

Updates in the Management of Brain Metastases

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Disclosures

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- Varian Medical Systems, Inc: Research grant, Honoraria, Consulting

Case-based, Imaging-based, Interactive

- I will ask questions: Please yell out the answer!!



Case: Leptomeningeal disease

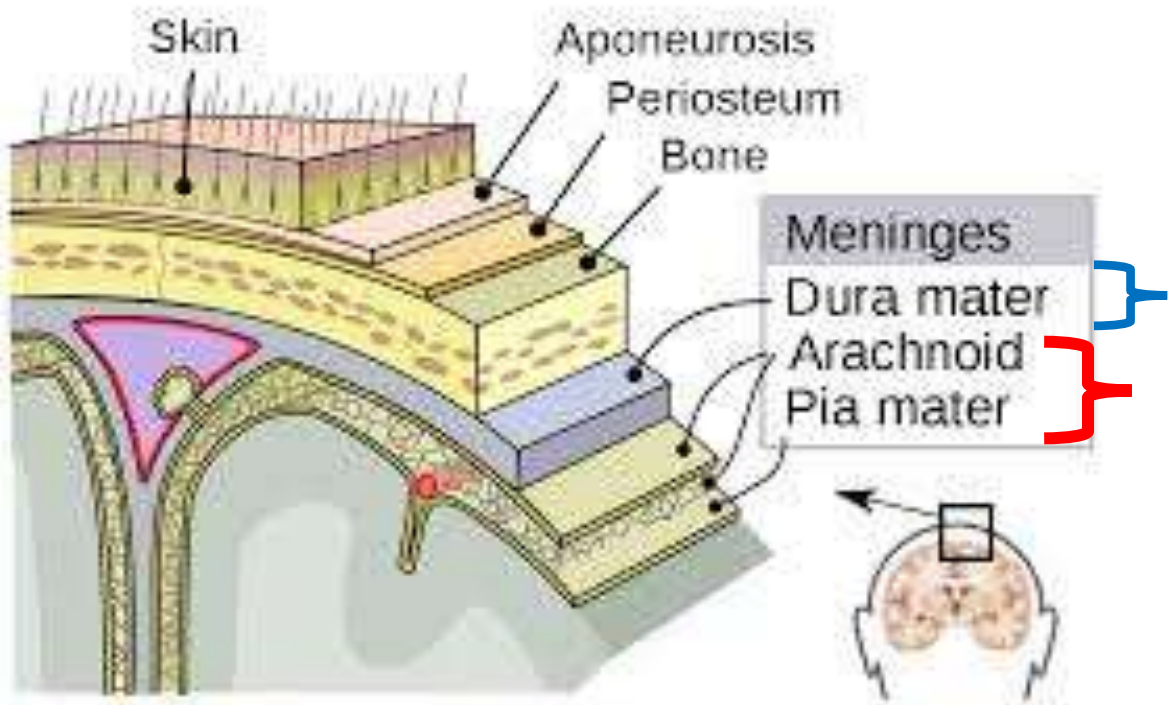
- 54F with triple neg metastatic breast cancer p/w headaches, nausea
- Systemic disease: stable



Management?

- WBRT
- Hippocampal-sparing WBRT
- SRS
- Change systemic therapy

What is the leptomeninges?

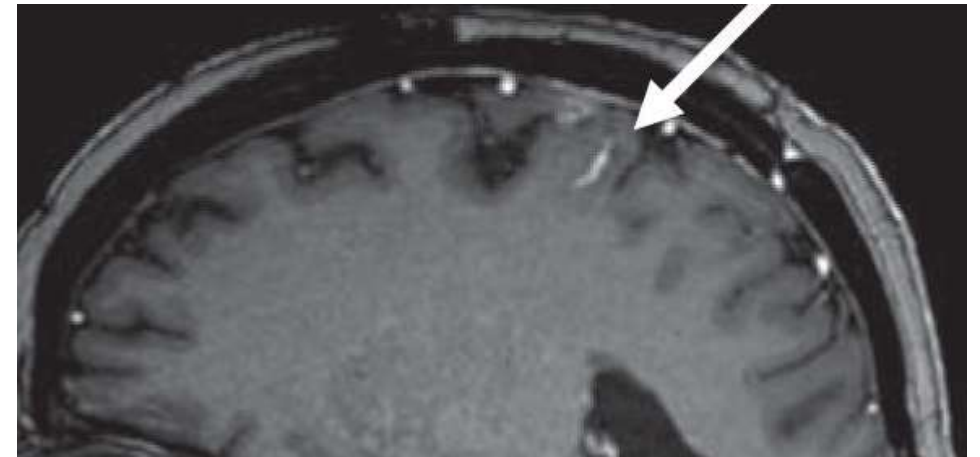
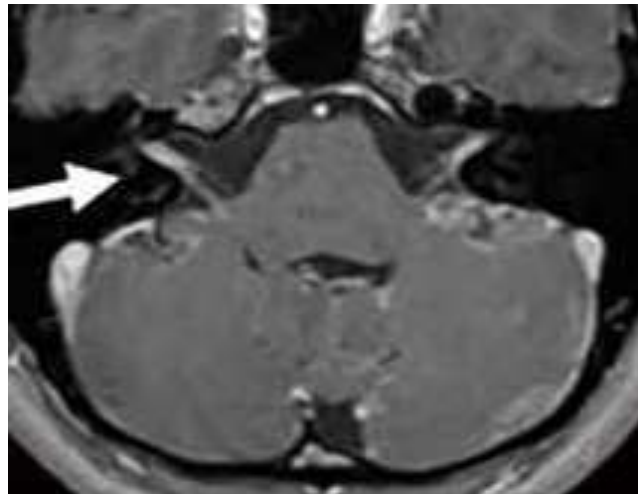
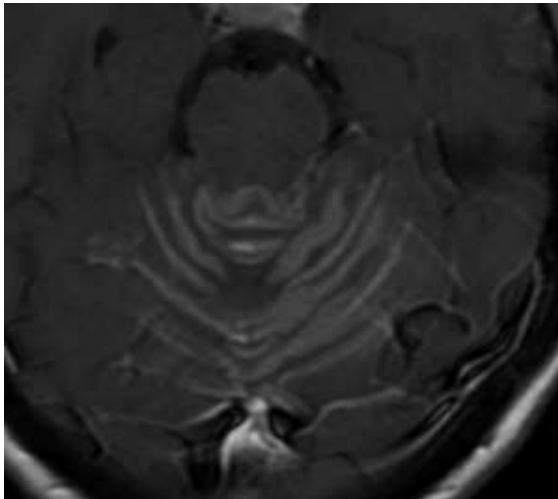


Pachymeninges → No BBB

Leptomeninges → Beyond BBB
(CSF between)

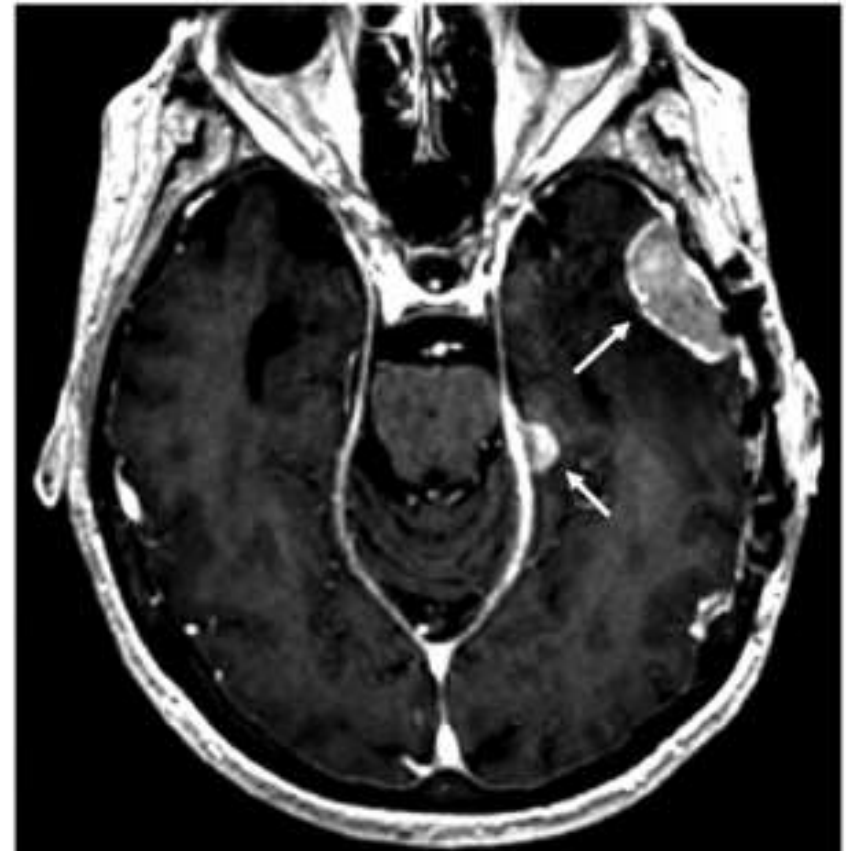
How do we diagnose LM disease?

- CSF sampling/Lumbar puncture: High false negative rate
- Imaging: Talk to your neuroradiologist!
 - Cerebellar folia
 - Cranial nerves
 - Linear enhancement in sulci



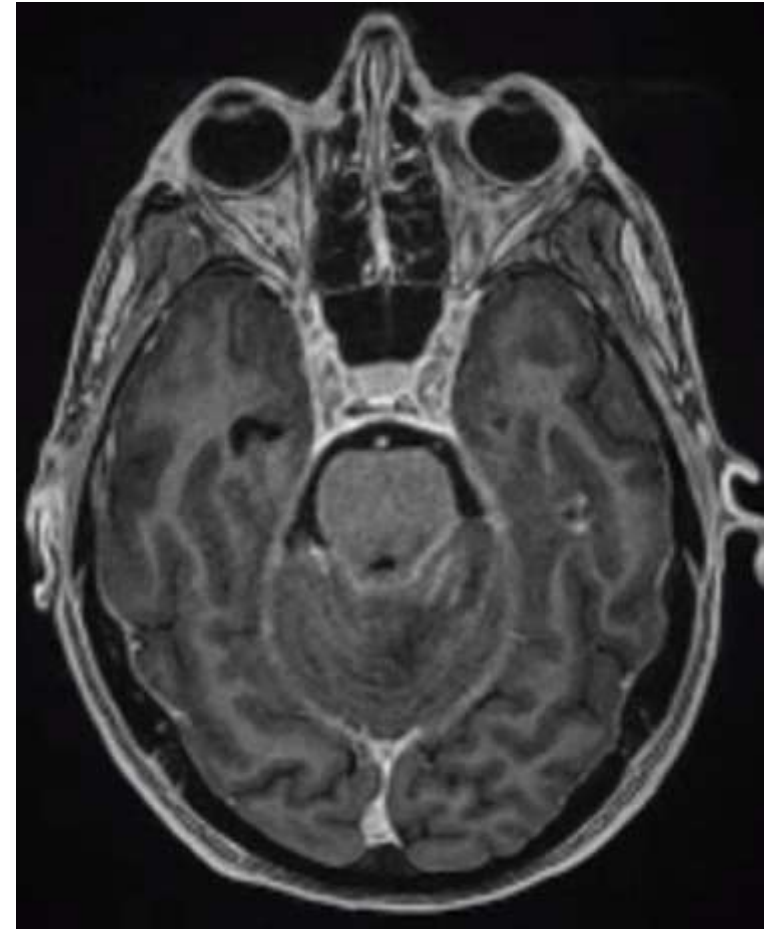
Nodular vs. Classic LM disease

- Nodular LMD: more commonly presents in resected surgical cavity after SRS; nodular/focal, not diffuse
- Less likely to be symptomatic
- Focal therapy (SRS) may be appropriate



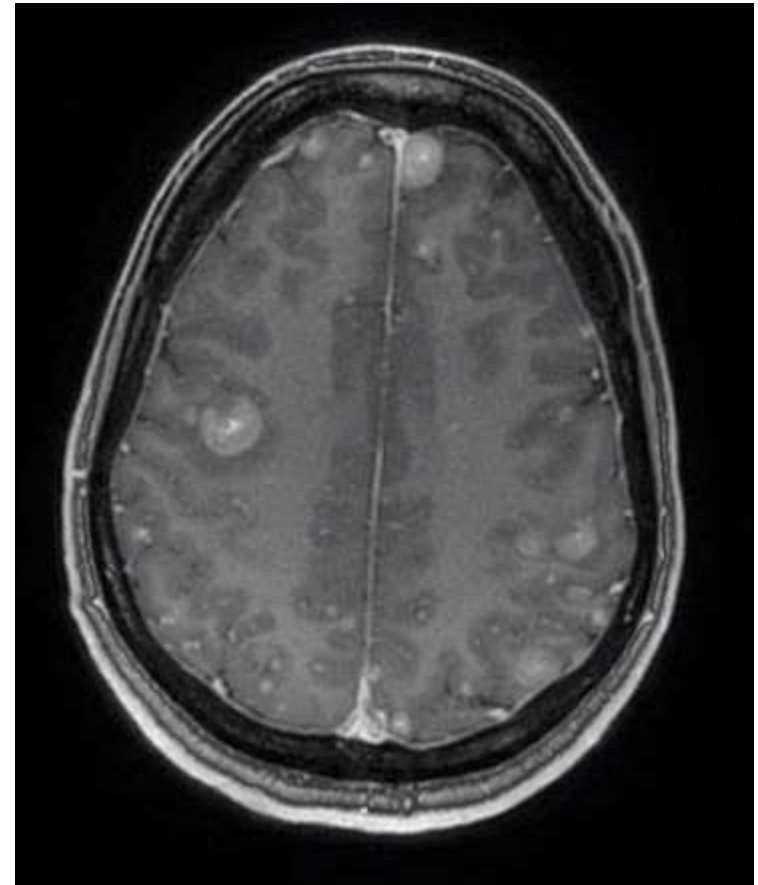
Management?

- WBRT ←
- Hippocampal-sparing WBRT
- SRS
- Change systemic therapy



Case: Multiple metastases

- 60F with met NSCLC, screening brain MRI for clinical trial shows **40+** brain metastases
- Multiple small/large lesions. Overall tumor burden > 20cc
- No lesions within 5mm of bilateral hippocampi



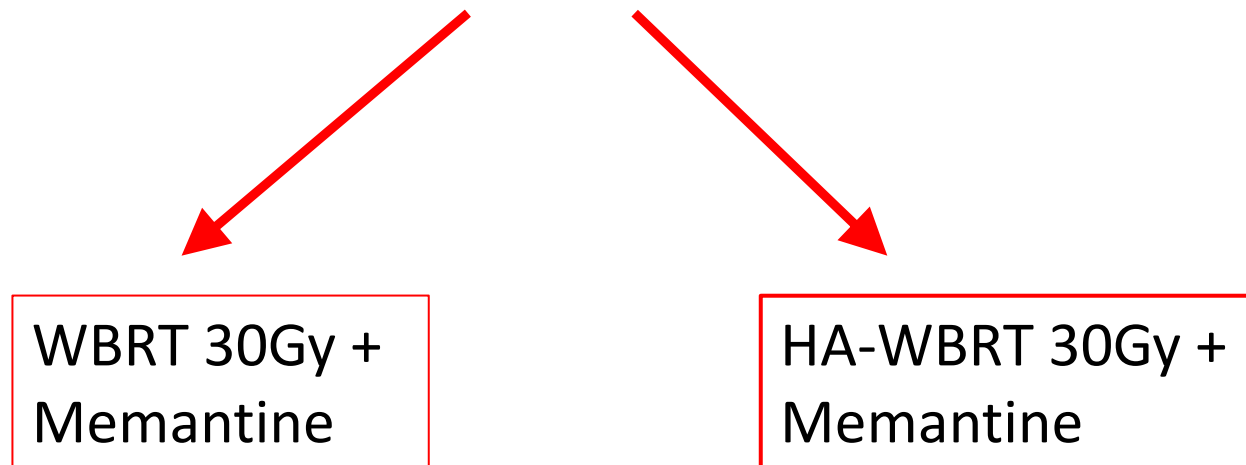
Management?

- Standard WBRT +/- Memantine
- Hippocampal-sparing WBRT +/- Memantine
- 30Gy or 37.5Gy?

Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001

- Eligibility: No LM disease; No mets within 5mm of HC; No hydrocephalus; KPS \geq 70.
Prior SRS ok

Stratified by: Previous treatment, RPA class



Bilateral hippocampi^a

$D_{100\%}$

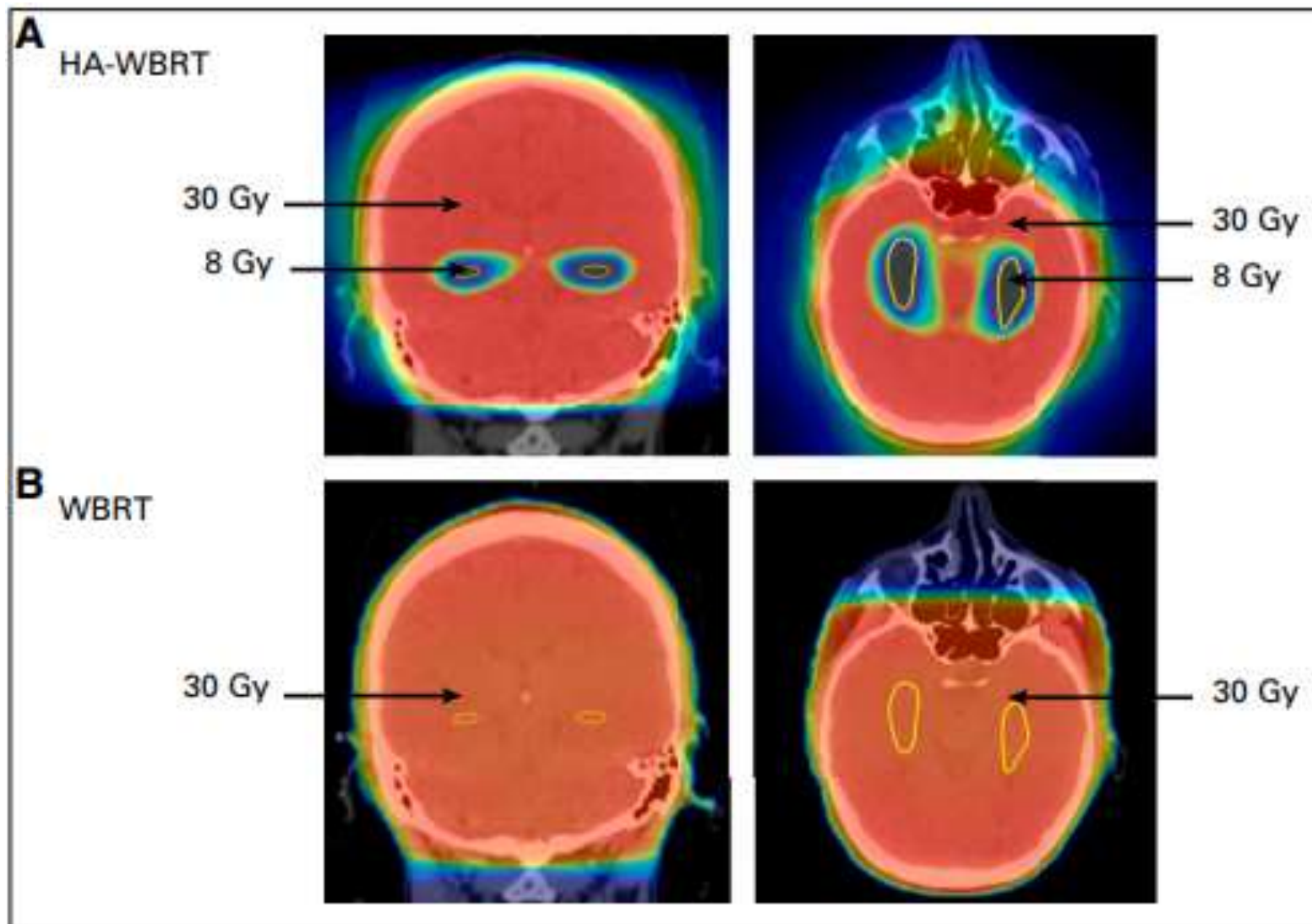
≤ 9 Gy

Dose to 100% of bilateral hippocampi

D_{max}

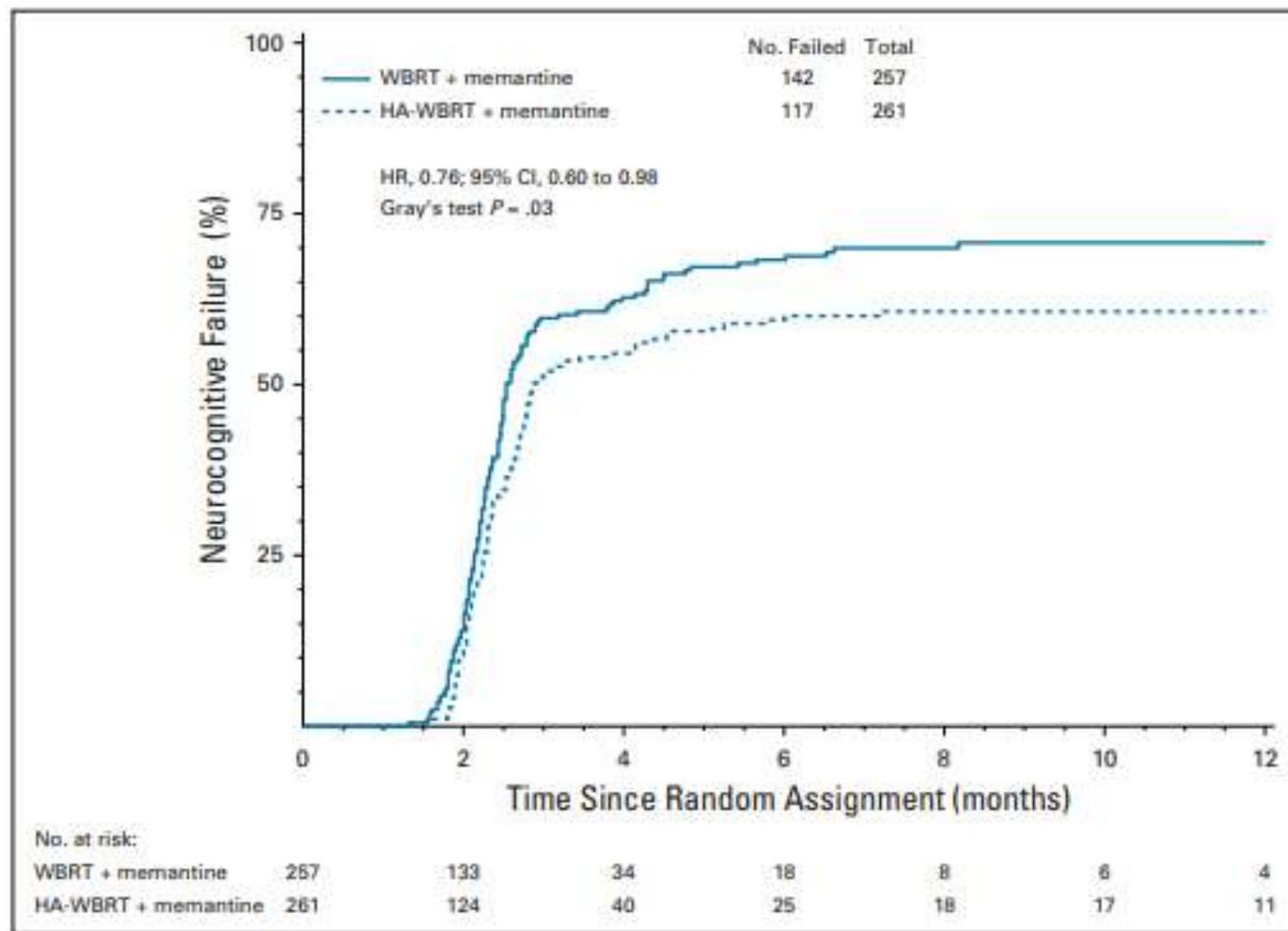
≤ 16 Gy

Dose to hottest 0.03-cc volume of bilateral hippocampi



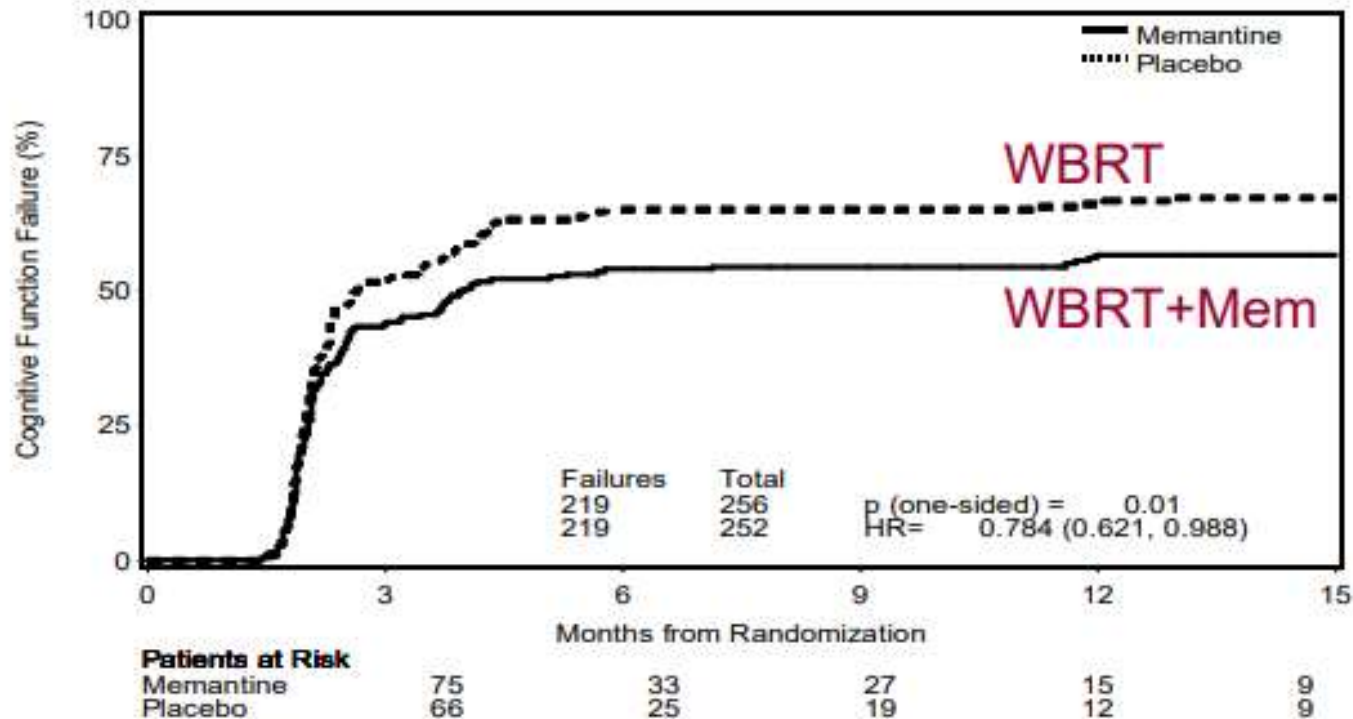
26% lower risk of cognitive failure w/ HA-WBRT

- Less deterioration in executive function, learning and memory
- Less fatigue, fewer cognitive symptoms
- Similar toxicity, intracranial PFS, OS



Why Memantine?

- NMDA receptor antagonist: used in vascular dementia
- RTOG 0614: Placebo controlled double blind trial



30Gy/10 vs 37.5Gy/15 WBRT

- Post-hoc analysis of 92 brain met patients from Alliance N107C treated with surgery + WBRT
- Analyzed cognitive and QOL outcomes
- No difference in time to cognitive failure, local control, or survival
- Grade 3+ adverse events higher in 37.5Gy group

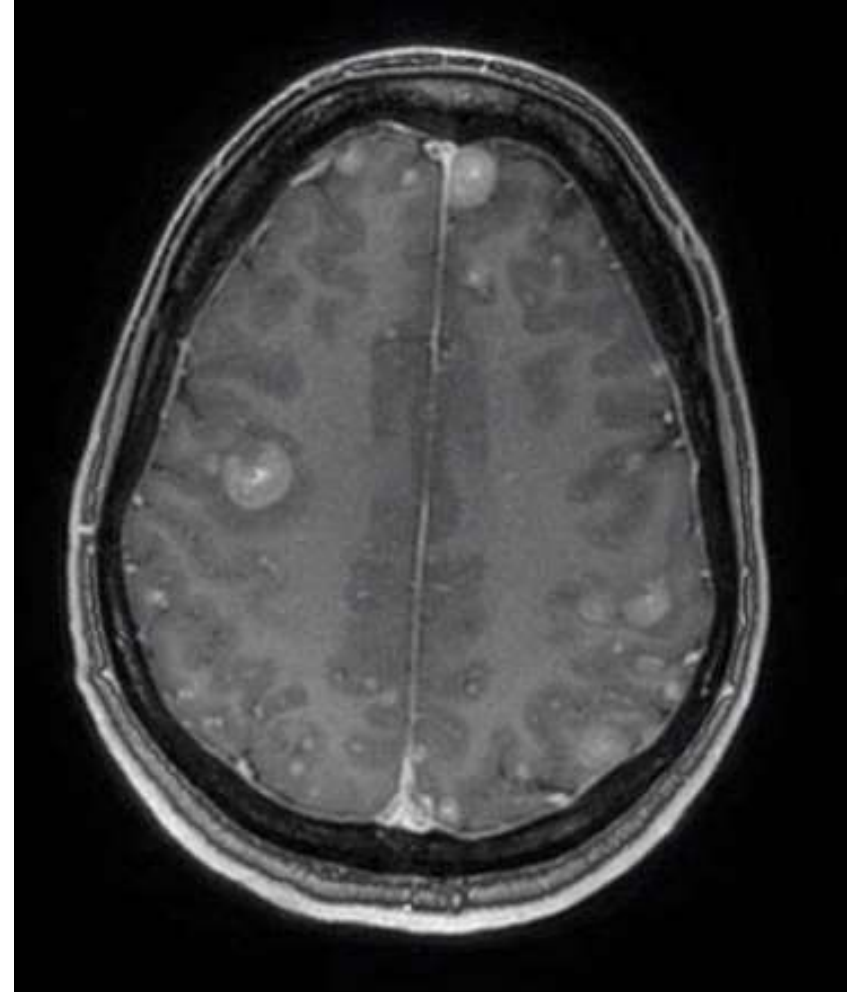
 30Gy in 10 fractions is preferred

Management?

- Standard WBRT +/- Memantine

- Hippocampal-sparing WBRT +/- Memantine

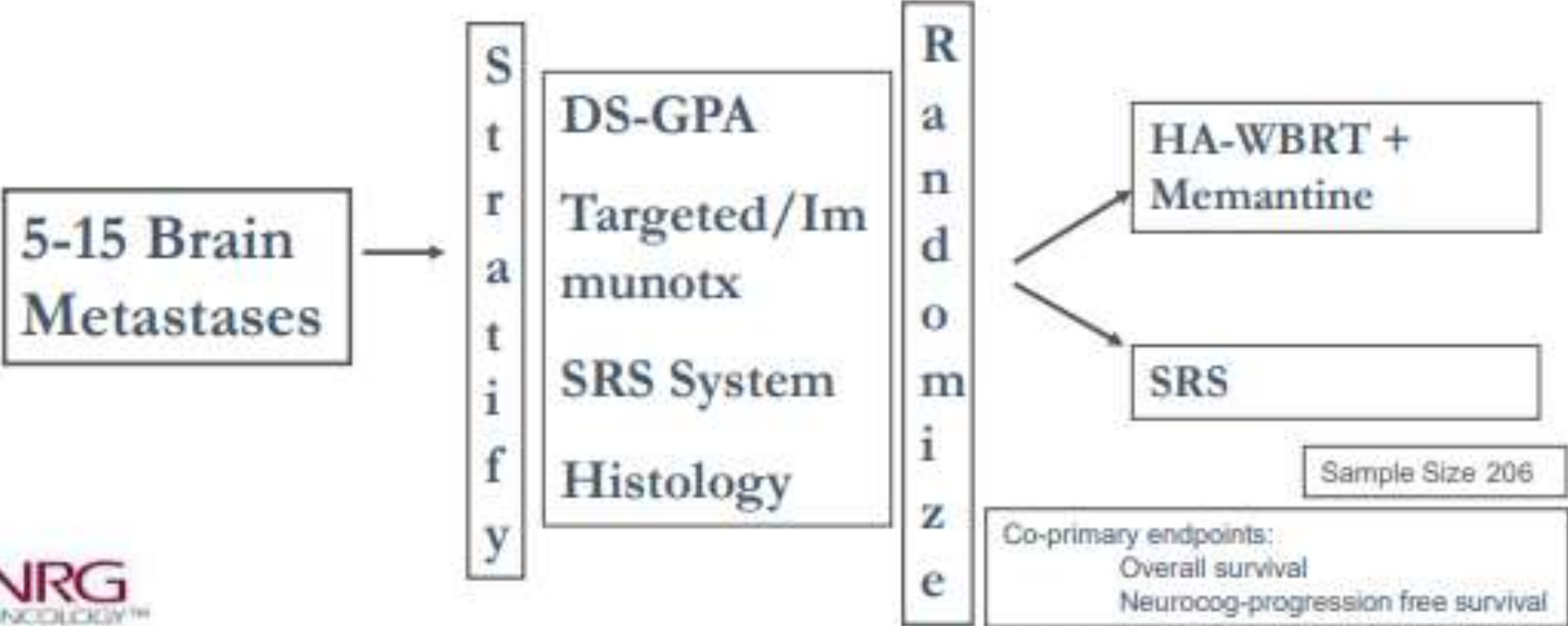
- 30Gy or 37.5Gy?



Multiple metastases: What about SRS?

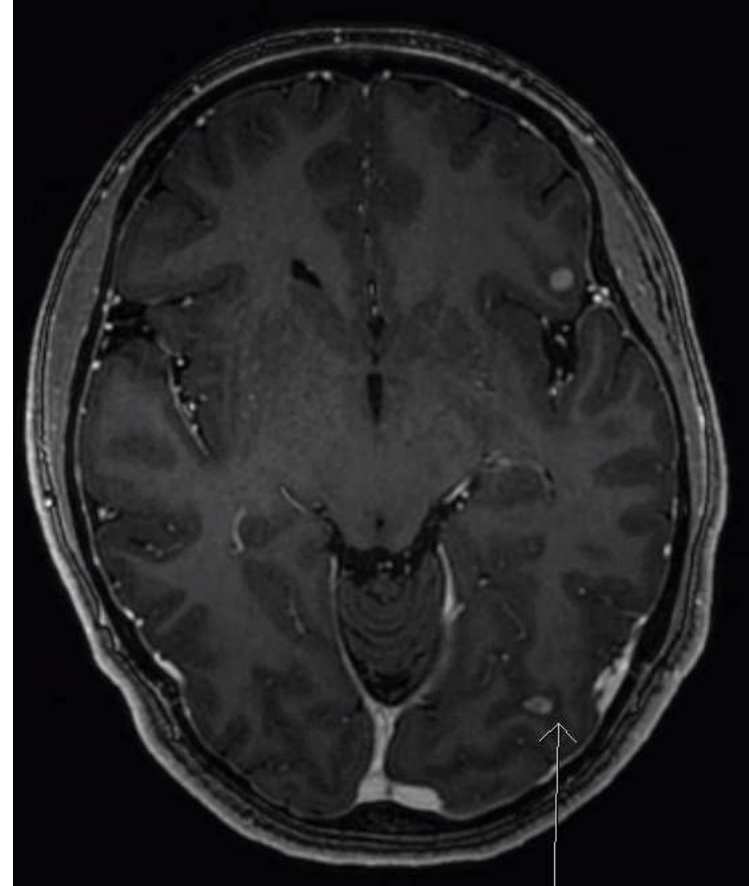
CCTG CE.7: Phase III Trial Stereotactic Radiosurgery versus Hippocampal Avoidant WBRT+memantine for 5-15 Brain Metastases

Basic Eligibility: 5-15 brain mets; largest met <2.5cm; total brain met vol ≤30cc



Case: Multiple metastases

- 24F with met HER2+ breast ca, previous SRS, routine MRI
 - 11 new lesions (2mm-10mm)
- Systemic disease is stable



Management?

- SRS
- Hippocampal-sparing WBRT +/- Memantine

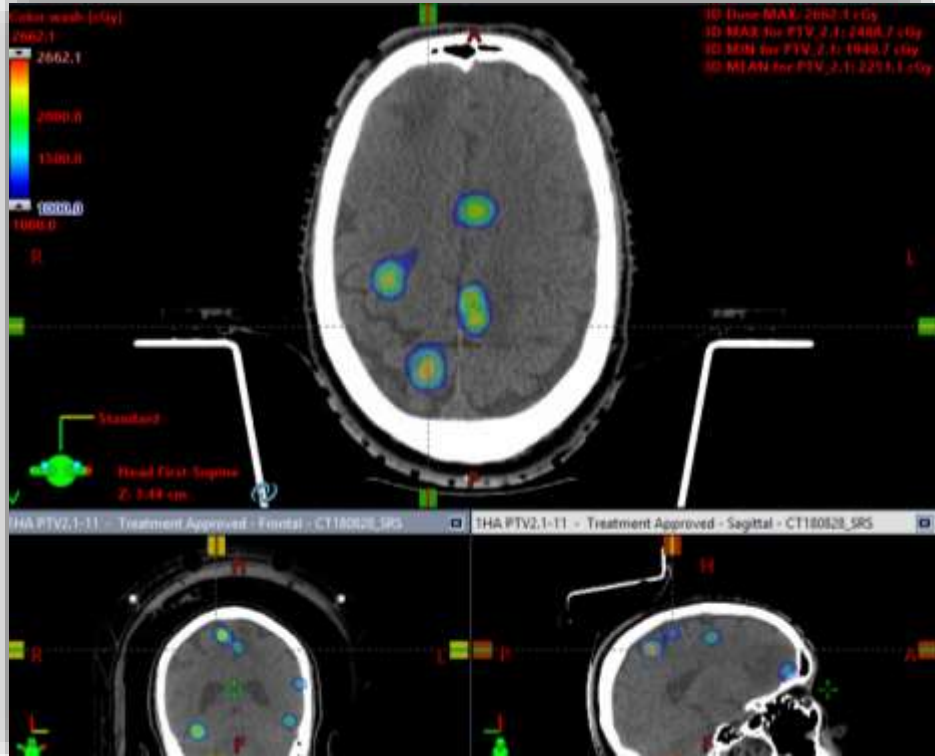
SRS is feasible and safe for multiple metastases

- Volume and geometry is more important than number
- Feasibility: institution/SRS system dependent
- Patient selection is critical
 - Systemic disease: do they have treatment options?
 - Performance status
 - Reliability in follow up/ MRs

SRS Planning

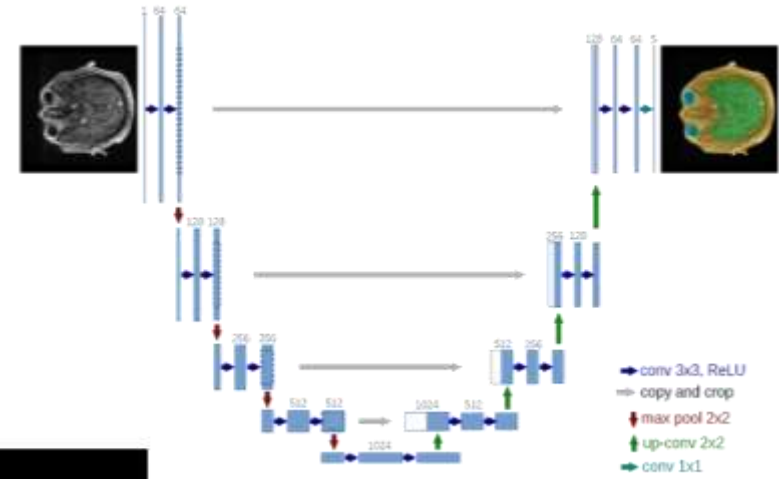
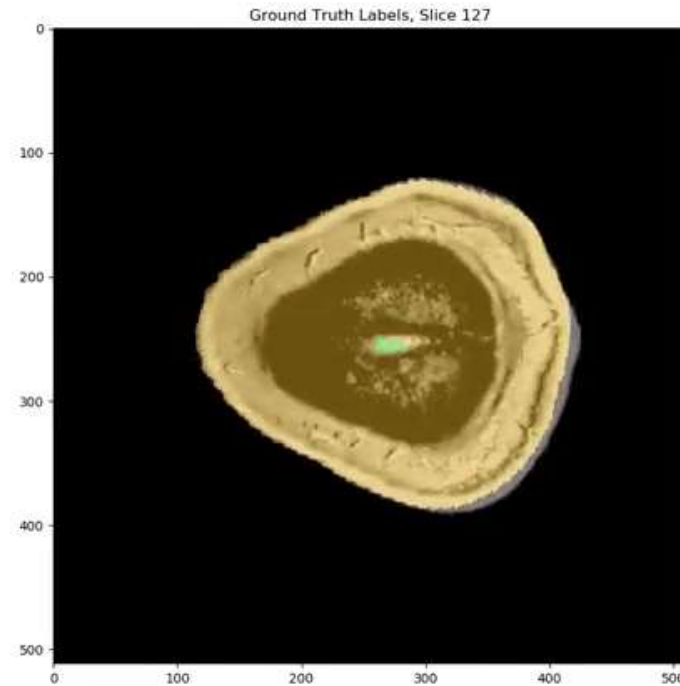
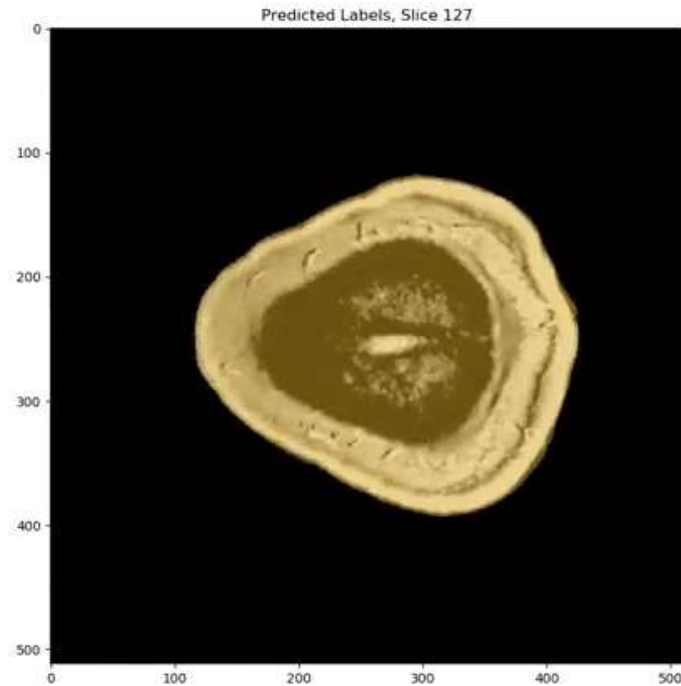
- MRI T1+c thin slice (Brainlab/FSPGR): must be ≤ 14 days old on day of treatment
- Metastases $>2-3\text{cm}$: fractionated SRS (8-9GY x3; 6GY x5) preferred over single fraction
- Improved image-guidance, immobilization masks, correction of set up errors, image registration/distortion correction \rightarrow smaller PTV margin

Single iso-center, Linac SRS



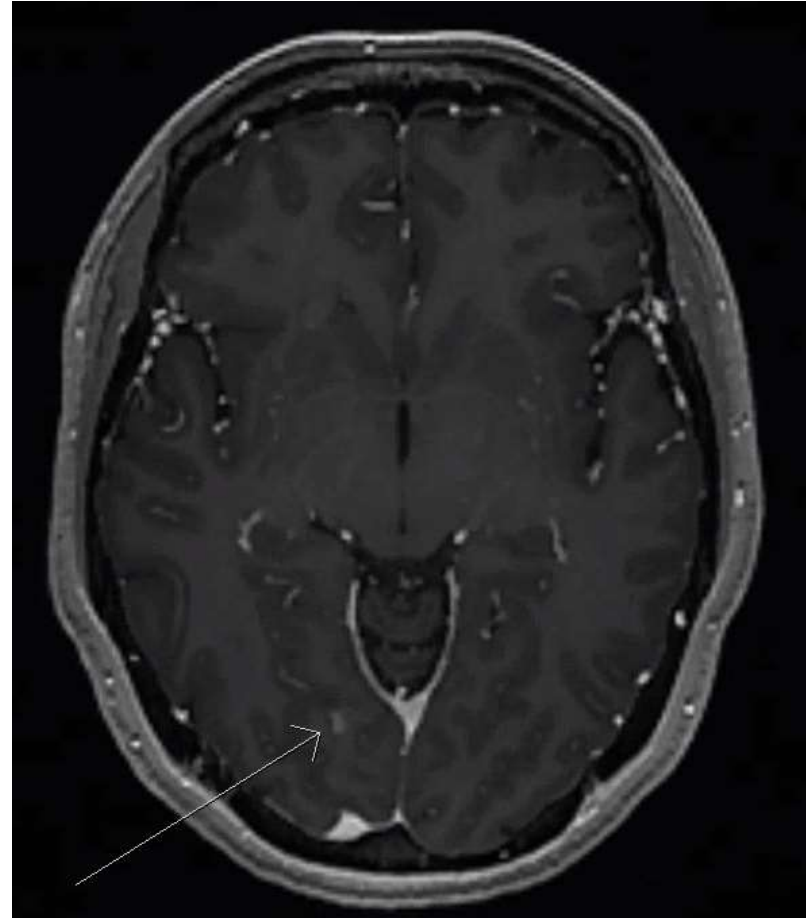
- Normal brain ALARA:
 - V10<10cc is for single target
 - Mean normal brain dose 3.2Gy
- Single fraction/ Single iso
- Delivery time ~12 minutes

AI solution: Our lab

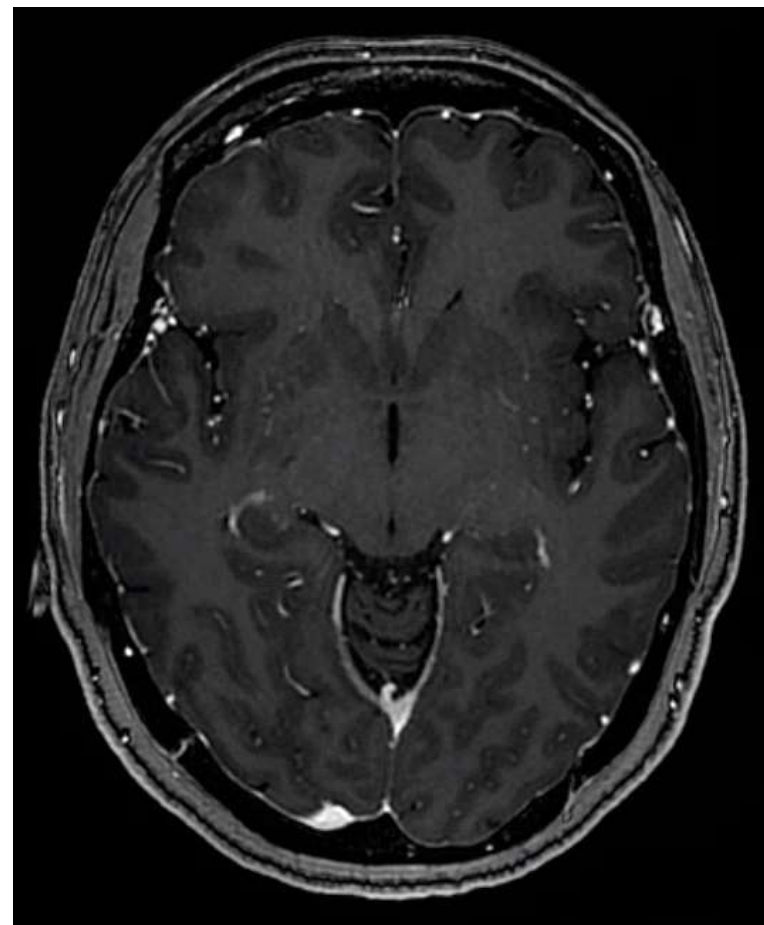
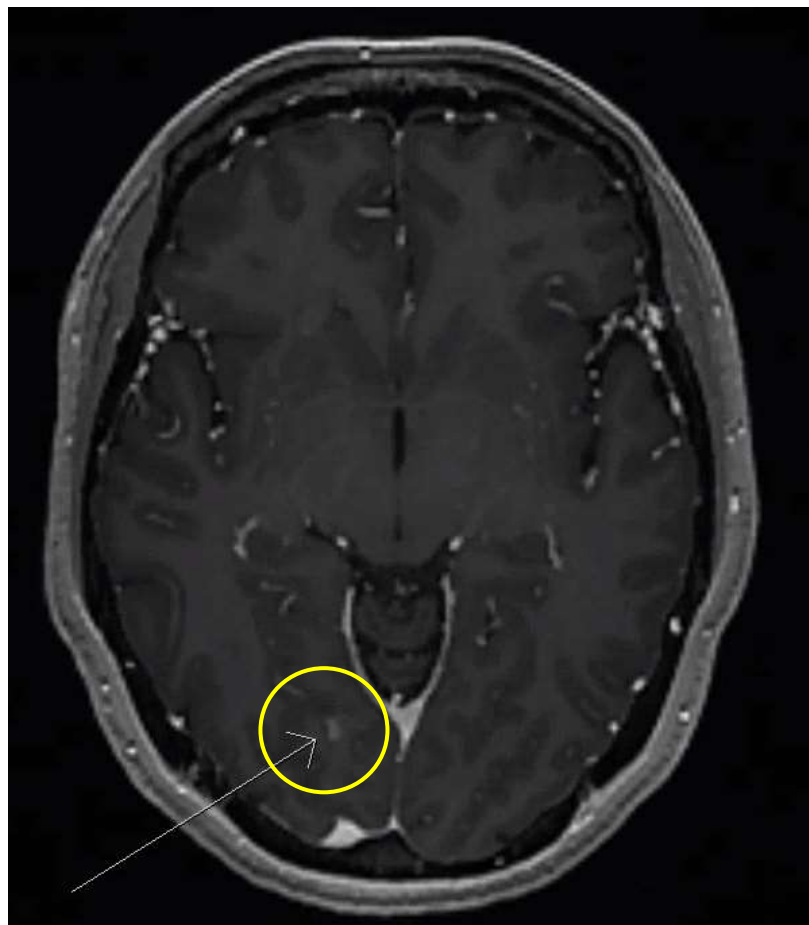


Case: Targeted therapy/Immunotherapy

- 44F w/ met EGFR_{mut} NSCLC,
MRI shows occipital metastasis
- Switched to osimertinib



Repeat MRI for planning



Management?

- SRS
- Continue targeted therapy

Targeted therapy for brain mets: Melanoma

- Checkpoint inhibitors: CNS response ~ systemic response, better with combined CTLA-4/PD-1
- Checkmate 204: phase II single arm Ipi/Nivo → Nivo
 - At least 1 brain met, 0.5-3cm
 - No neurologic symptoms, no steroids
 - CR 26%, PR 30%
 - Intracranial clinical benefit **57%** (CR, PR or stable disease for 6+months)

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab
in Melanoma Metastatic to the Brain

Other targeted agents for brain mets: NSCLC & melanoma

- NSCLC
 - EGFR mut: Osimertinib (3rd generation TKI, better BBB penetrance)
 - ALK mut: Lorlatinib (3rd generation, better BBB penetrance)
- BRAF-mutated melanoma
 - BRAF: Dabrafanib, Vemurafenib
 - MEK: Trametinib
- Response rates 50-60%

Targeted therapy for brain mets

- Best outcomes in small, asymptomatic brain metastases
- Has not been compared with SRS!!!!!! Need further studies
- Some patients may progress rapidly and become symptomatic
- Multidisciplinary input

Case: Resected brain metastasis