



## NRG CC001

Phase III Trial Memantine and Whole-Brain Radiotherapy with or without Hippocampal Avoidance in Patients with Brain Metastases

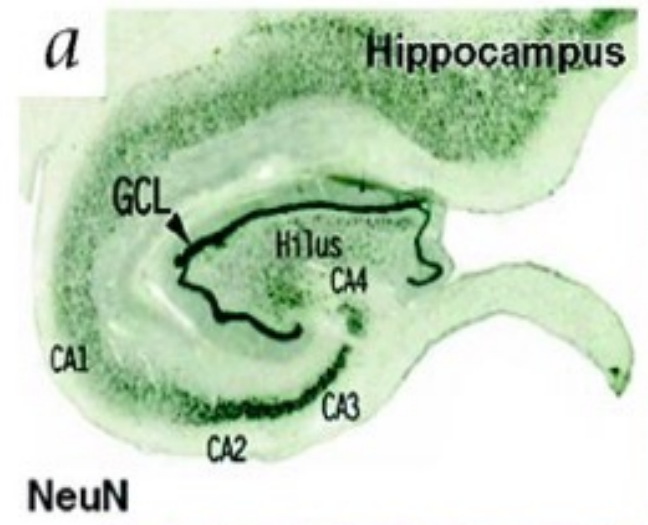
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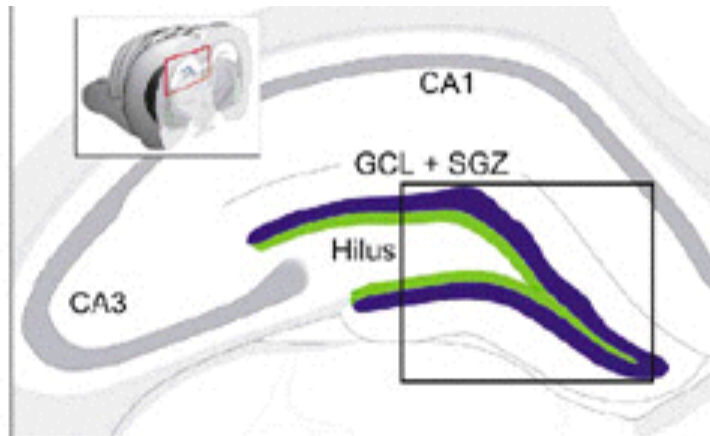
No significant financial interest or affiliations to disclose  
There will be discussion of off-label use of Memantine

# Hippocampal Physiology

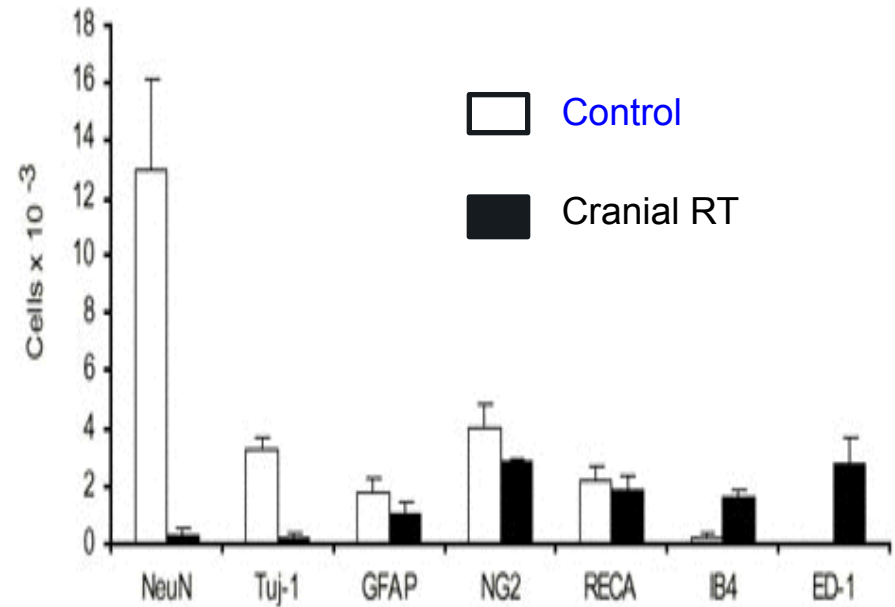
- Generation of new hippocampal neurons arises from neural stem cells located in the subgranular layer of the hippocampus.
- Hippocampal neurogenesis vital to memory-related function



# RT Ablates Hippocampal Neurogenesis



Blue: GCL,  
Green: SGZ



Monje, M et al. Nat Med 2002

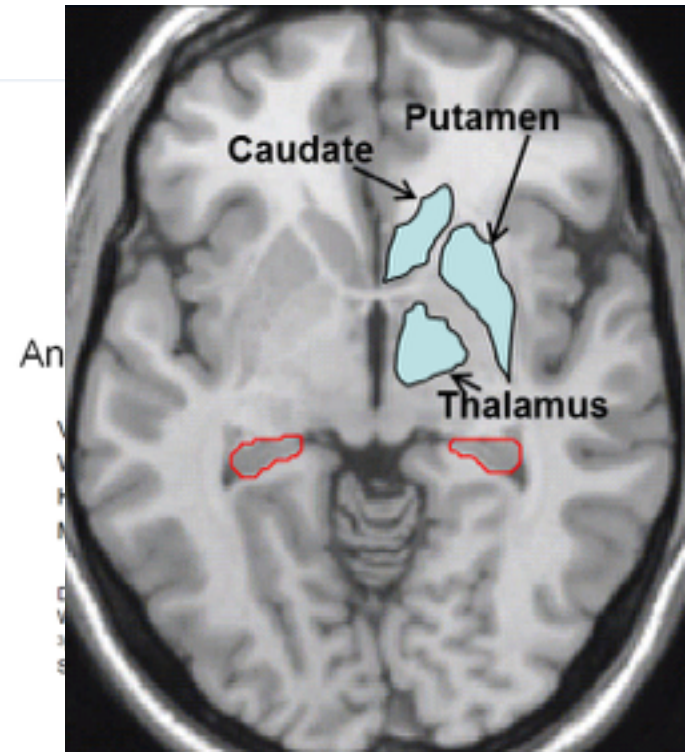
- 97% reduction in newborn neurons 2 months after cranial RT

# RTOG 0933

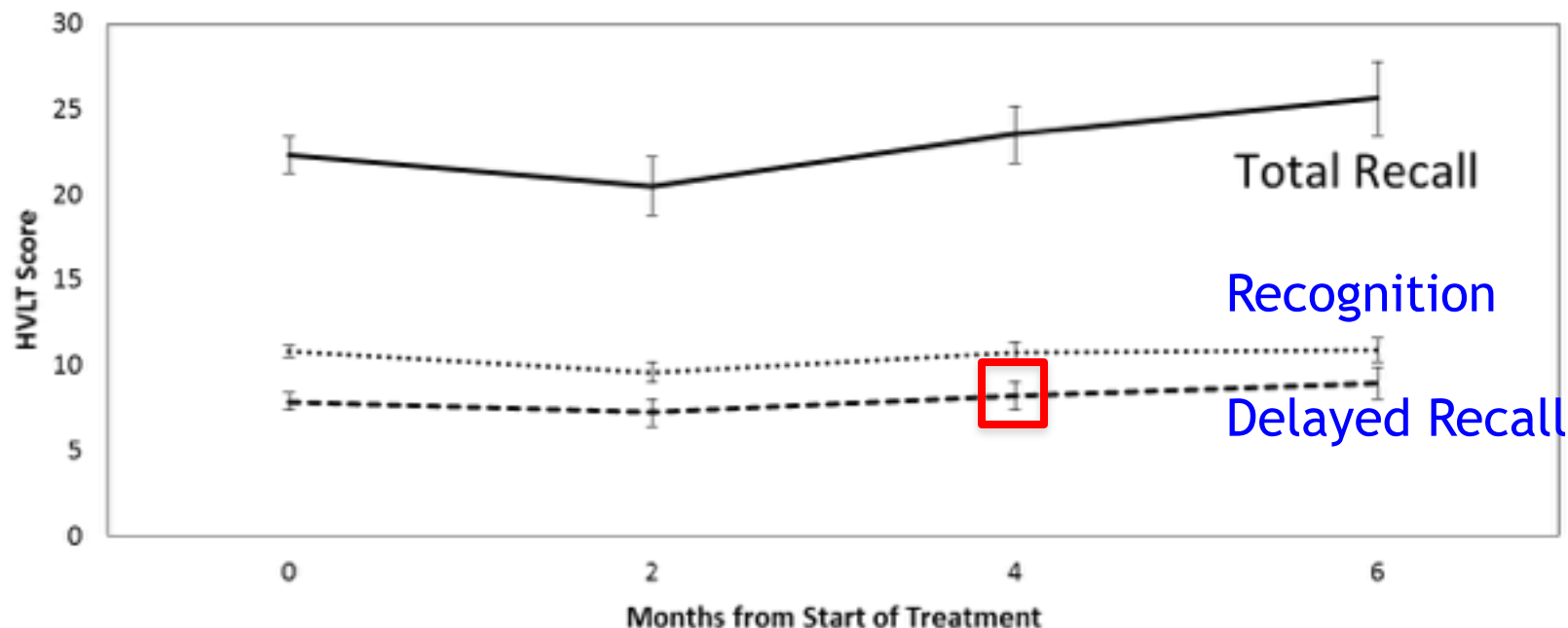
- Phase II study of HA-WBRT (30 Gy in 10 fractions)
- Primary endpoint: HVLT-delayed recall at 4 months
- Historical control: WBRT without hippocampal avoidance on prior published phase III trial
  - 30% mean relative decline in HVLT-delayed recall from baseline to 4 months after WBRT

# Centralized Quality Assurance

- Credentialing
  - Hippocampal contouring, IMRT planning
  - Biannual training workshops
  - 113 physicians, 84 community, academic and international institutions
- Central Review
  - Real-time pretreatment rapid review

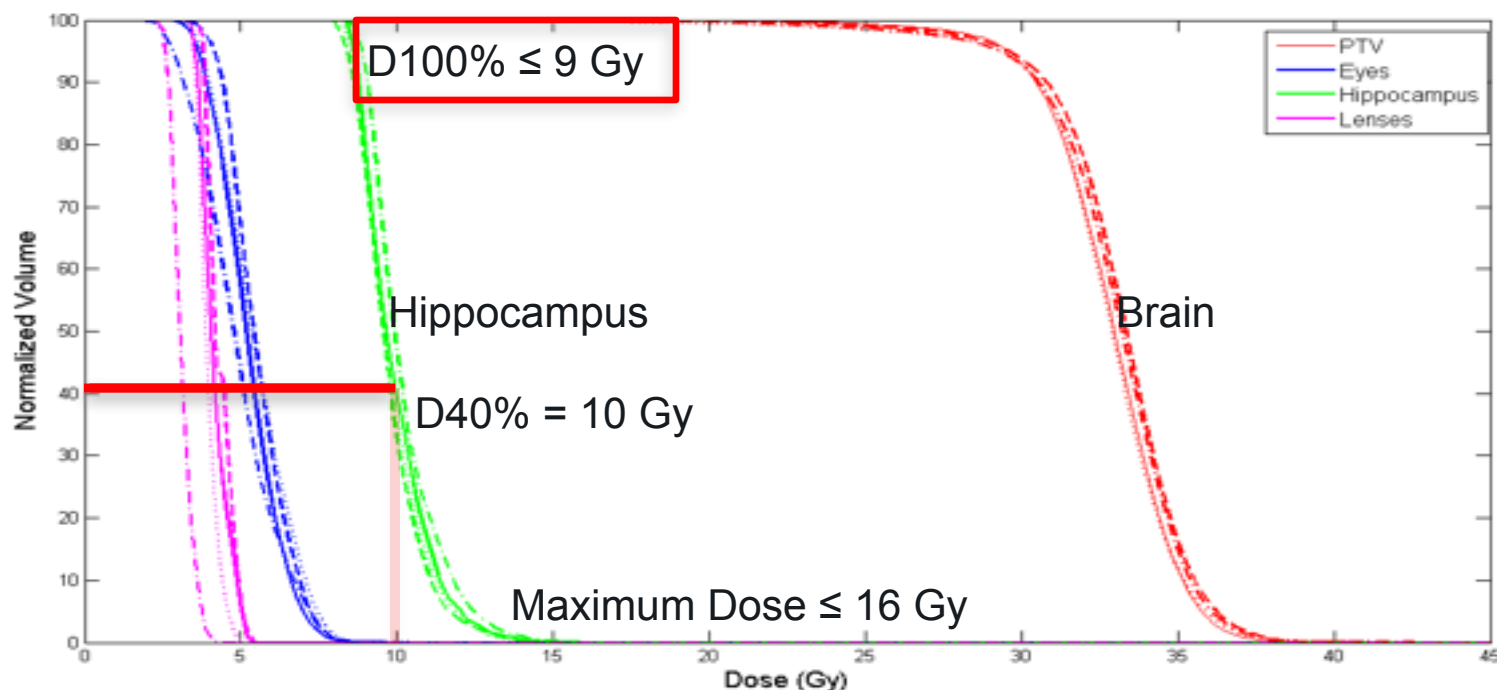


# RTOG 0933 HVLT Results



- **Mean relative decline in HVLT-Delayed Recall from baseline to 4 months: 7.0% (95% CI: -4.7 to 18.7%)**
- Significant compared to historical control: 30% ( $p=0.0003$ )

# Predictors Decline HVLT-R Delayed Recall



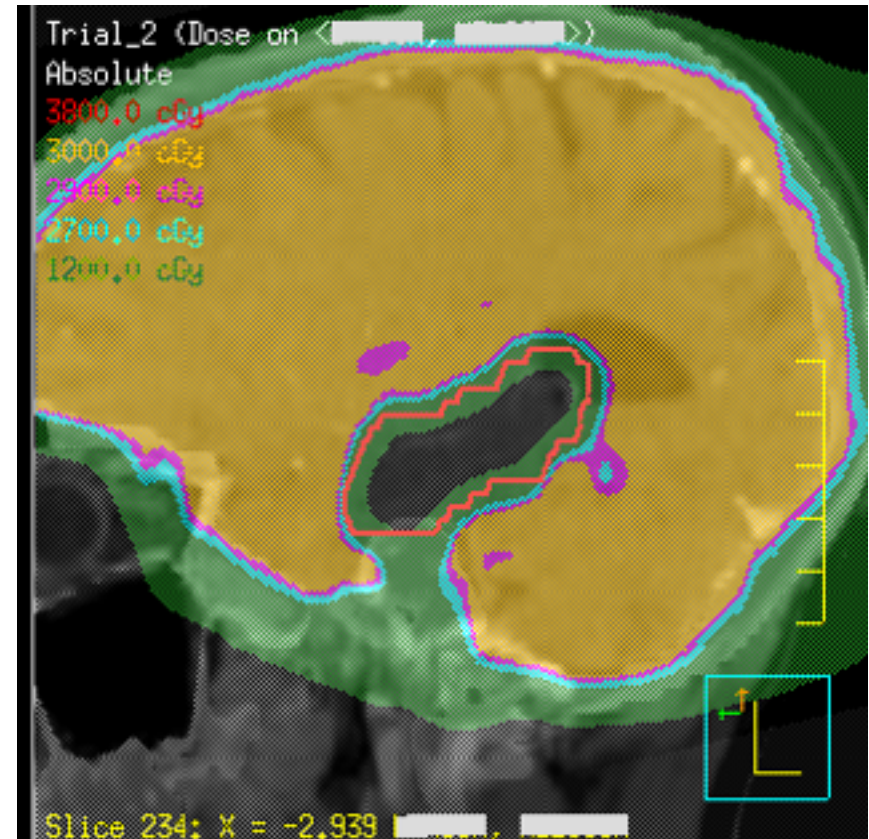
- Age  $\geq 60$  ( $p < 0.01$ )
- Baseline neurologic symptoms ( $p < 0.01$ )
- Hippocampal D100% ( $p < 0.01$ )



# RTOG 0933

## HA-WBRT Safe

- No grade 4-5 AE
- 4.5% with progression in the hippocampal avoidance
  - Lower than published estimates of 8.6%



## Conformal Avoidance of the Hippocampal Neural Stem Cells



# Summary

HA-WBRT a/w most significant impact on RT-induced cognitive outcomes to date

- Need phase III trial for level I evidence
- HA-WBRT not straight forward:
  - Pre-treatment centralized review:
    - 24% major deviations
    - Emphasizes need for conducting on trial with central review

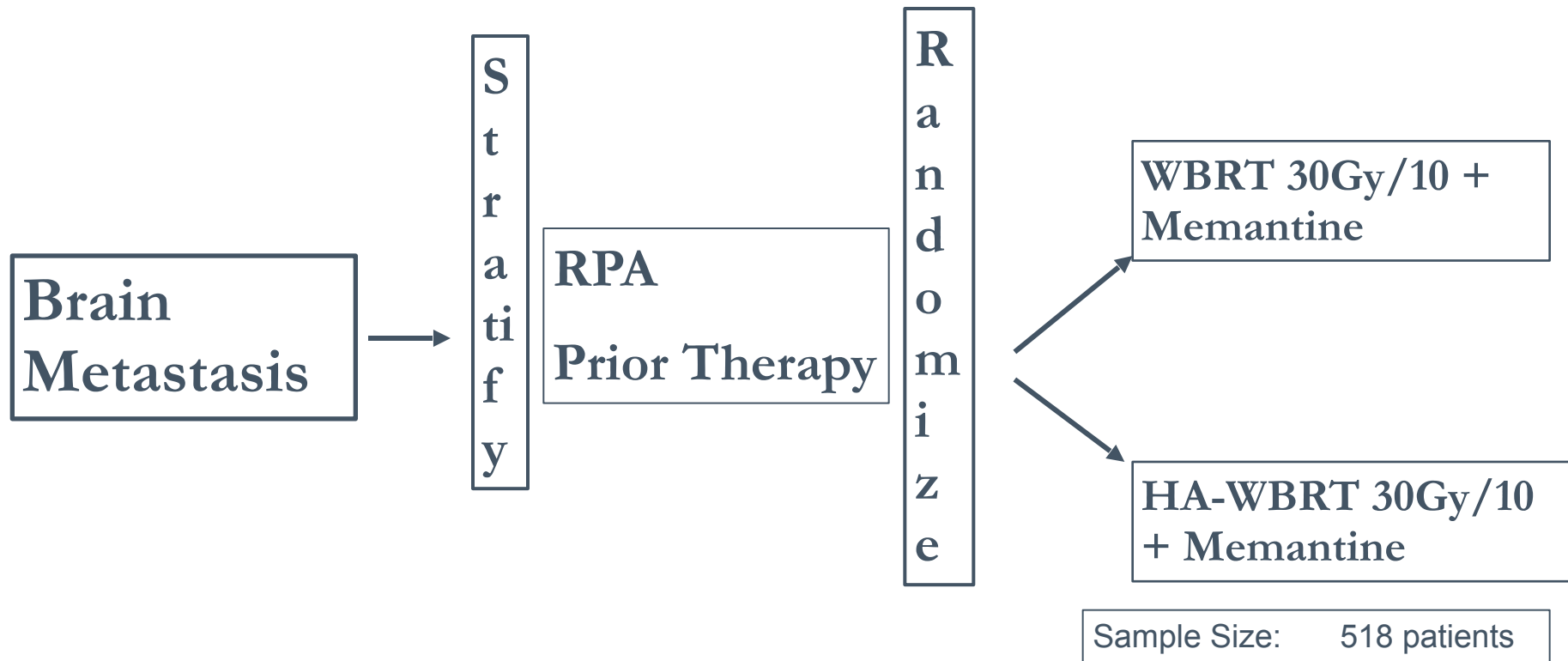
# Background

- Building on positive results of prior phase III RTOG 0614<sup>1</sup> (WBRT + memantine vs. WBRT + placebo) and phase II RTOG 0933<sup>2</sup> (HA-WBRT) trials

# NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

PIs: Paul Brown (MDACC) + Vinai Gondi (Cadence)

Basic Eligibility: Brain Mets 5mm outside hippocampus; KPS $\geq$ 70; MRI scan



Primary endpt: Time to cognitive failure--HVLt-R, COWA, and TMT A and B

Basic Statistical Design:

Cognitive fxn failure 53.8% at 6 months with WBRT vs. 42.8% with HA-WBRT. 388 analyzable pts.

Protocol approved by NCI, **Activated July 2015!!!**

# Enrollment Criteria

- Brain Mets 5mm outside hippocampus
- KPS>70
- Prior SRS or surgery allowed
- No hydrocephalus or architectural distortion ventricular system, including placement of external ventricular drain or ventriculoperitoneal shunt.
- English or French primary language\*
- No cytotoxic chemotherapy during the WBRT
- “Volumetric” MRI scan

# Assessments

Baseline, 2, 4, 6, 12 months

- Neurocog battery (HVLT-R, COWAT, TMT)
- PRO - MDASI-BT, EQ-5D-5L
- MRI scan\*
- Serum chemo profile + translational studies

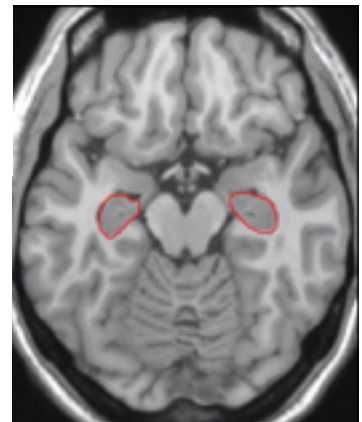
# Thank You

# NRG ONCOLOGY

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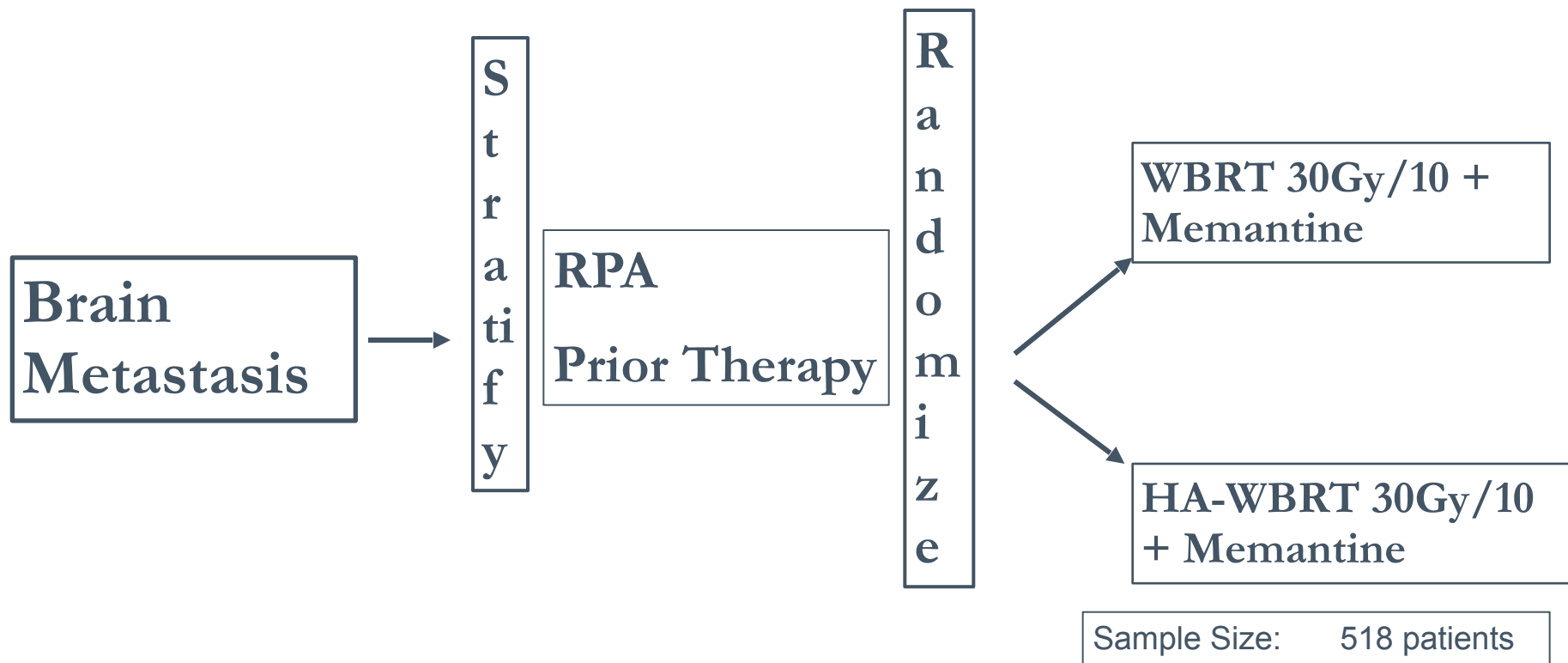




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