Laser Ablation for Brain Tumors

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Definition

- Radiation necrosis is one form of radiation injury
  - Classification based on temporal relationship to radiation treatment
    - Acute injury: During or after completion of radiation
      - Reversible; Characterized by edema
    - Early delayed injury (pseudoprogression): Up to 12 wks after radiation
      - Reversible; Increased signal on FLAIR and T2
    - Late injury / radiation necrosis: Few mos to years
      - Irreversible
      - Focal pattern: circumscribed lesion
      - Diffuse pattern: wide spread periventricular white matter changes

Incidence

- The exact incidence of cerebral radiation necrosis is unknown
  - This is due to difficulties in the diagnosis of radiation necrosis
    - Imaging techniques are imperfect
    - Low rates of re-operation and autopsy
- Following single fraction SRS (Kohutek et al. J Neurooncol 2015)
  - 5.2% at 6 months, 17.2% at 12 months and 34.0% at 24 months

Pathophysiology

- From rat brain experiments, white matter necrosis is a function of duration of exposure and cumulative dose (Calvo et al. Br J Biol, 1988)
  - Endothelial cell damage is an early event
  - Also seen is astrocyte hyperplasia
- VEGF- Triggered by injury or hypoxia, increasing BBB permeability and leakage of pro-inflammatory cytokines (Wu and Levin, Controversies in Neuro-oncology, 2010 and Nonoguchi et al. J Neurooncol, 2011)

VEGF as Mechanism for Radiation Necrosis

- Nonoguchi et al. (J Neurooncol 2011)
  - Assessed 11 pathological samples of radiation necrosis with anti-VEGF antibody and anti-HIF-1α
    - Within necrosis, no VEGF expression
    - Perinecrotic tissue, VEGF positive astrocytes
    - This stimulates endothelial cell proliferation within necrosis and perinecrotic tissue
    - HIF-1α also seen in perinecrotic tissue, but little is seen within necrotic tissue

VEGF as Mechanism for Radiation Necrosis (continued)

- VEGF is an angiogenic peptide and a vascular permeability factor
  - Possibly produced by reactive astrocytes
- Would explain why anticoagulants work in maintaining microcirculation within telangiectasias (acting as collaterals) during the early phase of radiation necrosis
- Bevacizumab may work to stop radiation necrosis
- Inflammation may also play a part in addition to angiogenesis (Yoritsune et al. J Radiat Res 2014)
  - Pro-inflammatory cytokines IL-1α, IL-6 and TNF-α are also expressed
- RN as a self-propagating vasculopathy/vasculitis with central necrosis

Treatment

- Since radiation necrosis is associated with significant edema, steroids are often used
- Because radiation necrosis is blamed on vascular changes, anticoagulants / antiplatelet medications have been used to halt progression
  - Trental and Vitamin E (Williamson et al. Stereotactic Functional Neurosurgery 2008)
  - Clinical improvement have been reported with heparin and warfarin
  - Free radical scavenger – edaravone (Tang et al, J Neuro-onc, 2014)
- Open surgery for steroid refractory / dependent patients

Treatment – Hyperbaric Oxygen

- 100% oxygen increased to 2.5 x atmosphere for 60 min per day for at least 10 days
- May take 5 days a week for 30-40 treatments to see benefit
- Limited to case reports showing improvement of radiation necrosis following SRS
  - Kohshi et al. J Neurol Sci, 2003
  - Leber et al. Stereotact Funct Neurosurg, 1998
  - Per Vince Ferrini, MD of Mobile Hyperbaric Centers, 65 patients in the literature, 70% of which improved

Treatment – Bevacizumab

- 14 patients in a placebo-controlled randomized double-blind study results in improvement in radiation necrosis (Levin VA Int J Radiat Oncol Biol Phys. 2011 Apr 1; 79(5): 1487–1495)
  - Bevacizumab (7.5 mg/kg) was given for 4 cycles, 3 weeks apart
  - 0 of 7 patients receiving placebo responded
  - 5 of 5 randomized and 7 of 7 crossover responded
  - All patients receiving bevacizumab showed improvement in neurologic symptoms or signs
  - Of patients receiving all 4 study doses, only 2 developed recurrence of radiation necrosis
    - One patient received an additional dose, the other received 2 doses

Treatment - Bevacizumab

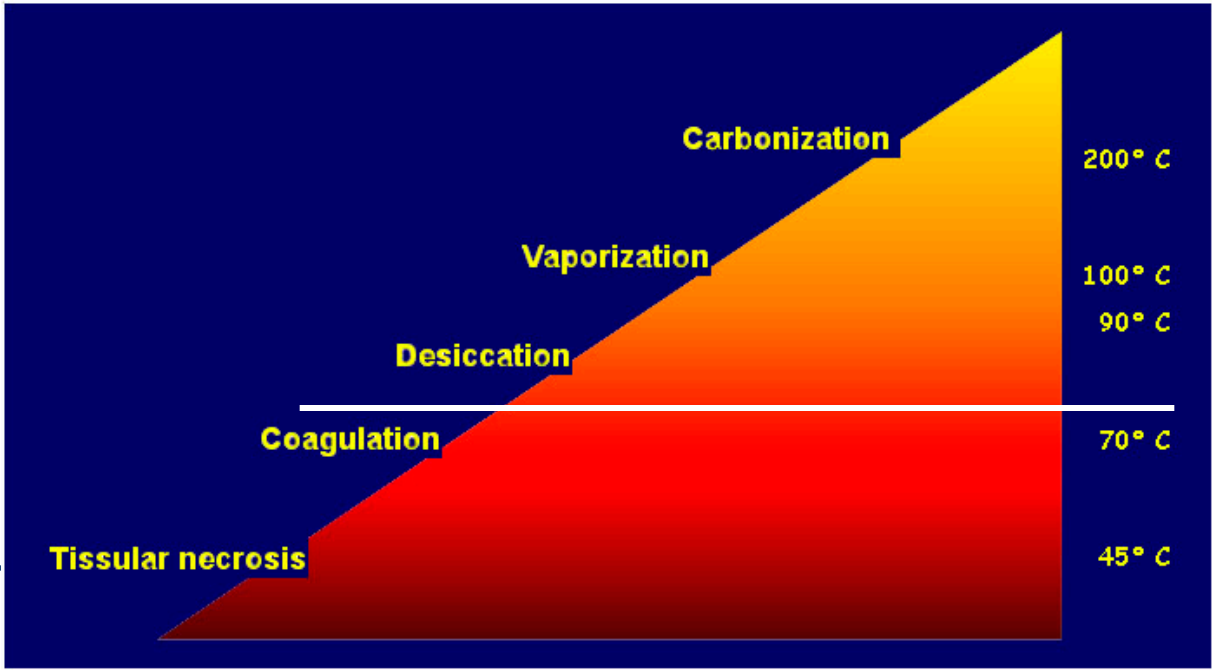
- Cleveland Clinic Data - Sadraei et al. (AJCO 2013)
  - Radiographic improvement was seen in 23 out of 24 patients
  - Using the McDonald criteria, the average change in the T1-weighted postcontrast MRI was a decrease of 48.1%, and the average change in the fluid-attenuated inversion-recovery images was a decrease of 53.7%.
  - There was a mean daily dose reduction of 9.4 mg of dexamethasone after initiation of bevacizumab in patients who were on steroids at the start of bevaciuzmab therapy for RN.
  - Only one patient with a Grade 3 adverse event

Laser Interstitial Thermal Therapy - LITT

- Uses LASER scatter to heat brain
- Bare fiber optics
- 1994 – Kahn, Schwarzmaier et al.
- 1998 - Morrison, Jolesz et al.
- Limitations:
  - Char – lack of cooling
  - Lack of Directionality – diffuse only
  - Ineffective heat conduction prediction / monitoring – best guess

LITT - Background

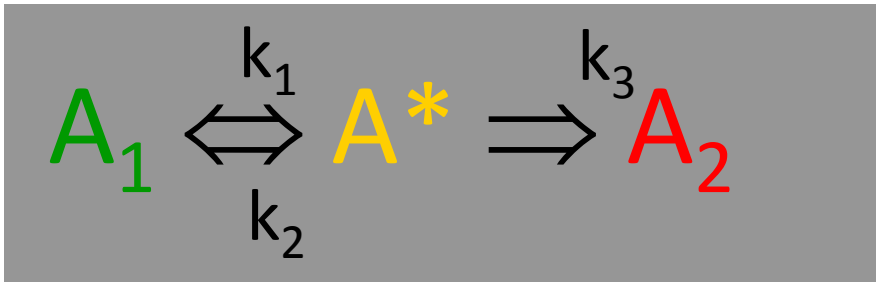
- Heat kills cell
  - (43-55 ºC) Apoptosis, necrosis
    - transmembrane proteins, melting lipid bilayer
  - (>57 ºC) Coagulation



LITT - Background

- Δt @ ΔT (dose) - predictive of damage
  - Arrhenius thermodynamic theory

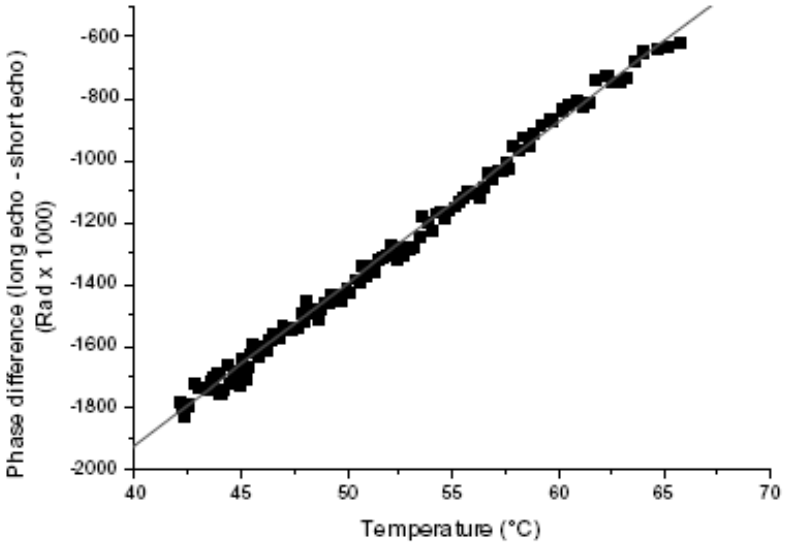
$$k = Ae^{-\frac{E_A}{RT}}$$

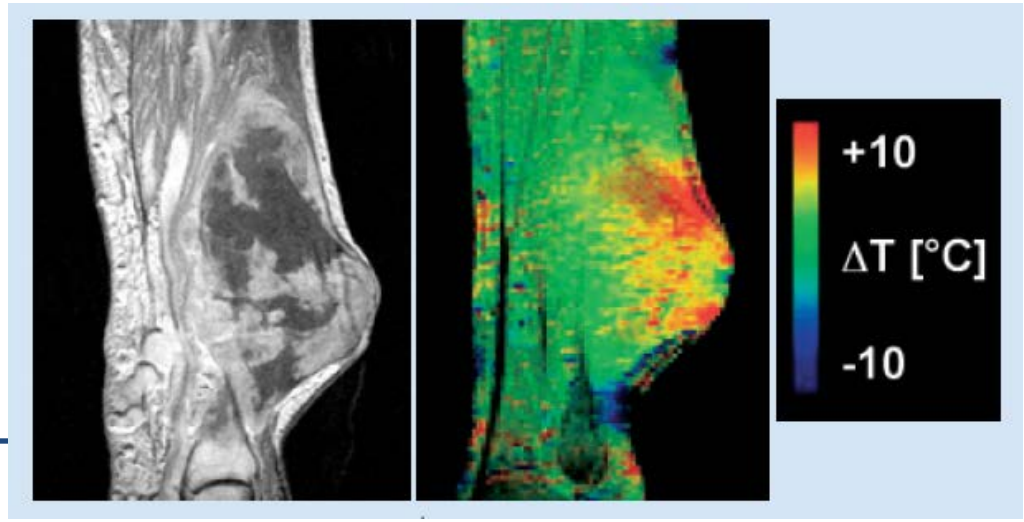


  - Thermal equivalent T_{43} for X minutes

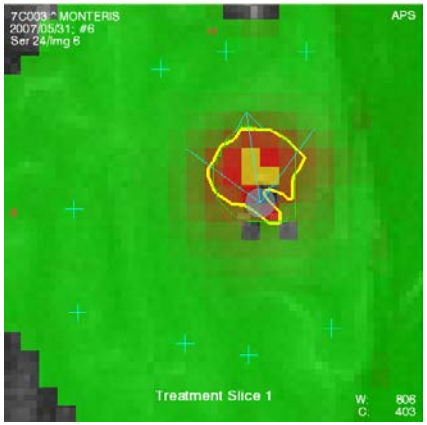
LITT – Contemporary Feasibility
MR Thermometry

- MR thermometry is accurate





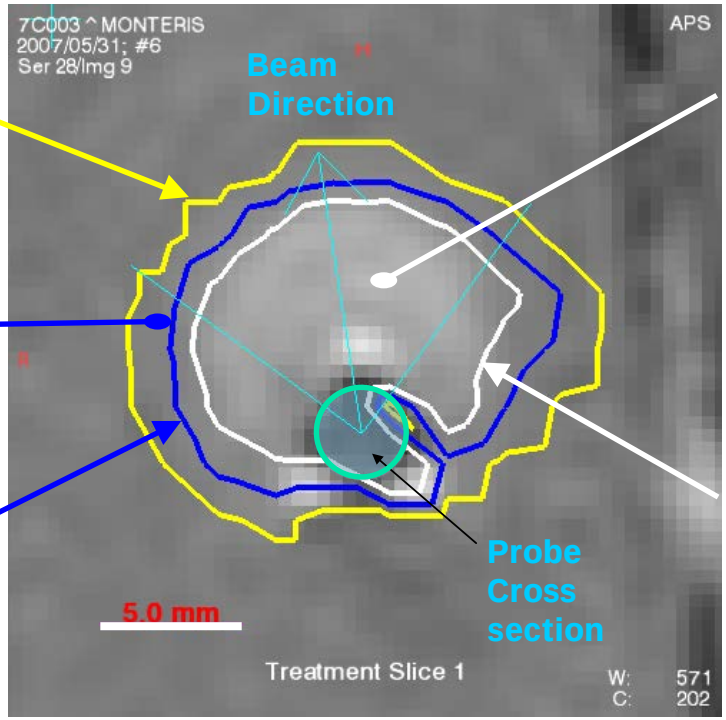
Thermal Damage Threshold Line



Outer Boundary T_{43} 2min

Intermediate Zone

Intermediate Boundary T_{43} 10min



Damage Area Boundary T_{43} 60min

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Editor's Choice -- **Free Access**

Case Report

Laser Interstitial Thermal Therapy for Focal Cerebral Radiation Necrosis: A Case Report and Literature Review

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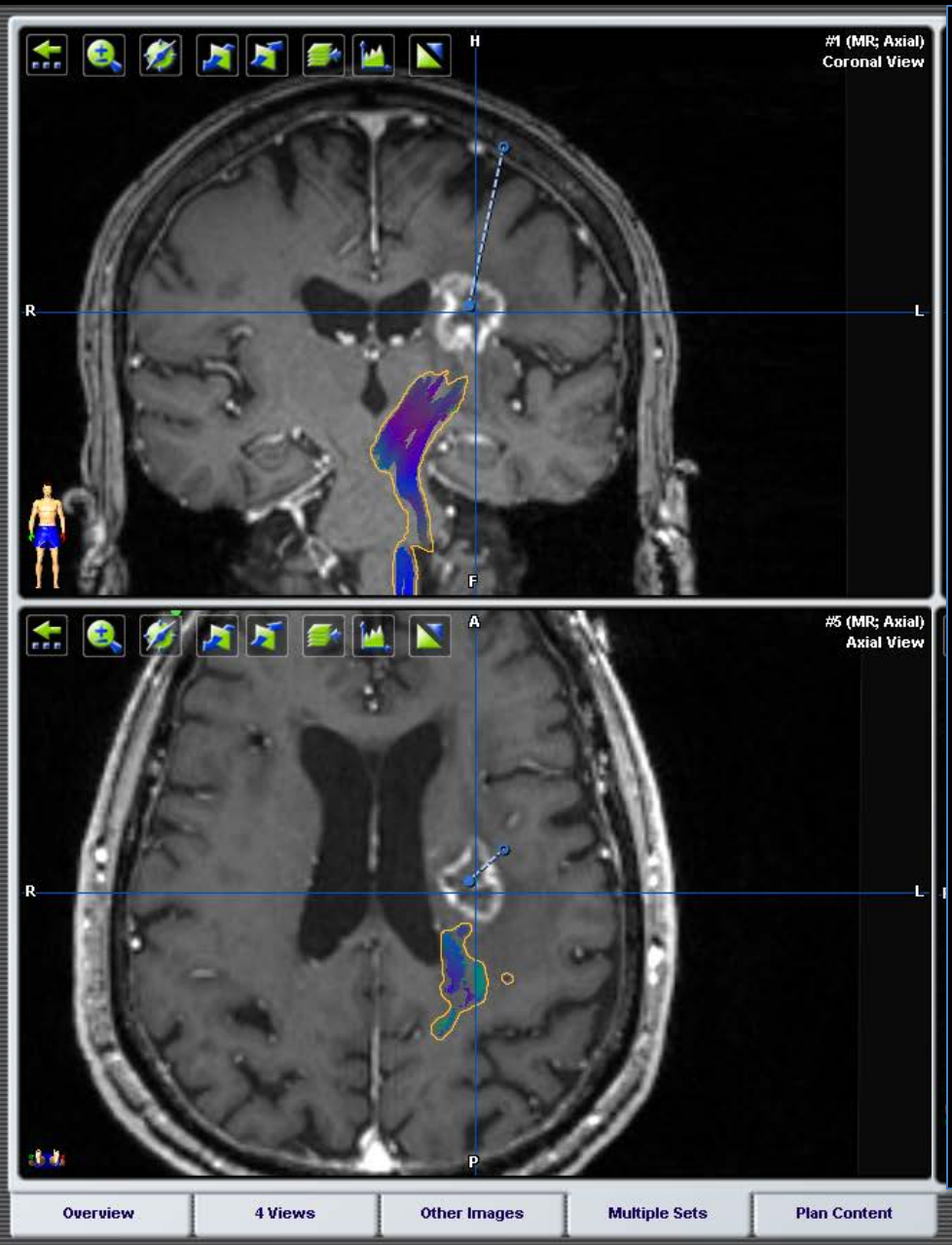
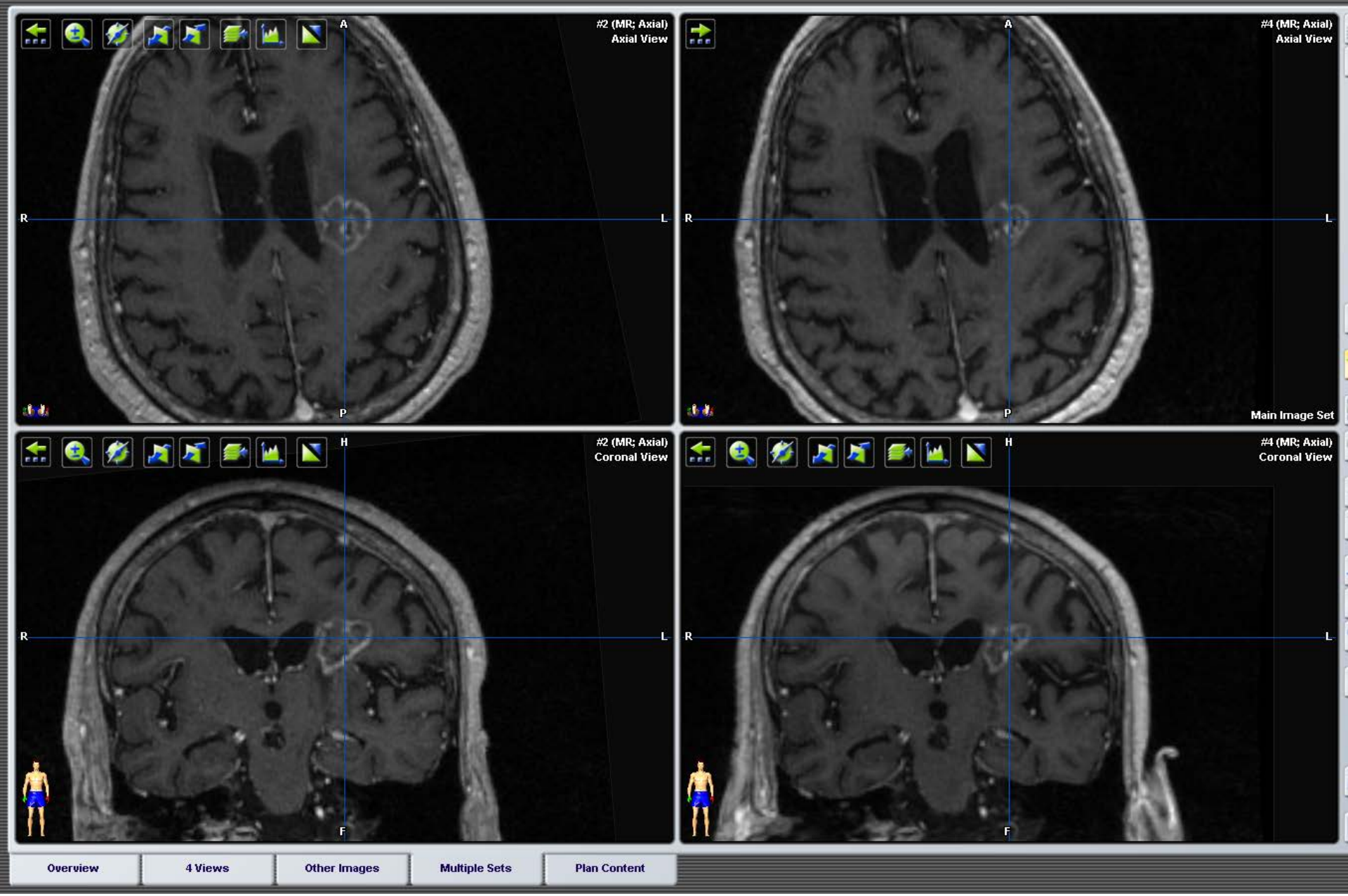
Stereotact Funct Neurosurg 2012;90:192-200 (DOI: 10.1159/000338251)



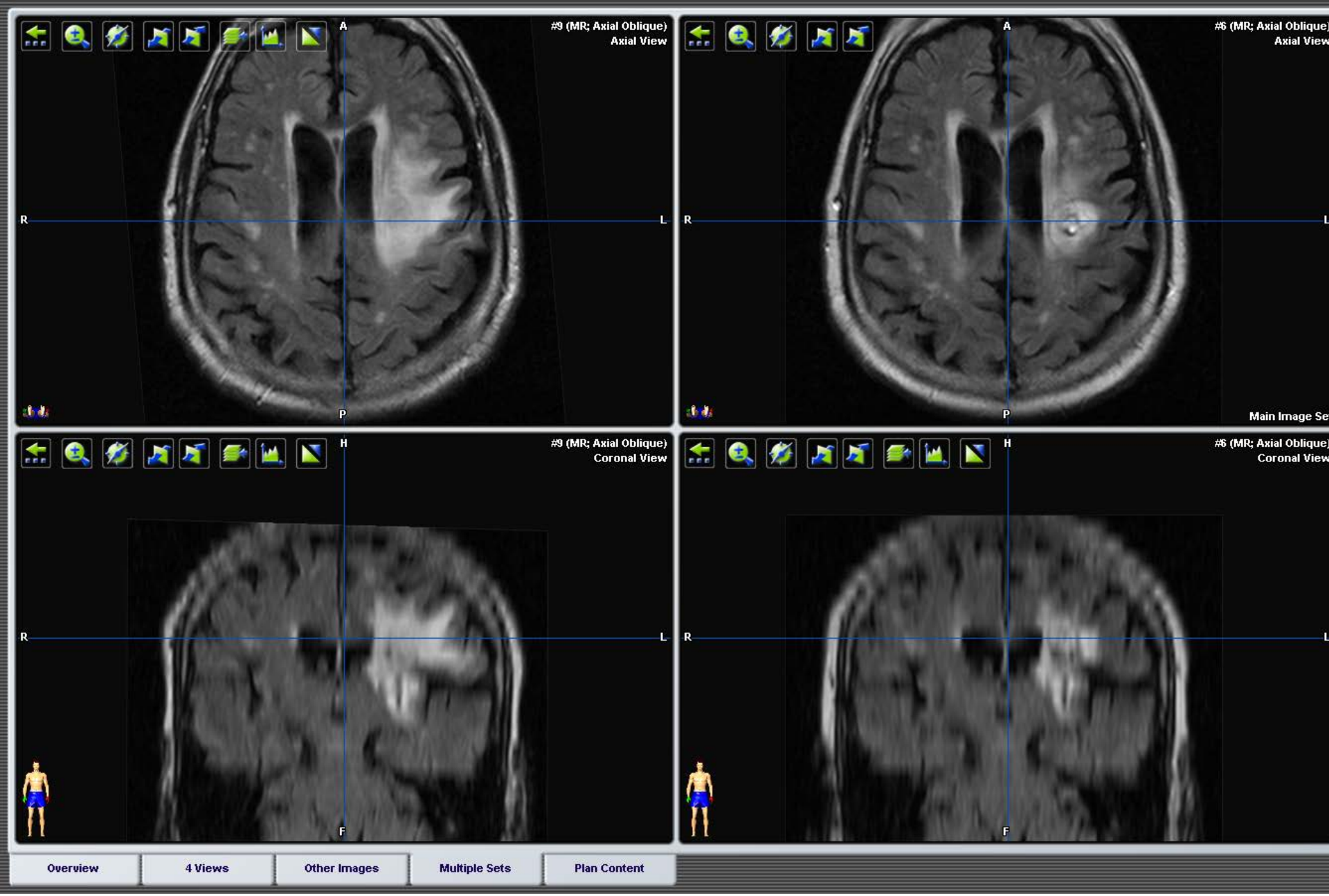
April ’11
4 mg Dex qid

May ’11
0 mg Dex



Jul ’11
3 mths

Oct ’11
6 mths



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Laser Ablation After Stereotactic Radiosurgery (LAASR)

Overall Study Principal Investigator:
Veronica Chiang

LAASR

- LAASR = Laser Ablation After Stereotactic Radiosurgery
  - 6 centers: CCF, WashU, WakeForest, KUMC, Jefferson, Yale
- Inclusion criteria:
  - Brain metastasis re-growing radiographically after prior treatment with stereotactic radiosurgery
  - KPS≥ 60 , Age >18 years
  - Able to undergo surgery
  - Known primary cancer type

- Outcomes:
  - Primary
    - Local CNS Progression Free Survival after LITT
  - Secondary
    - Overall Survival after LITT
    - Cognitive function and Quality of Life outcomes after LITT
    - Safety and tolerability of LITT

LAASR

- 42 patients treated (across 6 centers) with LITT between Oct 2012 and Dec 2015
- 27/42 completed 12 week f/u
- 16/42 completed 26 weeks f/u
- Mean age = 58.5 years (range 32 - 74)
- Female - 64.3% (27/42)
- Median baseline KPS = 85 (range 60-100)
- Initial tumor pathology
  - NSCLCa 43%, breast 17%, melanoma 10%, other 30%

- Tumor Volume – mean 6.5cc (range 0.4 – 38.6) – equivalent to 2.2cm diameter
- Tumor Location – 41% frontal, 29% parietal, 14% cerebellum
- Pathology at time of laser ablation
  - 45% (19/42) radiation necrosis, 48% (20/42) tumor, 7% (3/42) no diagnosis
- Median procedure time = 3.0 hours (range 1.4 – 9.7)
- Median LOS = 2 days (range 0.4 – 12.0)

LAASR

	CR	PR	SD	PD
12 weeks (n=27)	37% (10/27)	22% (6/27)	15% (4/27)	26% (7/27)
PFS 12 wks		74%		
At last f/u 12+ weeks*	48% (13/27)	15% (4/27)	11% (3/27)	26% (7/27)
PFS at last f/u		74%		

**Only 16/42 (38%) patients had follow-up to 26 weeks*

LAASR – Secondary outcomes

- Overall Survival:
  - 86.5% at 12 weeks
  - 72.2% at 26 weeks

- KPS unchanged or improved after LITT in 60% of patients
- Median change in KPS = 0.0 (range -40 to +20)

- 27% of patients had a neurological improvement from baseline to last f/u

- 30% of patients able to stop or reduce steroid usage at 12 and 26 weeks

LAASR – QoL and Cognitive

Measure	12 week timepoint (n=27)	26 week timepoint (n=16)
FACT-Br	-2.5 ± 25.7 (27) 3.8 [-71.8, 40.0] 0.6244	4.9 ± 15.7 (16) 7.0 [-34.7, 34.3] 0.2362
FACT-Br (SWB)	**-1.5 ± 3.8 (27)** **-1.0 [-12.0, 8.2]** **0.0443**	-1.2 ± 3.8 (16) -0.3 [-13.0, 5.0] 0.2379
FACT-Br (EWB)	1.9 ± 4.9 (27) 2.0 [-9.0, 14.0] 0.0519	**3.0 ± 4.5 (16)** **3.5 [-5.0, 11.0]** **0.0170**
FACT-Br (FWB)	-0.9 ± 5.4 (27) 0.0 [-16.0, 10.5] 0.4116	-0.4 ± 4.4 (16) 0.5 [-13.0, 5.0] 0.7385
HVLT-R Total Recall	-0.3 ± 4.3 (26) -1.0 [-6.0, 7.0] 0.7519	0.5 ± 5.1 (15) 1.0 [-10.0, 11.0] 0.6930
MMSE	-0.2 ± 1.7 (25) 0.0 [-5.0, 2.0] 0.5691	-0.3 ± 2.7 (14) 0.0 [-9.0, 2.0] 0.6987

LAASR - EOA

- Local PFS at 12 weeks
  - total ablation – Complete remission seen in:
    - 100% of the RN lesions
    - 75% of tumor lesions
      - Remaining 25%
  - Tumor with sub-total ablation:
    - 0% complete response
    - 63% progressive disease
  - Radiographic CR was shown to be statistically significantly related to having received total ablation ($p<0.001$)
  - Of the lesions where progressive disease occurred at 12 weeks, all were biopsy-confirmed tumor tissue and had an incomplete ablation at the time of LITT treatment

LAASR - Safety

- No unanticipated adverse device events
- 5/42 (12%) patients with LITT-related neurological adverse event (n=5)
  - 4/5 with worsened motor/sensory deficit
  - 1/5 with intracerebral hemorrhage without neurological consequence
- 14/42 (33%) of patients had surgery-related non-neurological adverse events (n=30 events)
  - Most common non-neurological adverse event was nausea/vomiting
- Timing of AEs:
  - 35% of events (15/43) occurred on day of surgery
  - 49% (21/43) occurred after day of surgery, prior to discharge
  - 14% (6/43) occurred after discharge
- 1/42 (2.4%) rate of re-hospitalization within 90 days
  - AE causing readmission was pulmonary embolism

LAASR - Summary

- Compared to an expected progressive decline in this patient population, LITT treatment resulted in:
  - 74% local lesional control radiographically at last f/u beyond 12 weeks
  - 72% survival at 26 weeks
  - 60% Stabilization or improvement of KPS
  - 30% reduction in steroid usage by 12 weeks
  - Stability of cognitive function
  - No perceived change in QoL
  - With a low neurological adverse event rate
  - EOA is important

- Laser Ablation can be used safely for the effective treatment of brain metastases re-growing after radiosurgery due to both radiation necrosis and tumor regrowth and should be considered in patients who are surgically eligible.

Collaborators

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UCSD

A Team Approach to Individualized Care

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