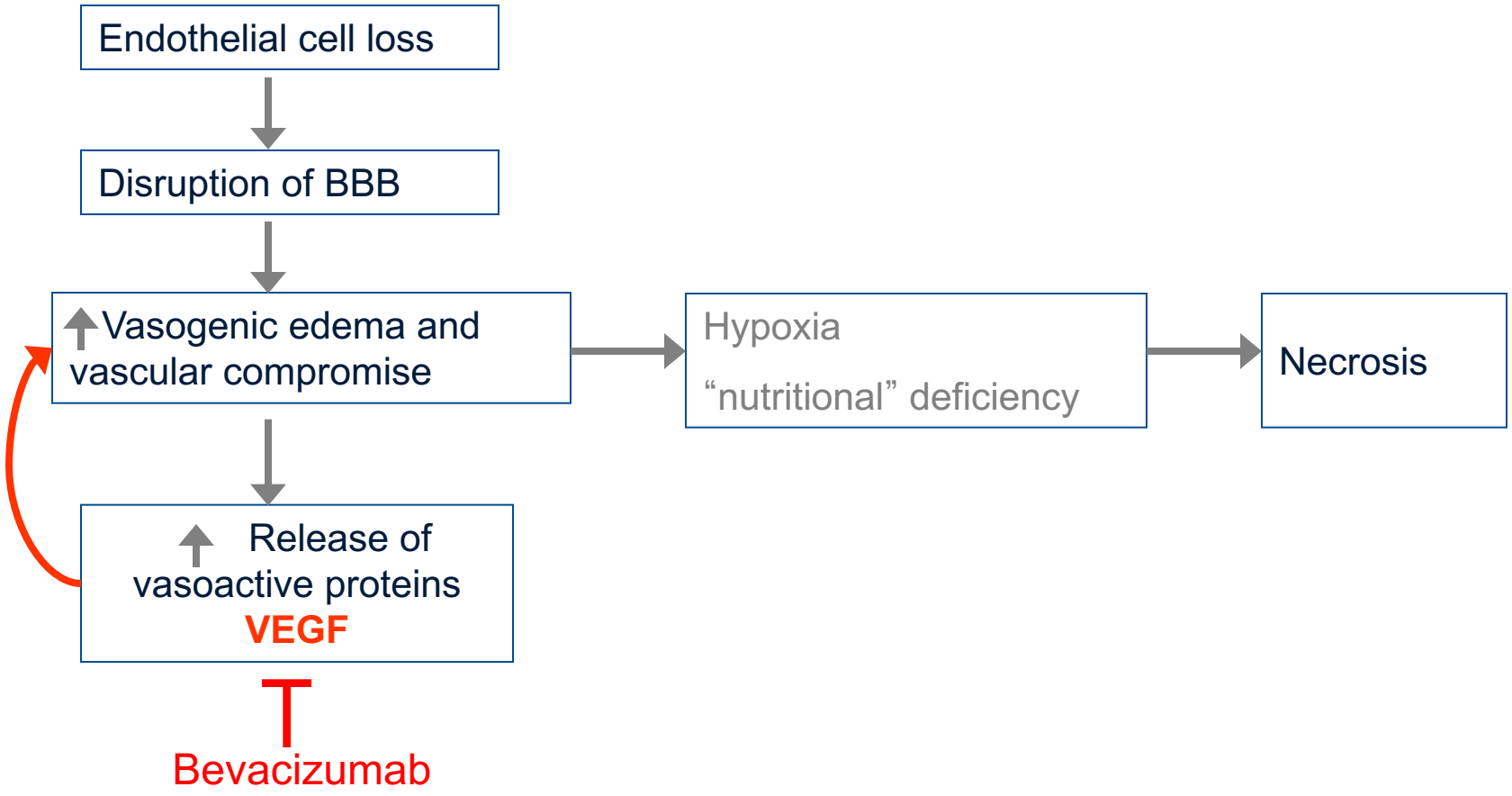


Enhancement pattern "cut green pepper"



Cyst formation

Pathophysiology of Brain Radionecrosis



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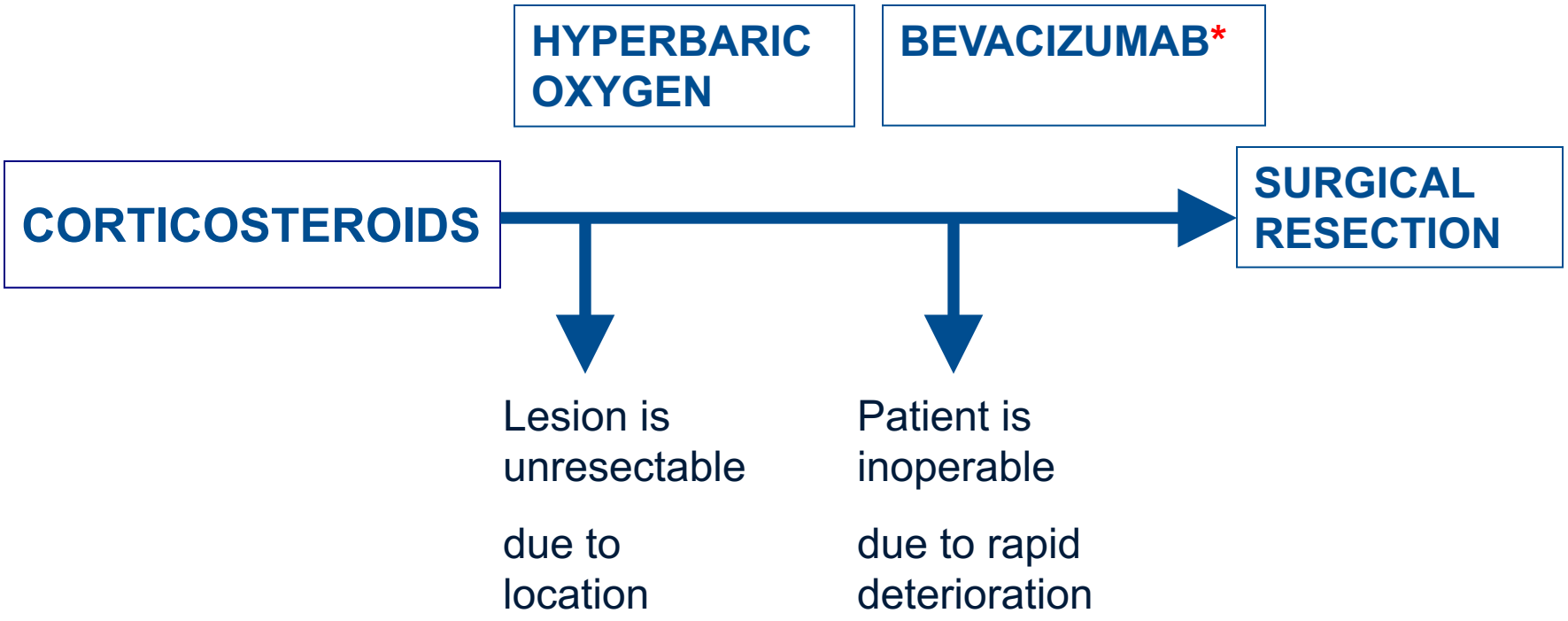
Current Management of Radionecrosis



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

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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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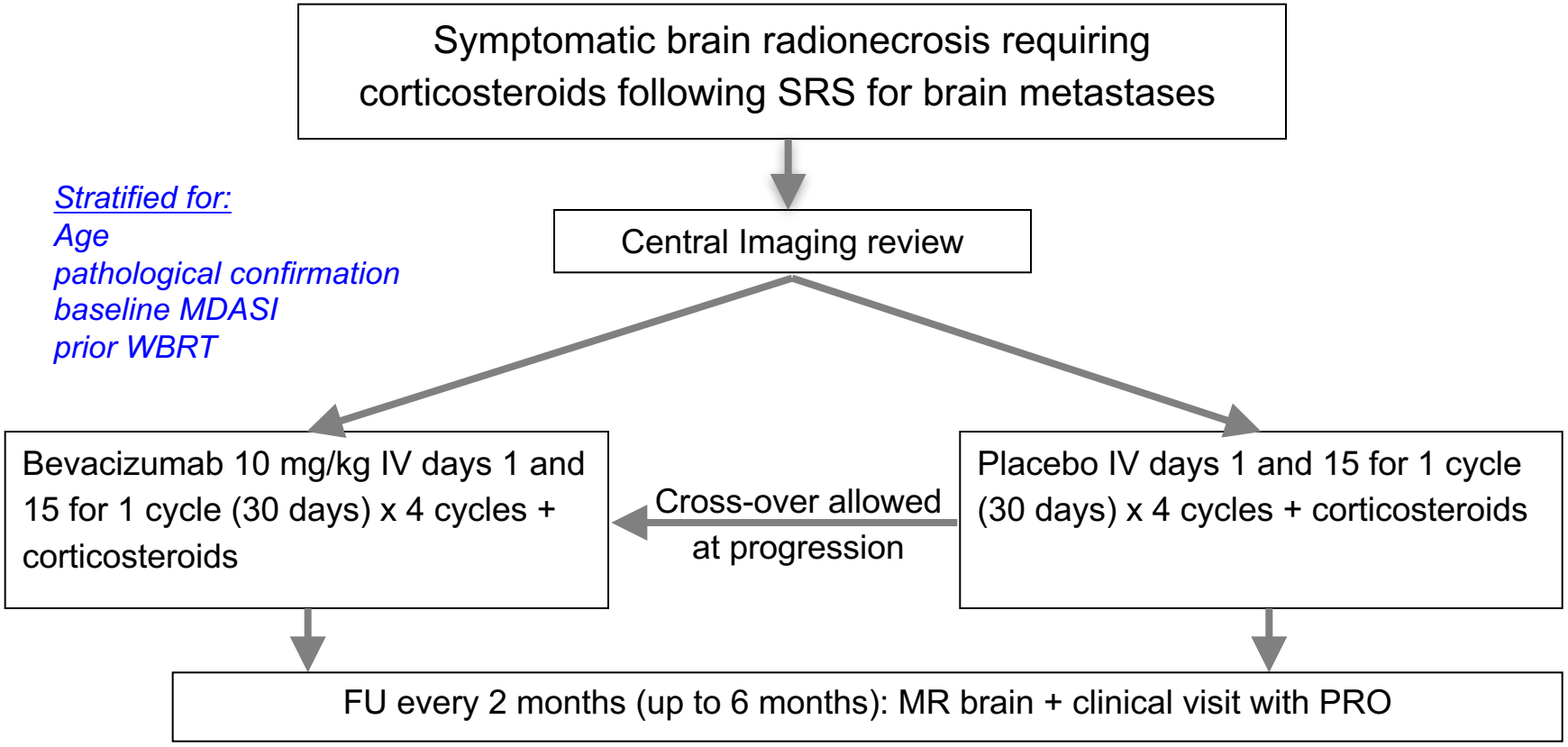
Study Schema

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

Drug is provided

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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] **OR**
  - DSC [2]- At least 1:
    - rCBV <1.5
    - PSR ≥ 76%
- Life expectancy > 6 months
- KPS ≥ 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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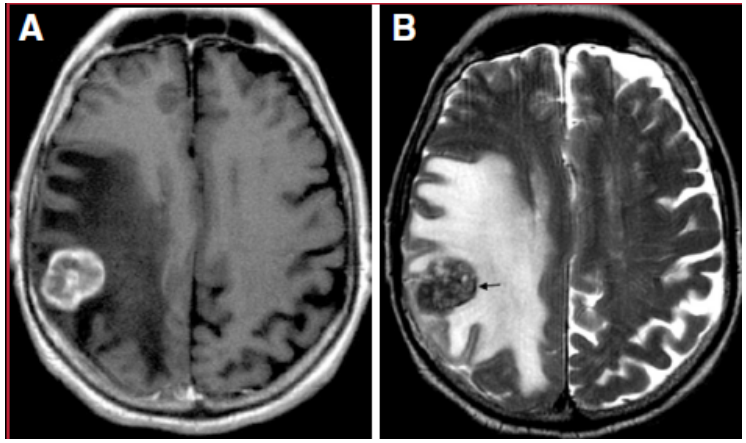
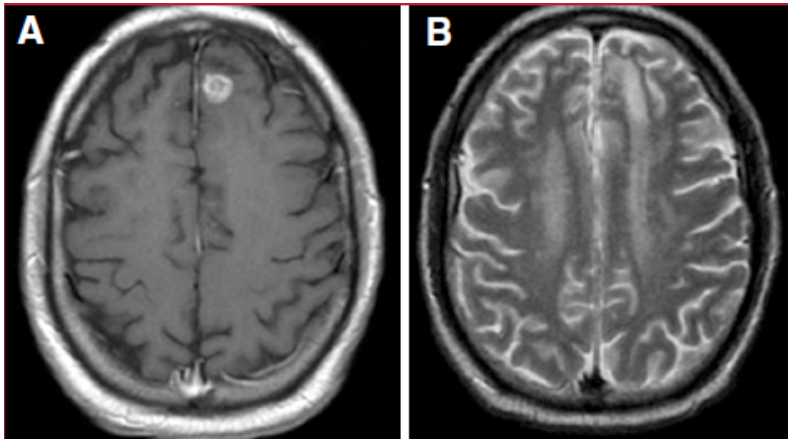
[1]Kumar – Radiology 2000
[2] Barajas – AJNR 2009

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 hypointensity / maximal cross-sectional area of T1-gad enhancement

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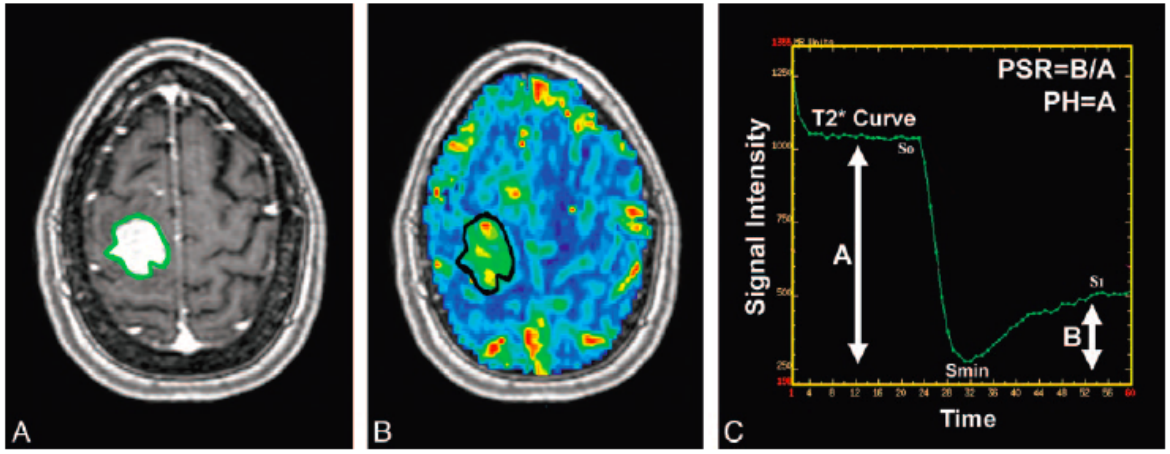
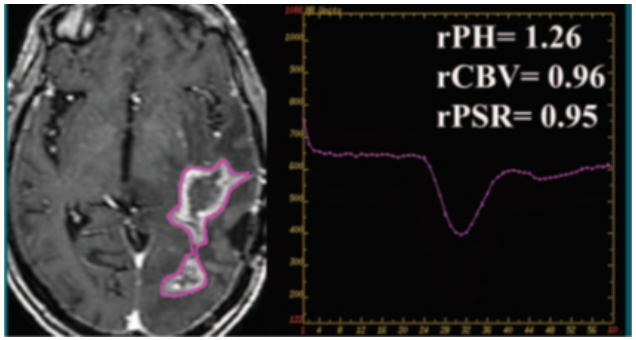
Kumar – Radiology 2000

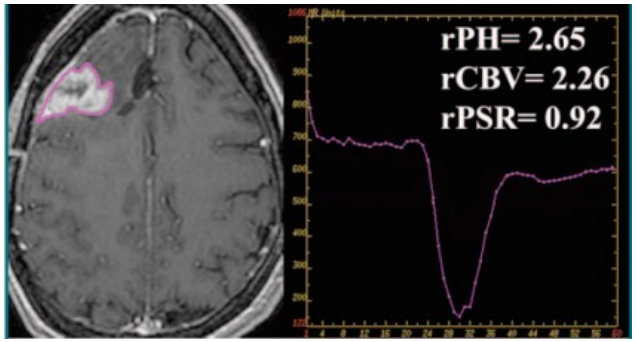
Radionecrosis & Perfusion Imaging



Eligibility Criteria:
rCBV <1.5
PSR ≥ 76%



Radionecrosis



Tumor

Table 3: Sensitivity and specificity for the detection of radiation necrosis using PSR, rCBV, and rPH values*

Statistic	PSR COV = 76.3	rCBV COV = 1.54	rPH COV = 0.69
Sensitivity	95.65	91.30	86.96
Specificity	100.00	72.73	45.45

Note:—COV indicates cutoff value.
*All data are presented as percentages.

Barajas – AJNR 2009

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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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Amendment

- Real-time central review: OPTIONAL
  - Need to submit images for secondary analysis
- Correlative biomarker studies are optional for institution and patient
- Drug administration cost language clarified

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Highlights

- Drug provided for initial randomization & cross-over
  - ***All patients who clinically need bevacizumab will receive it on study***

- Contact: cchung3@mdanderson.org

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Conclusion

- Questions from Audience
- Answers from Presenter

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