



# From Bench to Bedside to Beam: The Role of TomoHelical in the Development of Hippocampal Avoidance

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# Accuray Disclaimers and Disclosure

## Disclosure

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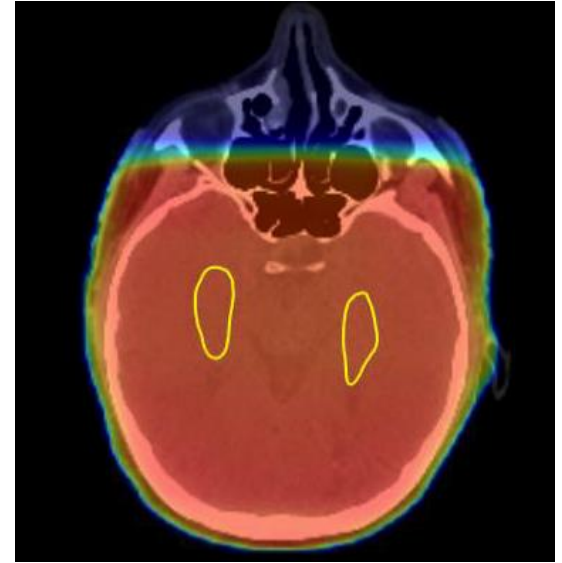
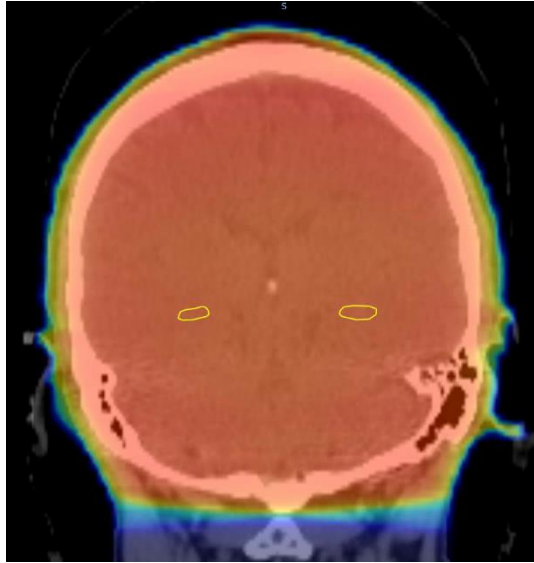
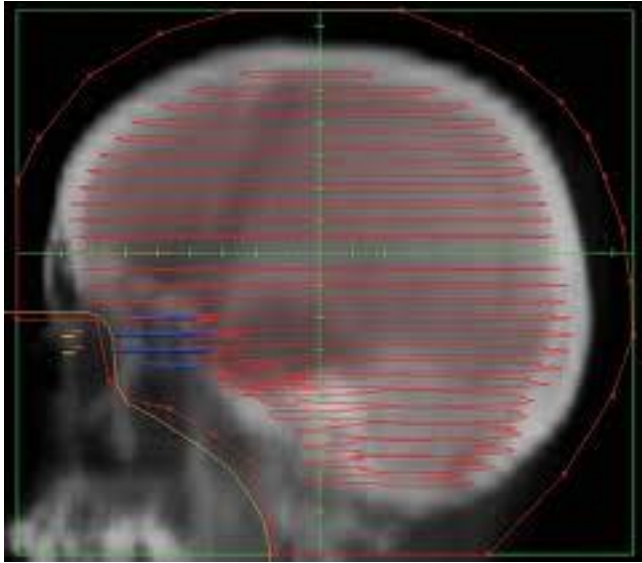
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## Safety Statement

Most side effects of radiotherapy, including radiotherapy delivered with Accuray systems, are mild and temporary, often involving fatigue, nausea, and skin irritation. Side effects can be severe, however, leading to pain, alterations in normal body functions (for example, urinary or salivary function), deterioration of quality of life, permanent injury and even death. Side effects can occur during or shortly after radiation treatment or in the months and years following radiation. The nature and severity of side effects depend on many factors, including the size and location of the treated tumor, the treatment technique (for example, the radiation dose), the patient's general medical condition, to name a few. For more details about the side effects of your radiation therapy, and if treatment with an Accuray product is right for you, ask your doctor.

# Brain Metastases: Whole-Brain Radiotherapy



Used since the 1950s due to

- 1) effectiveness in palliation
- 2) widespread availability
- 3) ease of delivery/planning

# Brain Metastases: WBRT and Cognitive Toxicity

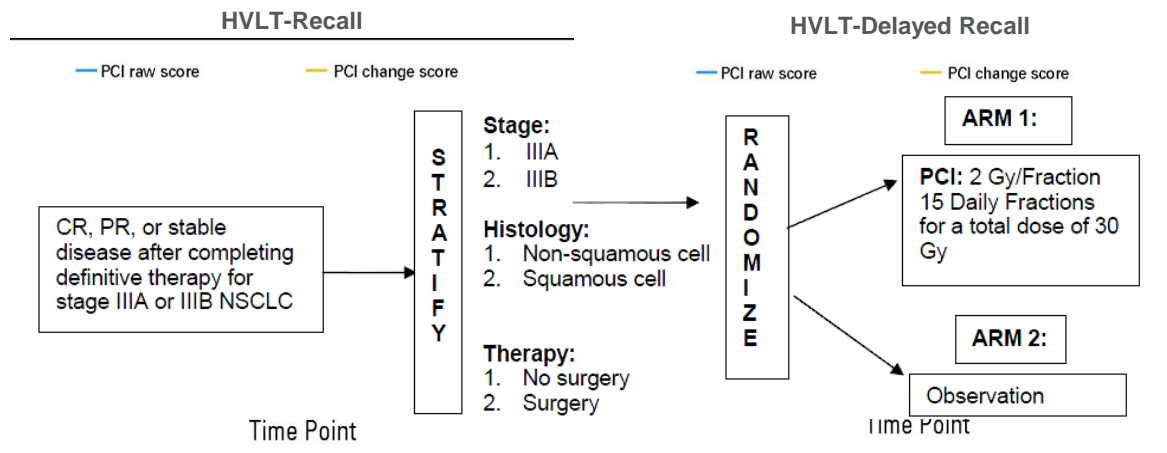
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Overall cognitive toxicity	63.5%	91.7%	<0.001
HVLT Total Recall	8.2%	30.4%	0.004
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COWAT	1.9%	18.6%	0.01
Pegboard-Dominant	29.3%	47.7%	0.07

NCCTG 0574/Alliance phase III trial, N=213

## Brain Metastases: WBRT and Cognitive Toxicity

Cognitive Test	WBRT	SRS	P-value
HVLT Total Recall	47.9%	17.3%	<0.0001
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TMT Part A	37.5%	17.3%	0.0308
TMT Part B	43.5%	19.6%	0.0724
COWA	14.9%	7.7%	0.2733

# PCI and Cognitive Toxicity



- RTD6/w/24h PCI in HVLN stratified for Stage IIIA/IIIB NSCLC
- primary endpoint: Hopkins Verbal Learning Test

## Does HVLТ Decline Matter?

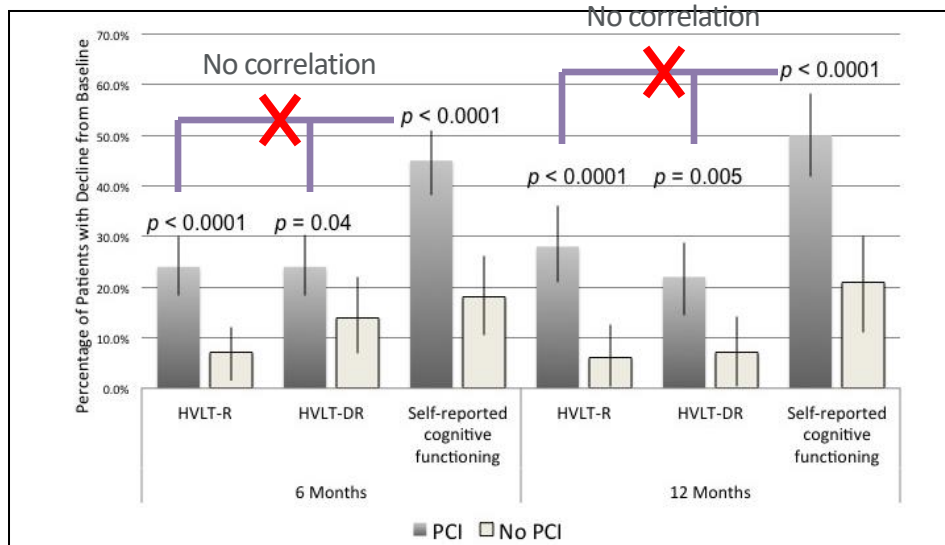
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N107C/N0754: Cognitive decline =

1 std dev change from baseline score → 1-2 word change

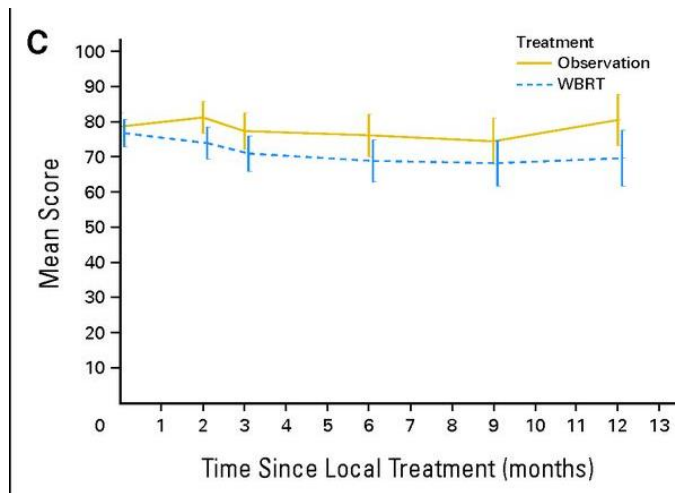
- Is this intensive memory test clinically relevant?

# Effect of PCI on Self-Reported Cognition



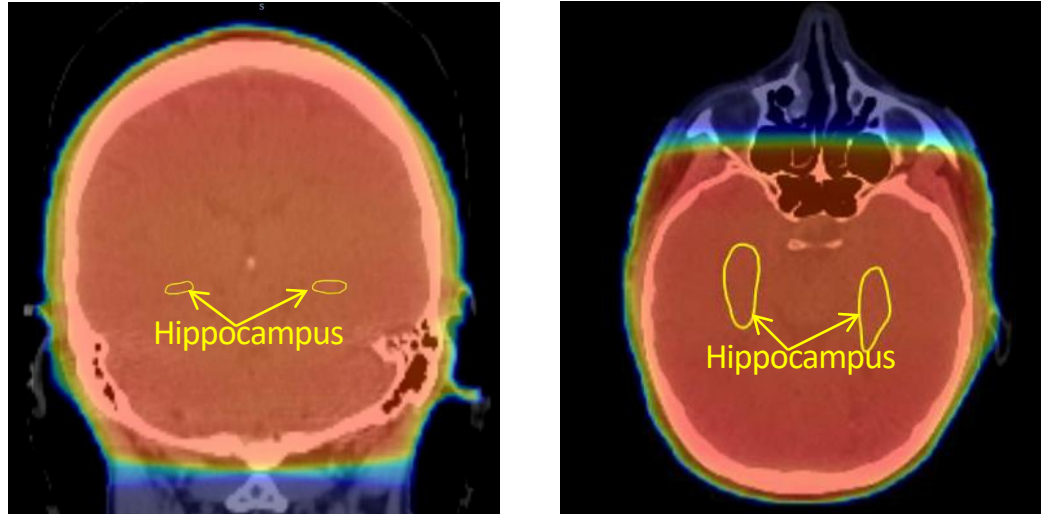
PCI leads to decline in HVLt and self-reported cognitive functioning at 6 and 12 months

# Effect of WBRT on Self-Reported Cognition



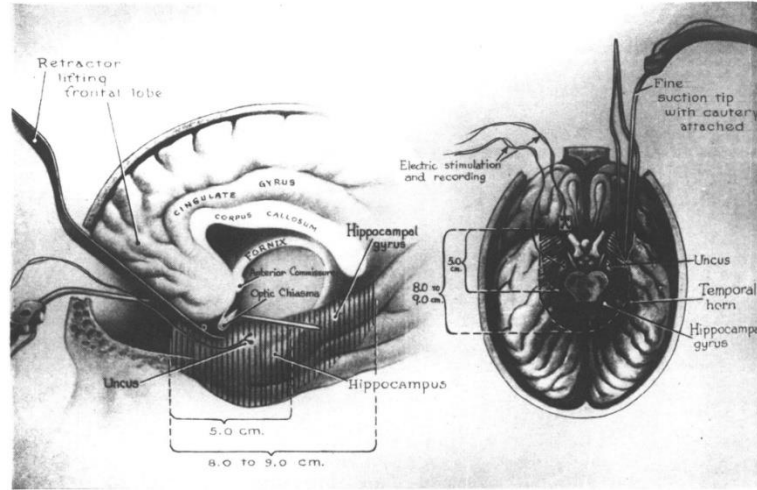
WBRT leads to decline in self-reported cognitive functioning

# Brain Metastases: WBRT and Cognitive Toxicity



**Why are memory-related domains so exquisitely sensitive to WBRT?**

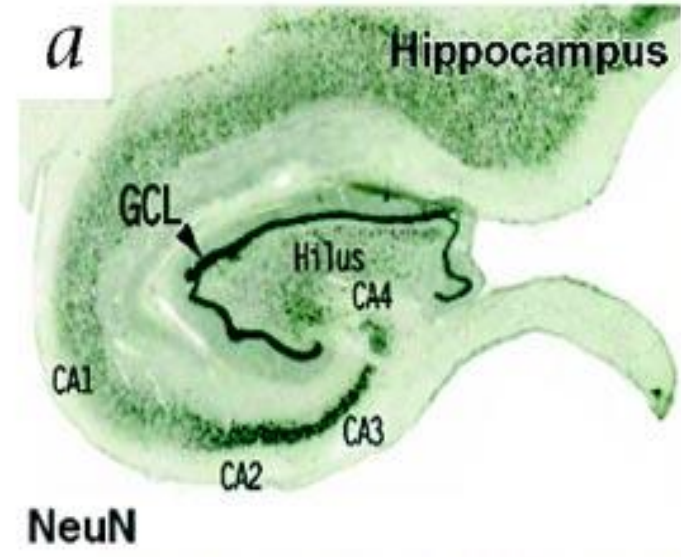
# Mr. H.M. (1926-2008)



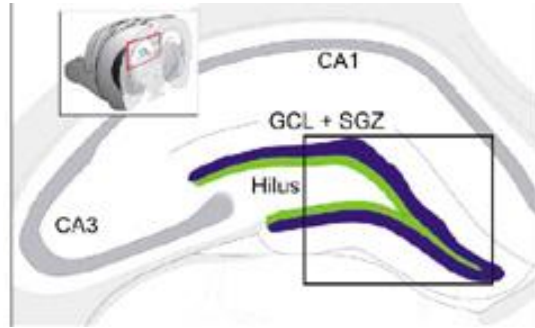
- 1957: bilateral medial temporal lobectomy for relief of medically intractable epilepsy
- Severe anterograde amnesia immediately following the procedure
  - Impairment of declarative memory (conscious recollection of facts and events)
  - No effect on perception, intelligence, and motor skill learning

# Hippocampal Physiology

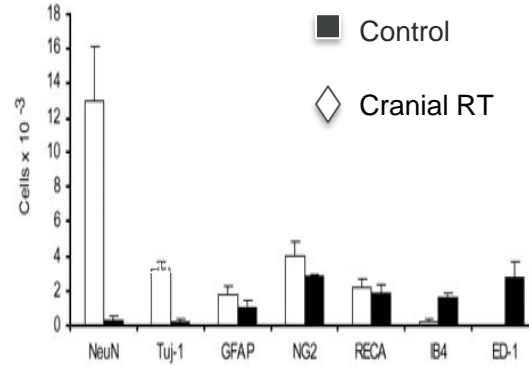
- Generation of new hippocampal neurons arises from neural stem cells located in the subgranular layer of the hippocampus.
- Hippocampal neurogenesis vital to memory-related function and ...



# RT Ablates Hippocampal Neurogenesis

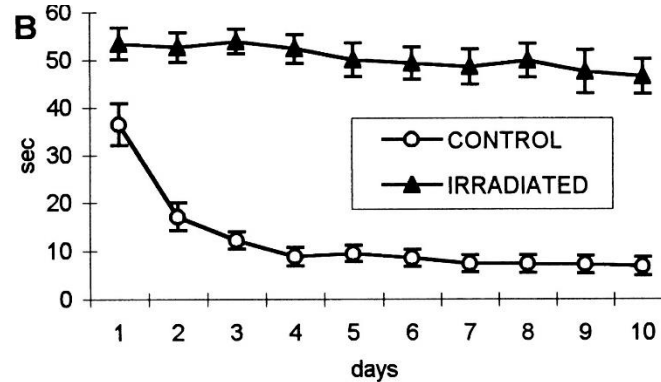
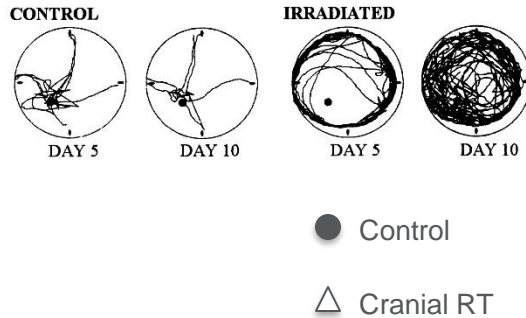


Blue: GCL,  
Green: SGZ



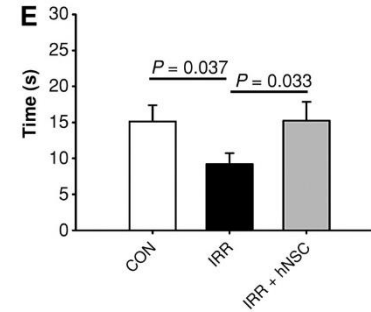
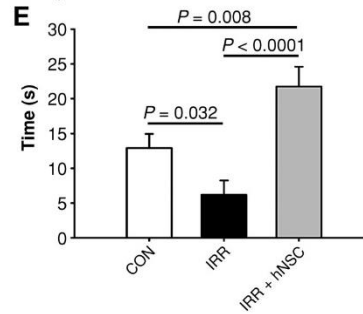
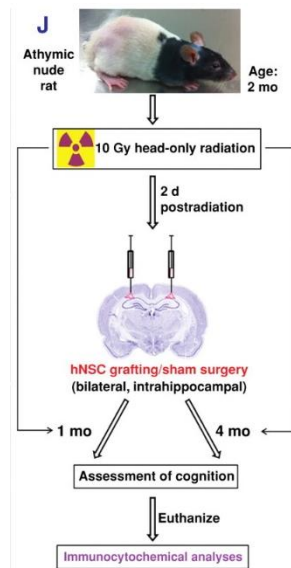
- 97% reduction in newborn neurons 2 months after cranial RT
- NeuN: nuclear antigen for mature neurons; Tuj-1: immature neurons; GFAP: astrocytes; NG2: immature oligodendrocytes; RECA: endothelial cells; IB4: microglial lineage; ED1: activated microglia

# RT Impairs Hippocampal-Dependent Memory



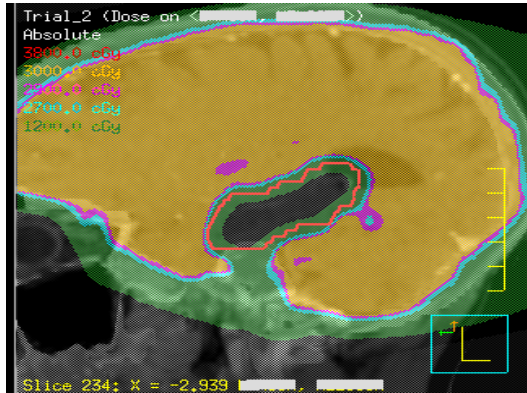
- Morris Water Maze: Test of hippocampal-dependent memory function
- Cranial RT impairs performance on Morris Water Maze

# Hippocampal Stem Cell Transplantation



- Intra-hippocampal transplantation of NSCs after cranial RT reverses RT-induced memory decline
- CON: Control; IRR: Irradiated; hNSC: human neural stem cells

# Hippocampal Avoidant WBRT



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Radiotherapy and Oncology

journal homepage: [www.thegreenjournal.com](http://www.thegreenjournal.com)



Review

Why avoid the hippocampus? A comprehensive review

Vinai Gondi<sup>a,\*</sup>, Wolfgang A. Tomé<sup>a,b</sup>, Minesh P. Mehta<sup>a</sup>

- Preserve neurogenic fate of hippocampal neural stem cells.
- Preserve memory function after cranial RT

# Brain Metastases: WBRT and Cognitive Toxicity

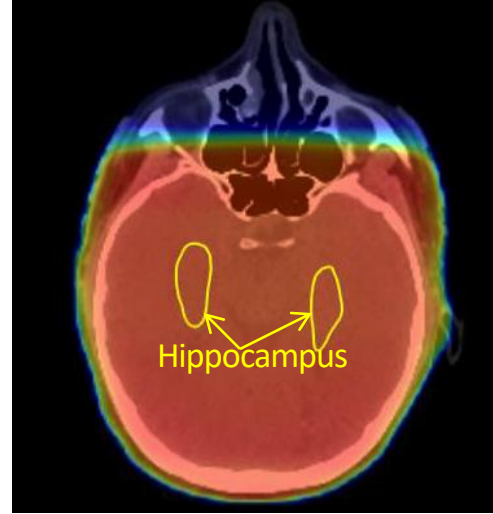
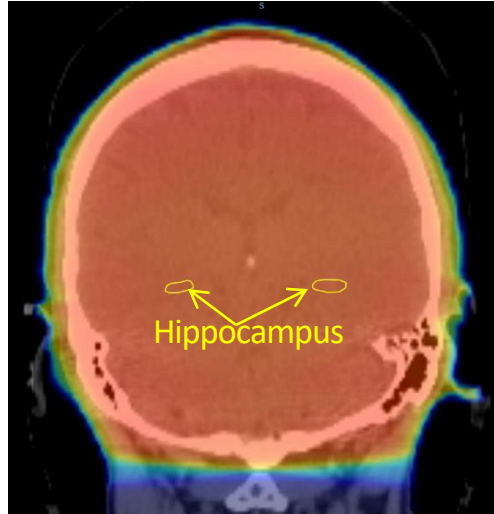
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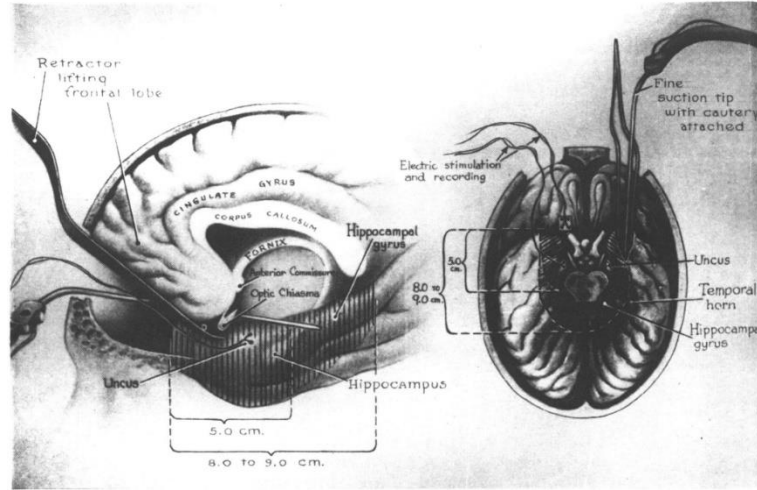
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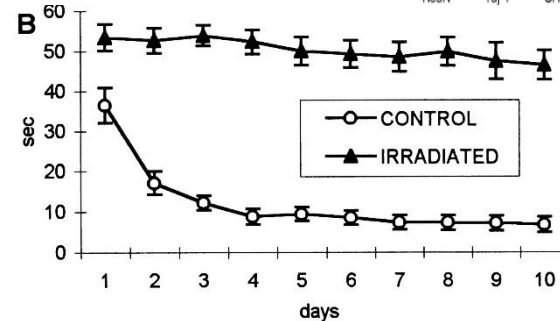
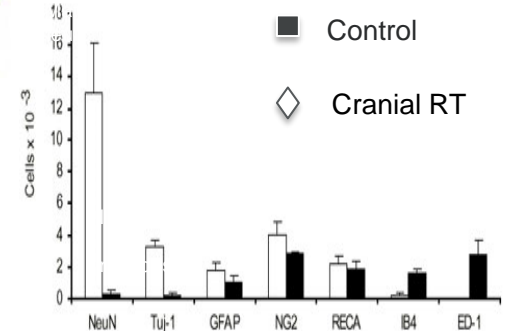
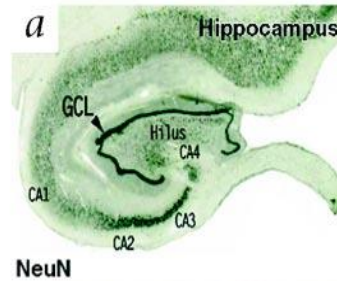
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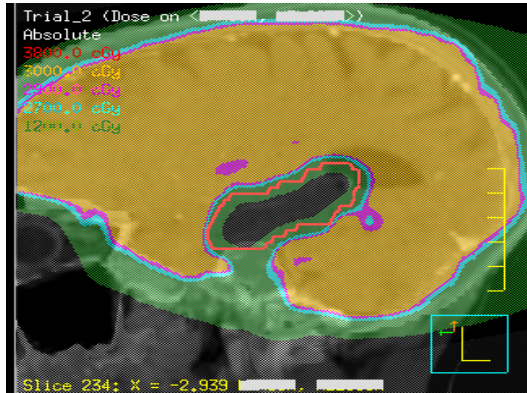
- Generation of new hippocampal neurons arises from neural stem cells located in the subgranular layer of the hippocampus.
- Hippocampal neurogenesis vital to memory-related function and ...

sensitive to low-doses of RT

- 97% reduction in newborn neurons 2 months after brain irradiation
- RT impact of hippocampal neurogenesis a/w impairment in memory



# Hippocampal Avoidant WBRT



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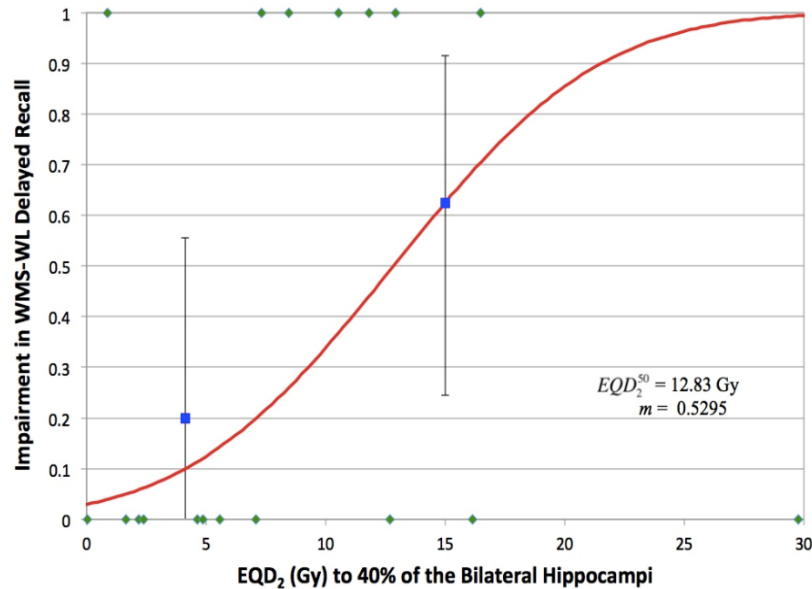
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# Hippocampal Dose-Response Relationship

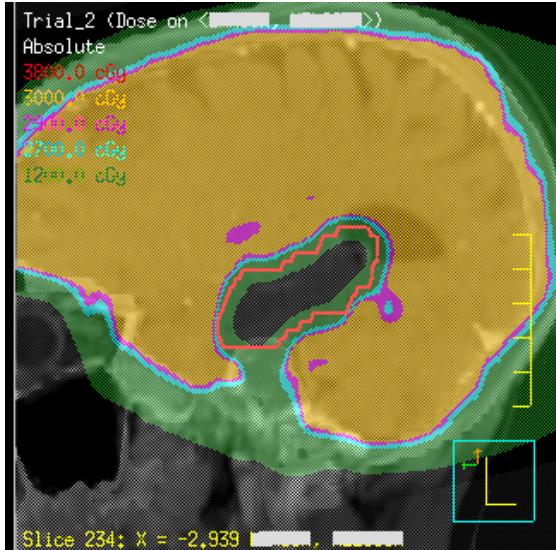


- Dose to 40% of the bilateral hippocampi > 10 Gy

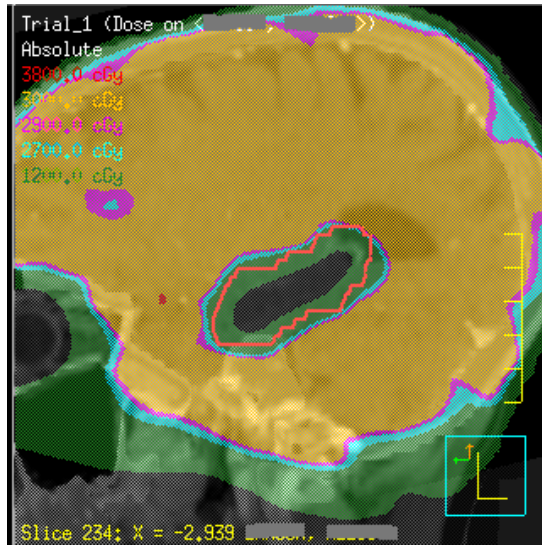
→ Impairment in list-learning delayed recall at 18 months (Odds ratio 19.3,  $p=0.043$ )

- Prospective observational analysis of patients with benign/low-grade brain tumors treated with partial brain irradiation
- Neurocognitive assessments at baseline and 18 months after treatment

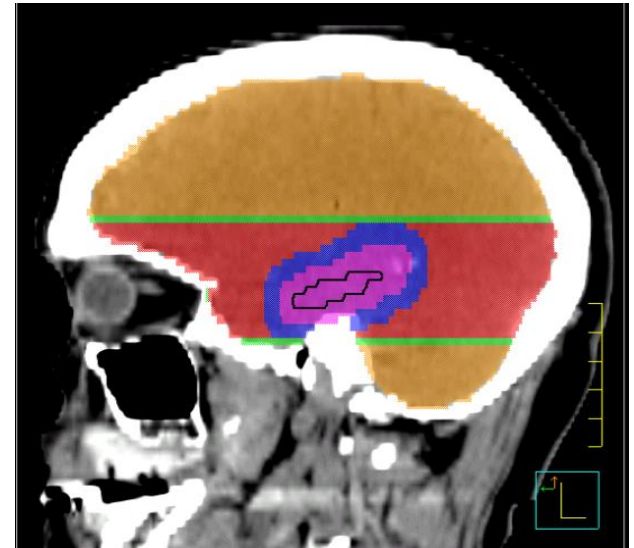
# IMRT for Hippocampal Avoidance during WBRT



Helical TomoTherapy

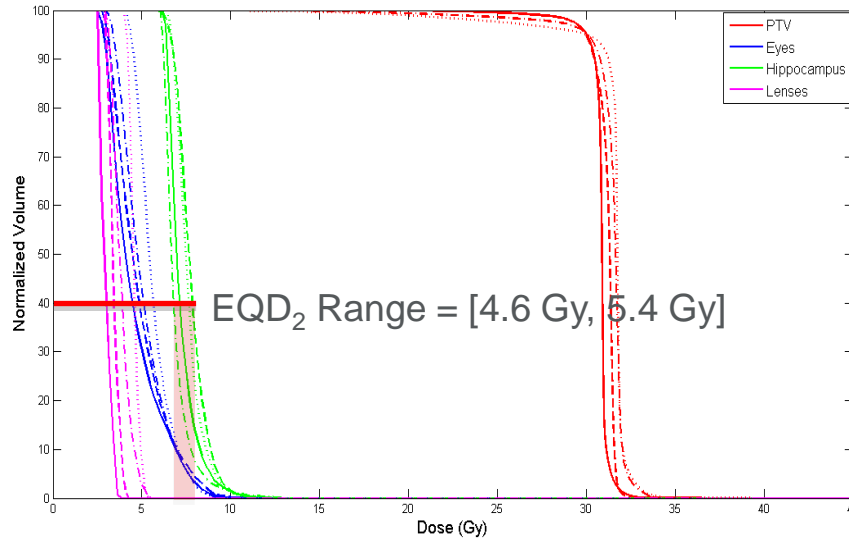


Static Gantry Angle IMRT

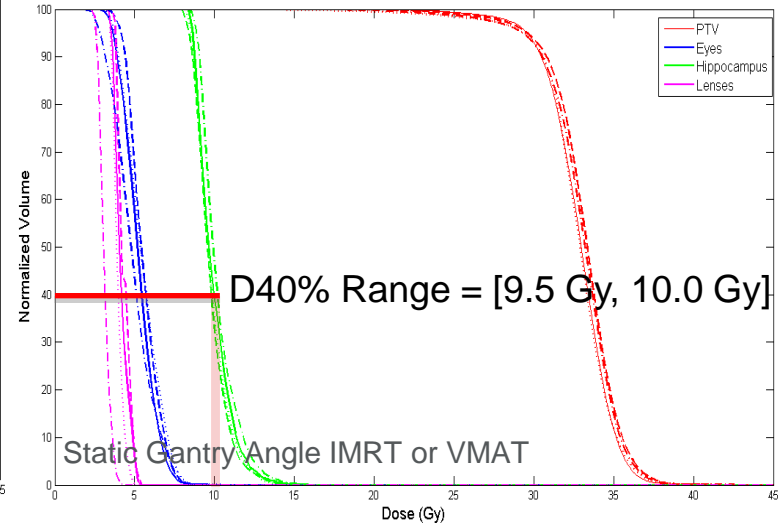


Volumetric Arc Therapy

# IMRT for Hippocampal Avoidance during WBRT



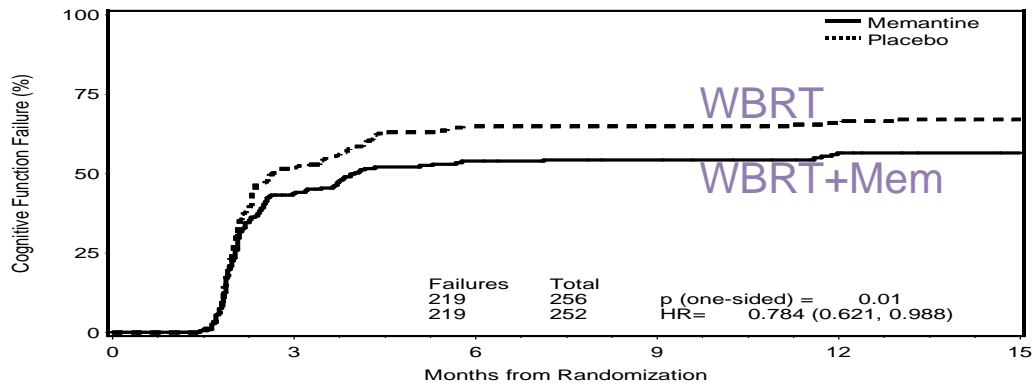
TomoTherapy System



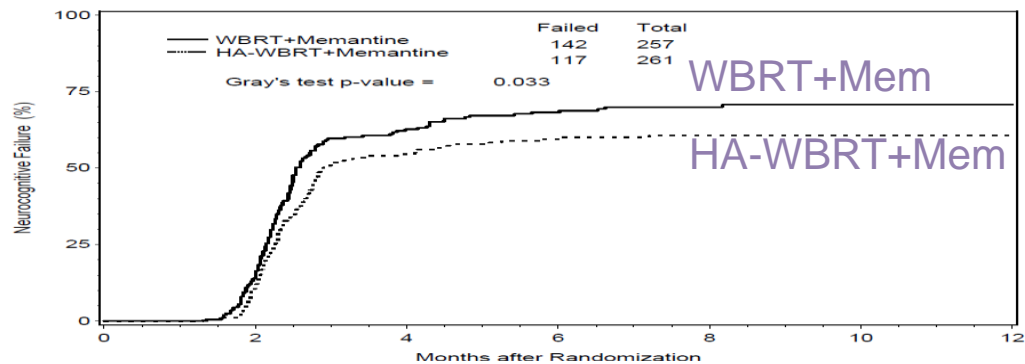
Static Gantry Angle IMRT or VMAT

Modern IMRT may sufficiently spare the hippocampus to yield clinical benefit

# Hippocampal Avoidance + Memantine: Safer Delivery of WBRT



RTOG 0614<sup>1</sup>: Hazard ratio=0.78  
Memantine provides  
22% relative reduction in cognitive  
toxicity



NRG CC001<sup>2,3</sup>: Hazard ratio=0.74  
Hippocampal avoidance with  
memantine provides additional  
26% relative reduction in cognitive  
toxicity

# Hippocampal Avoidance + Memantine: Safer Delivery of WBRT

## RTOG 0614: Memantine

- Preserves
  - 2 months: Verbal fluency  
(Controlled Oral Word Association Test)
  - 6 months: Learning and memory  
(HVLT-R Recognition)
- Trend to benefit in preserving
  - 2 months: Learning and memory  
(HVLT-R Delayed Recall) p= 0.69
  - 6 months: Learning and memory  
(HVLT-R Delayed Recall) p= 0.59

## NRG CC001: Hippocampal avoidance added to memantine

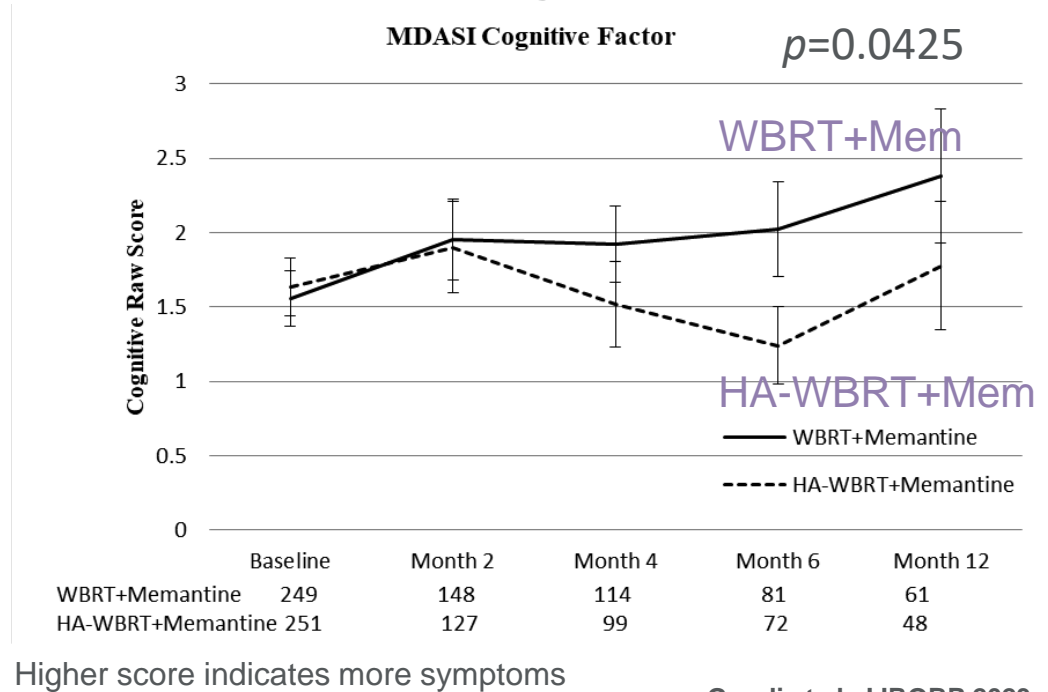
- Reduces deterioration of
  - 4 months: Executive function  
(Trail Making Test B)
  - 6 months: Learning and memory  
(HVLT-R Recognition)
- Preserves all learning and memory domains over time
  - HVLT-R total recall, delayed recall and recognition

Brown et al Neuro Oncol 2013 Gondi et al., IJROBP 2023

# HA Impacts Patient-Reported Neurologic Symptoms

- Hippocampal avoidance preserves patient-reported symptoms at 6 months:
  - Neurologic symptom burden
  - Interference of neurologic symptoms in daily activities
- Hippocampal avoidance preserves patient-reported cognitive factor over time:
  - Hippocampal avoidance associated with less problems remembering things at 6 months ( $p=0.016$ )

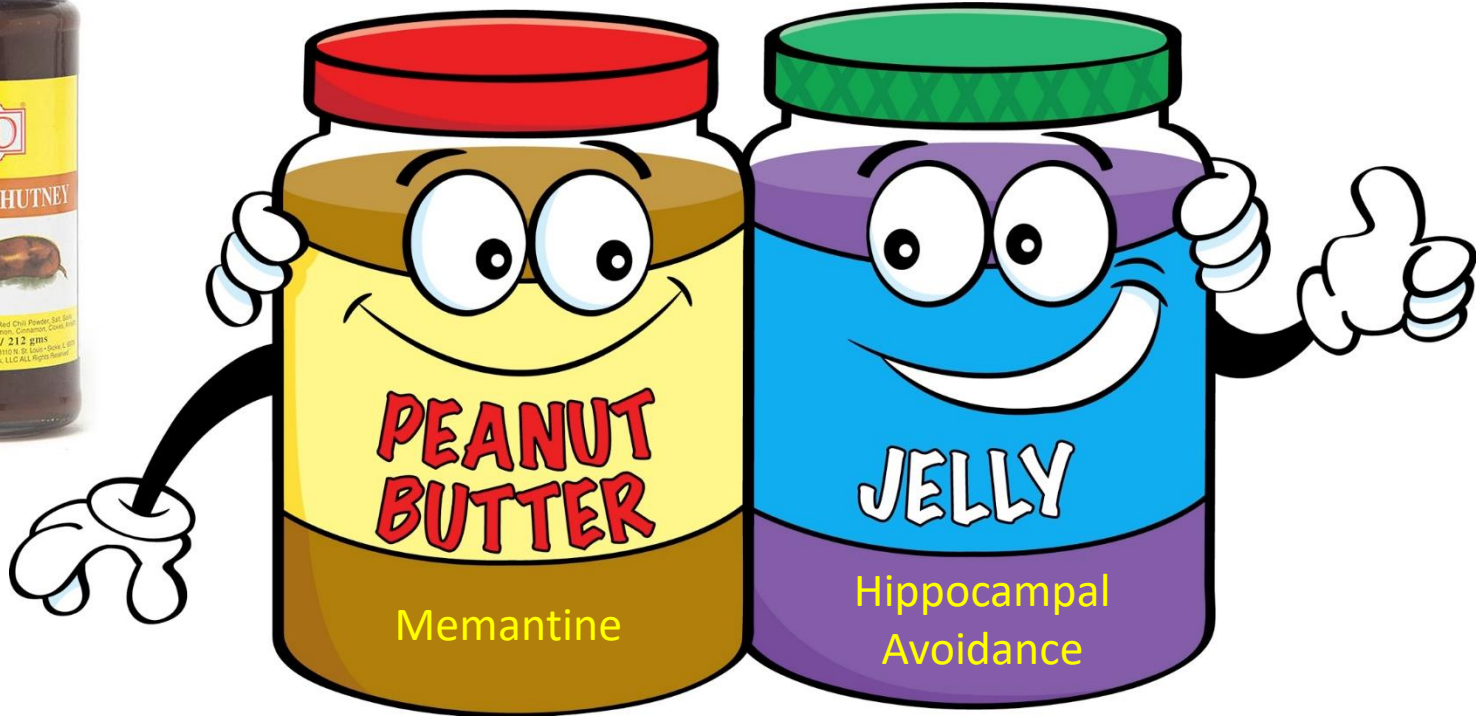
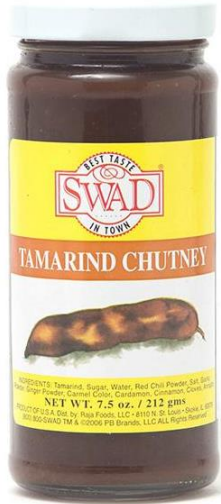
Mixed effects models using multiple imputation:



Gondi et al., IJROBP 2023

Median follow-up for alive patients: **12.1 months**

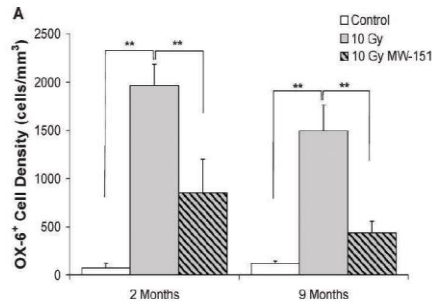
# Reinventing the Wheel: Safer Delivery of WBRT



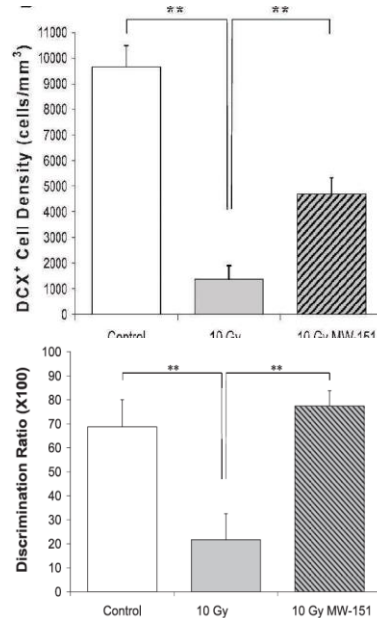
# Pharmacologic Strategies during WBRT

R42 CA236382: Mitigation of Radiation Therapy Induced Neuroinflammation and Cognitive Dysfunction (PI: Gondi V)

MW 151:

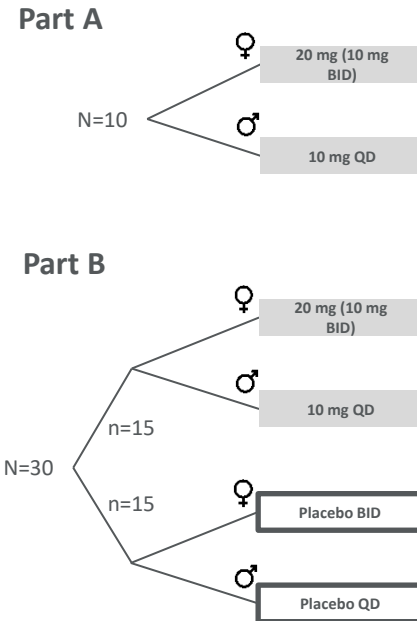


Courtesy of Dr. Linda Van Eldik



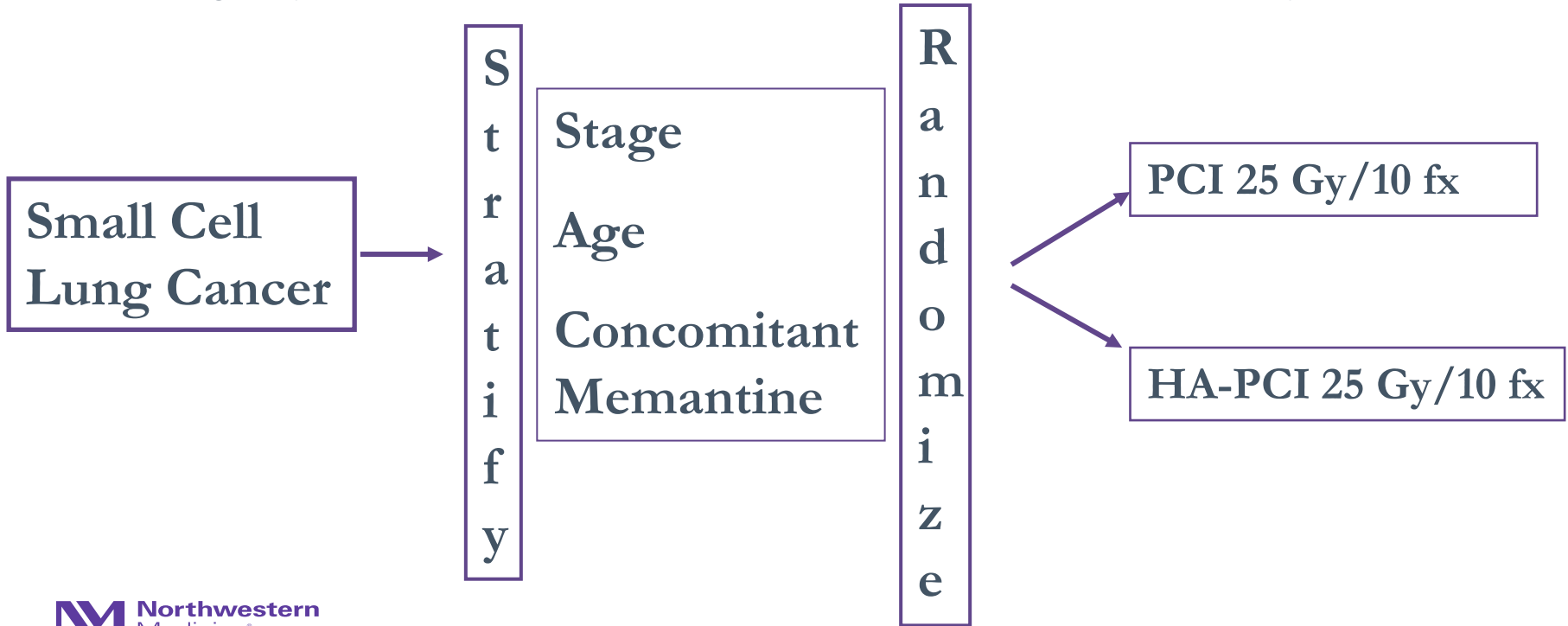
MW151 reduces neuro-inflammation and better preserves hippocampal neurogenesis and hippocampal-dependent memory following WBRT

## Phase I Trial



# NRG-CC003: Seamless Phase IIR/III Trial of Prophylactic Cranial Irradiation +/- Hippocampal Avoidance for Small Cell Lung Cancer

Basic Eligibility: PR or CR to chemo; ECOG PS 0-2; baseline HVLt-R Delayed Recall >2



# Secondary Endpoints

Gondi et al. ASTRO Plenary 2023

- Hippocampal avoidance prevents first failure in any cognitive test
  - 23% relative risk reduction
  - NRG-CC001: HR=0.74<sup>1</sup>

Variable	HR	95% CI	p value
<b>Treatment arm (HA-PCI vs. PCI [RL])</b>	<b>0.77</b>	<b>0.61-0.98</b>	<b>0.033</b>
Age* (≥60 vs. <60 [RL])	1.17	0.89-1.53	0.265
Stage* (Extensive vs. Limited [RL])	0.92	0.70-1.20	0.527
Memantine usage* (Yes vs. No [RL])	1.25	0.98-1.59	0.067

\*Stratification factor  
[RL]: Reference level

Median follow-up: **14.9 months** for all patients  
**24.0 months** for alive patients

<sup>1</sup>Gondi et al. IJROBP 2023

# Secondary Endpoints

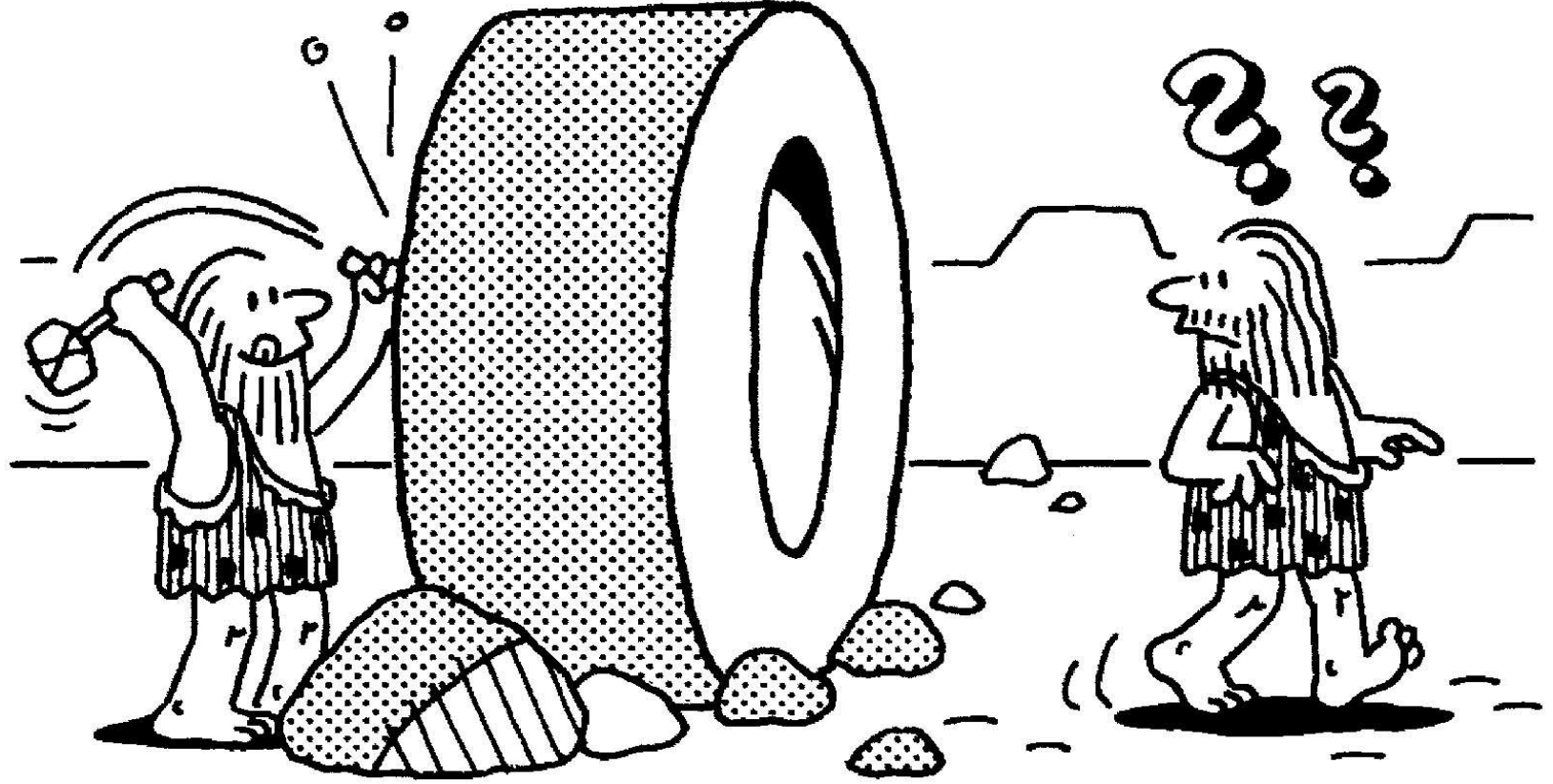
Gondi et al. ASTRO Plenary 2023

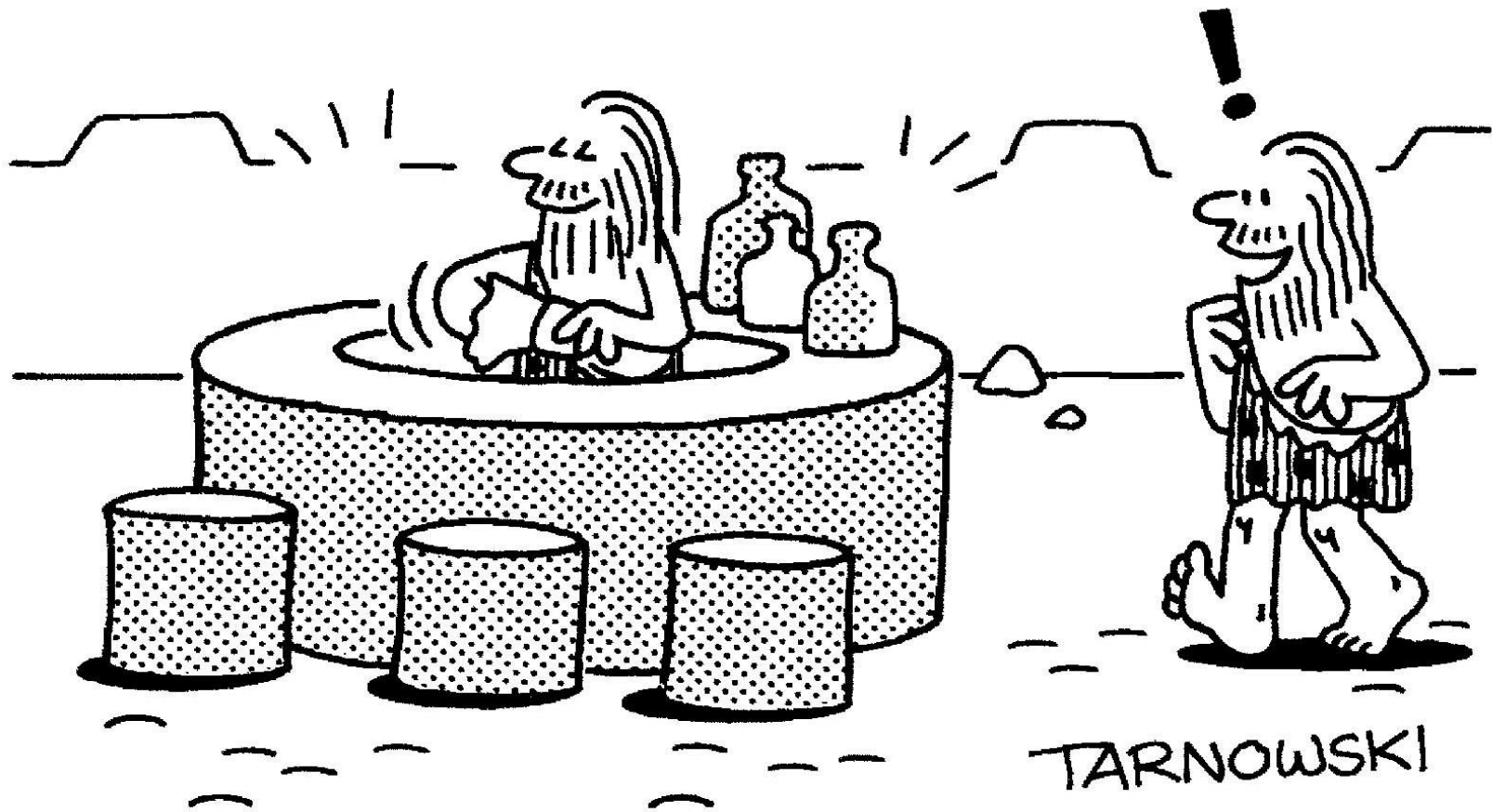
- Hippocampal avoidance prevents first failure in any cognitive test
  - 23% relative risk reduction
  - NRG CC001: HR=0.74<sup>1</sup>
- Memantine usage trended to higher first failure in any cognitive test
  - No interaction between treatment arm and memantine usage
  - Memantine usage predicted higher risk of intracranial relapse
    - Memantine: HR=1.60, p=0.03

Variable	HR	95% CI	p value
Treatment arm (HA-PCI vs. PCI [RL])	0.77	0.61-0.98	0.033
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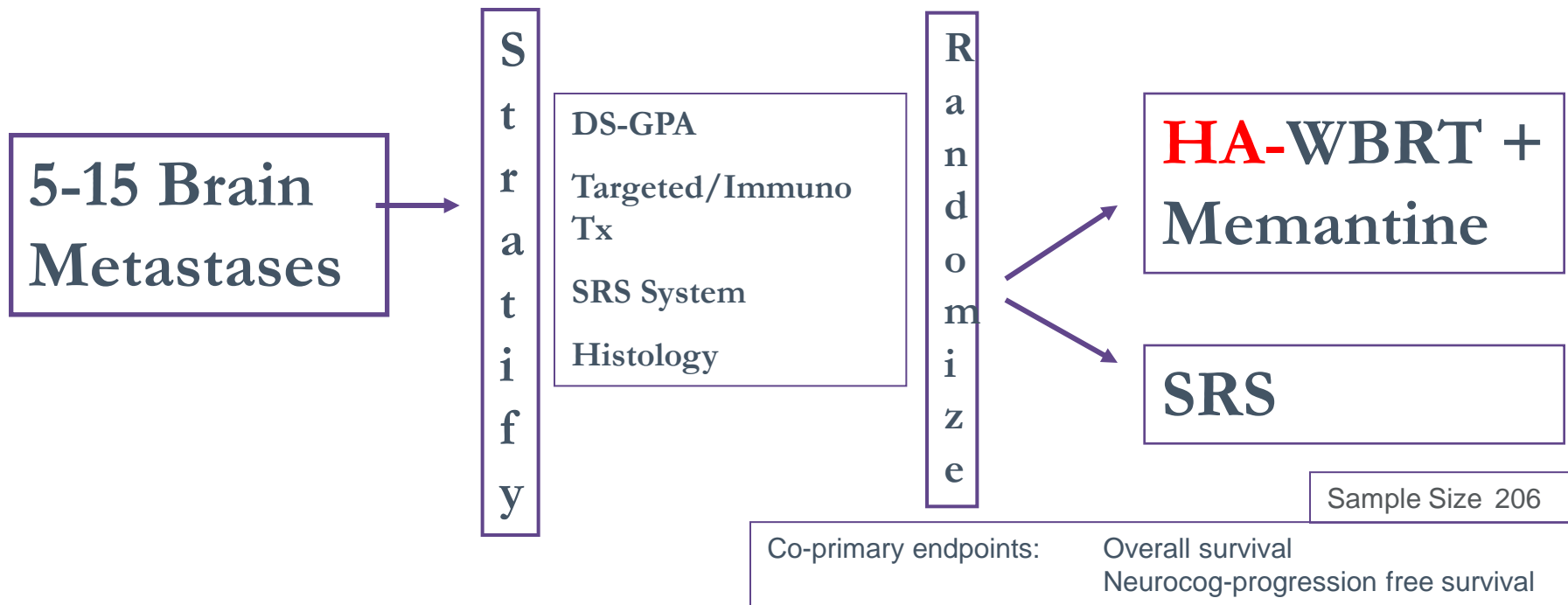




# CCTG CE.7: Phase III Trial Stereotactic Radiosurgery vs. Hippocampal Avoidant WBRT+Memantine for 5-15 Brain Metastases

PI: David Roberge (CHUM Montreal)

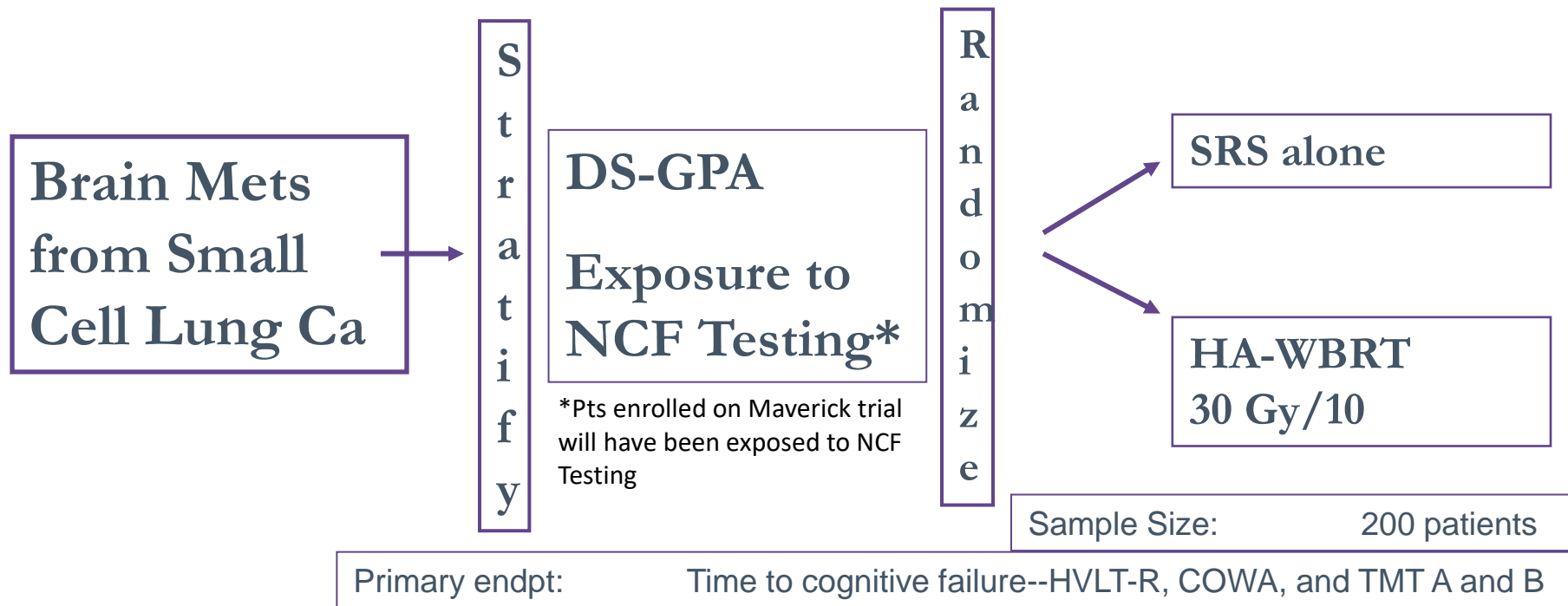
Basic Eligibility: 5-15 brain mets; largest met <2.5cm; total brain met vol ≤30cc



# NRG CC009: Phase III Trial Stereotactic Radiosurgery versus Hippocampal-Avoidant Whole-Brain Radiotherapy for 10 or Fewer Brain Metastases from Small Cell Lung Cancer

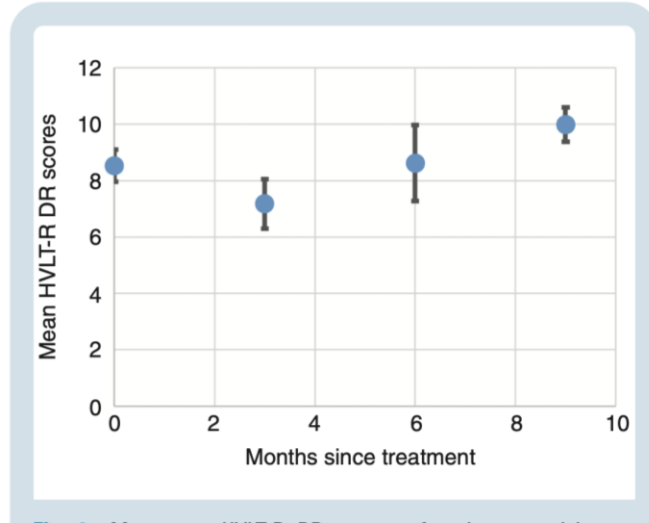
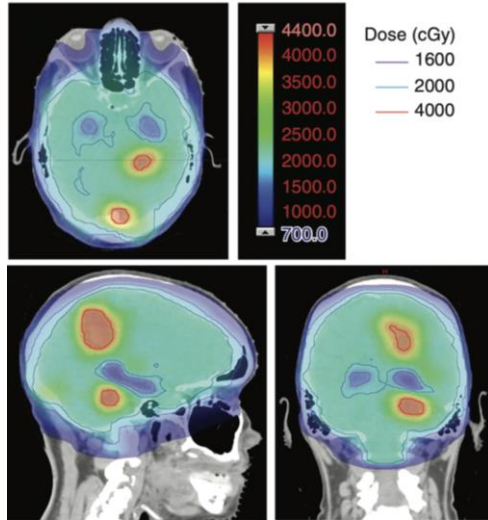
PIs: Chad Rusthoven (Univ of Colorado) + Vinai Gondi (Northwestern)

Basic Eligibility: Small cell lung cancer;  $\leq 10$  brain mets  $\leq 3$ cm; total vol 30cc; KPS  $\geq 70$



# HA-WBRT with Simultaneous Integrated Boost

UT-Southwestern Phase II Trial

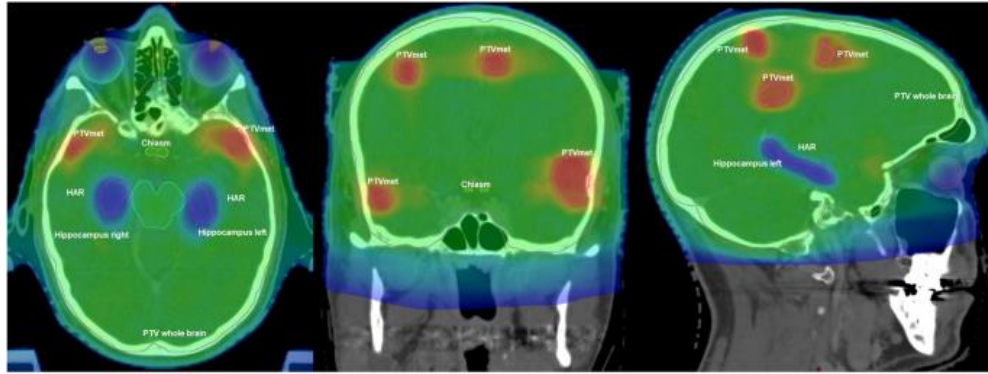


HA-WBRT+SIB had

- Improved HVLTR-DR outcomes vs. historical WBRT controls
- Similar intracranial control vs. historical WBRT+SRS controls

# HA-WBRT with Simultaneous Integrated Boost

HIPPORAD

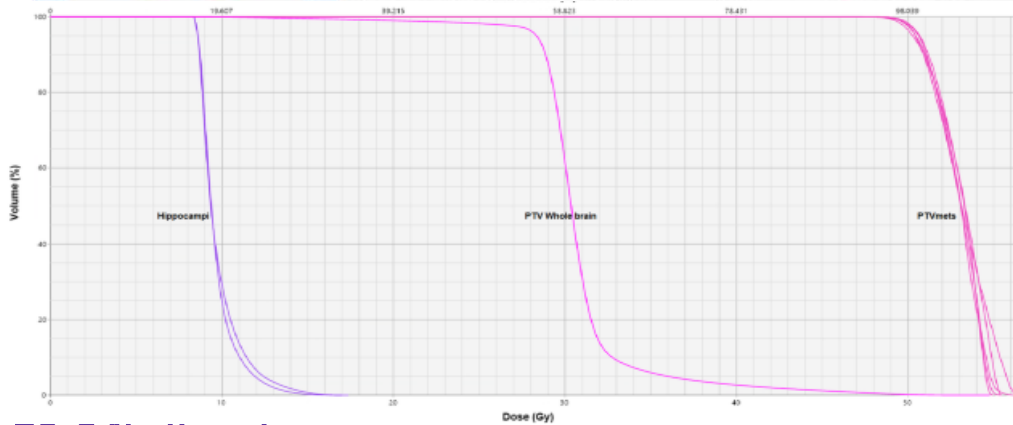


HIPPORAD (NOA-14, ARO 2015-3, DKTK-ROG):

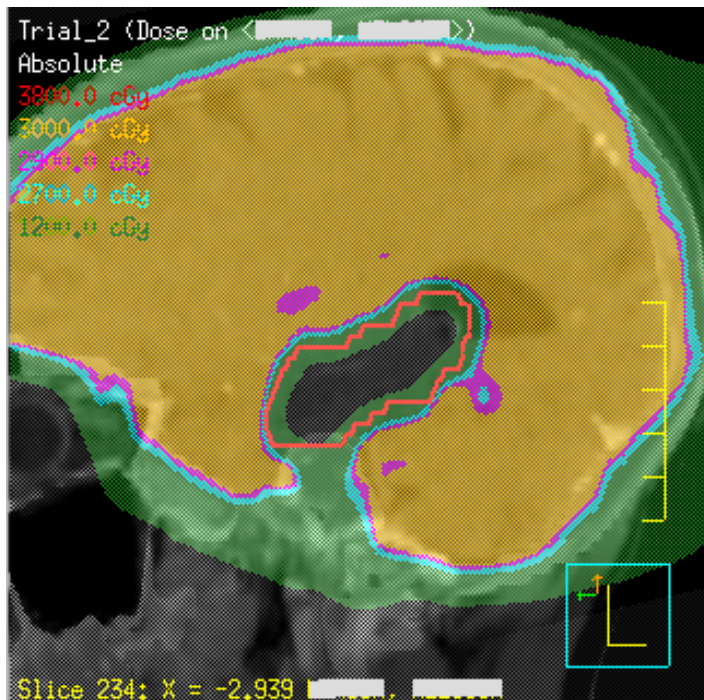
Randomized phase II trial of HA-WBRT (30 Gy/12 fx) with SIB for brain metastases (51 Gy/12 fx)

Developing NRG Trial:

Phase III trial of reduced-dose HA-WBRT+SIB vs. std-dose HA-WBRT+SIB for brain mets



# TomoHelical in the Development of HA-WBRT



**Critical to the  
Development of this  
Practice-Changing Line  
of Research**