



# Innovative Radiotherapeutic Techniques for Multiple Brain Metastases

Vinai Gondi, M.D.

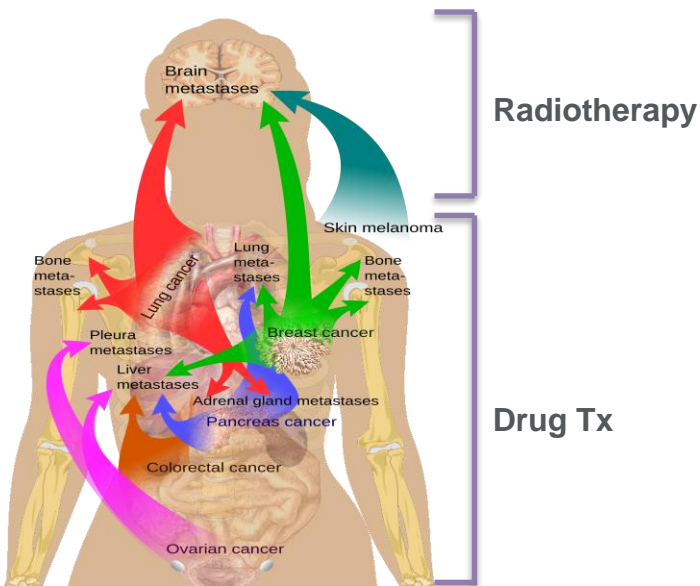
Director, Radiation Oncology

Co-Director, Brain Tumor Center,

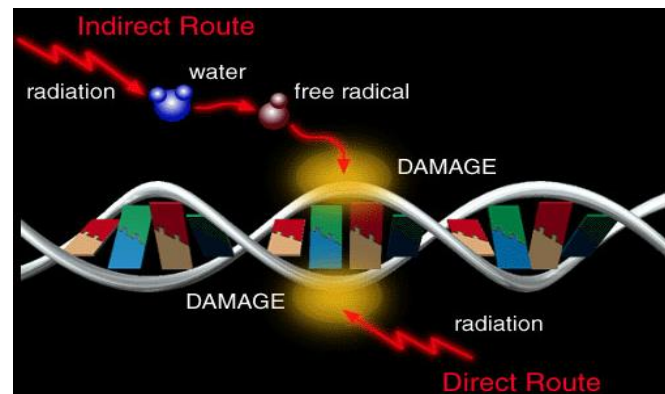
Northwestern Medicine West Region/Proton Center

Lou and Jean Malnati Brain Tumor Institute, Northwestern University

# Central Role of Radiotherapy in Neuro-Oncology



**There is no blood-brain barrier to radiotherapy.**



**Tumoricidal effect of radiotherapy is relatively mechanism-agnostic**

# Accuray Disclaimers and Disclosure

## Disclosure

The views contained and expressed in this presentation, including any accompanying oral commentary, are those of the presenter and do not necessarily reflect the views or policies of Accuray Incorporated or its subsidiaries. No official endorsement by Accuray Incorporated or any of its subsidiaries of any vendor, products or services contained in this presentation is intended or should be inferred.

An honorarium is provided by Accuray for this presentation.

## Medical Advice Disclaimer

Accuray Incorporated as a medical device manufacturer cannot and does not recommend specific treatment approaches. Individual results may vary.

## 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.

# Building Consensus

ASCO special art

## Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD<sup>1</sup>; Paul D. Brown, MD<sup>2</sup>; Hans Messersmith, MPH<sup>3</sup>; Priscilla K. Brastianos, MD<sup>4</sup>; Stuart Burri, MD<sup>5</sup>; Dan Cahill, MD, PhD<sup>4</sup>; Ian F. Dunn, MD<sup>6</sup>; Laurie E. Gaspar, MD, MBA<sup>7,8</sup>; Na Tosha N. Gatson, MD, PhD<sup>9,10</sup>; Vinai Gondi, MD<sup>11</sup>; Justin T. Jordan, MD<sup>4</sup>; Andrew B. Lassman, MD<sup>12</sup>; Julia Maues, MA<sup>13</sup>; Nimish Mohile, MD<sup>14</sup>; Navid Redjal, MD<sup>15</sup>; Glen Stevens, DO, PhD<sup>16</sup>; Erik Sulman, MD, PhD<sup>17</sup>; Martin van den Bent, MD<sup>18</sup>; H. James Wallace, MD<sup>19</sup>; Jeffrey S. Weinberg, MD<sup>20</sup>; Gelareh Zadeh, MD, PhD<sup>21</sup>; and David Schiff, MD<sup>22</sup>

Practical Radiation Oncology® (2022) 12, 265–282



37 physicians representing

- a) Radiation Oncology, Medical Oncology, Neuro-Oncology and Neurosurgery;
- b) Academic, community, and international practices; and,
- c) Multiple professional societies (ASCO, SNO, ASTRO, AANS/CNS)

### Clinical Practice Guideline

### Radiation Therapy for Brain Metastases: An ASTRO Clinical Practice Guideline

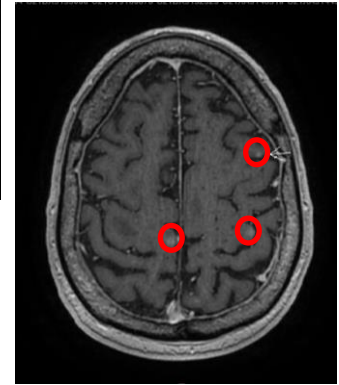
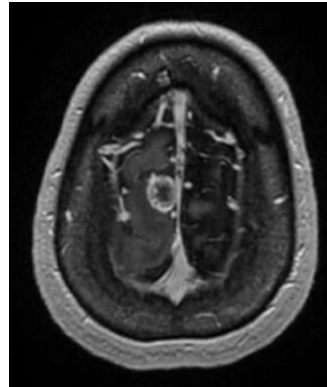


Vinai Gondi, MD,<sup>a,\*</sup> Glenn Bauman, MD,<sup>b</sup> Lisa Bradfield, BA,<sup>c</sup> Stuart H. Burri, MD,<sup>d</sup> Alvin R. Cabrera, MD,<sup>e</sup> Danielle A. Cunningham, MD,<sup>f</sup> Bree R. Eaton, MD,<sup>g</sup> Jona A. Hattangadi-Gluth, MD,<sup>h</sup> Michelle M. Kim, MD,<sup>i</sup> Rupesh Kotecha, MD,<sup>j</sup> Lianne Kraemer,<sup>k</sup> Jing Li, MD, PhD,<sup>l</sup> Seema Nagpal, MD,<sup>m</sup> Chad G. Rusthoven, MD,<sup>n</sup> John H. Suh, MD,<sup>o</sup> Wolfgang A. Tomé, PhD,<sup>p</sup> Tony J.C. Wang, MD,<sup>q</sup> Alexandra S. Zimmer, MD,<sup>r</sup> Mateo Ziu, MD,<sup>s</sup> and Paul D. Brown, MD<sup>f</sup>

## Case

62 yo woman presents with left leg weakness/focal seizure

- Anti-seizure meds and steroids →
  - Seizure activity stops
  - Left leg weakness persists
- MRI with 10 brain metastases
  - One impinging on precentral gyrus with edema
  - Extracranial CT imaging right lung mass
  - Biopsy: squamous cell carcinoma of the lung



# Case

- Indications for Surgery for Brain Metastases:
  - Diagnosis unknown and no extracranial accessible tumors
  - Mass effect related symptoms, regardless of whether diagnosis is known
  - Recurrent mass following initial local or systemic treatment where there is a question of diagnosis (treatment effect vs. tumor) or a need to re-interrogate tumor (mutational drift/selection)

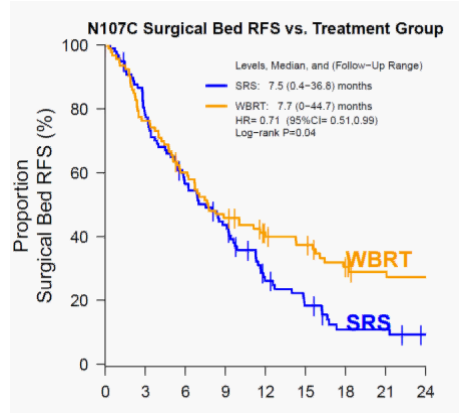
ASCO/SNO/ASTRO Guideline

**Recommendation 1.1.** Surgery may be offered for patients with brain metastases, considering the following factors:

- Patients with suspected brain metastases without a primary cancer diagnosis may benefit from surgery to attain a diagnosis and undergo tumor removal.
- Patients with large tumors with mass effect likely benefit from surgery.
- Patients with multiple brain metastases and/or uncontrolled systemic disease are less likely to benefit from surgery unless the remaining disease is controllable via other measures (Type: informal consensus; Evidence quality: mixed, see the Clinical Interpretation section; Strength of recommendation: moderate).

# Disadvantages of Postoperative Single-Fraction SRS

Inferior surgical bed control<sup>1</sup>



Iatrogenic seeding of meningeal/CSF spaces

Risk of LMD after surgery + postop SRS

- MDACC<sup>2</sup>: 28%
- Multi-Institutional<sup>3</sup>: 16.6%

- Surgical bed relapse difficult to manage
- Meningeal/CSF relapse can meaningfully impact overall survival

<sup>1</sup>Brown et al. Lancet Oncol 2017

<sup>2</sup>Mahajan et al. Lancet Oncol 2017

<sup>3</sup>Patel et al. Neurosurg 2016

# Strategies to Improve Outcomes with Focal RT

	Fractionated SRS
Approach	Treat larger area more safely (e.g., dural margin), Treat other macrometastases
Hypothesized to impact surgical bed	Yes
Hypothesized to impact meningeal surfaces	Yes
Hypothesized to impact CSF space	No
Potential Limitations	Longer treatment time; Target delineation remains important



# Strategies to Improve Outcomes with Focal RT

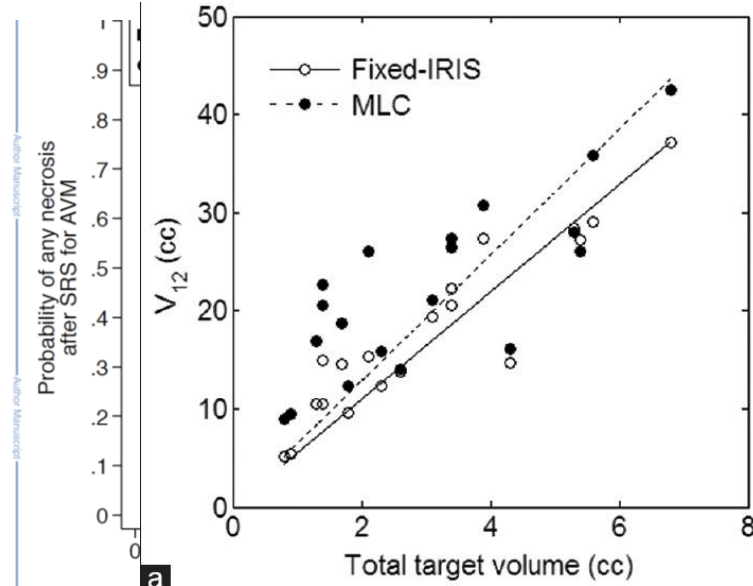
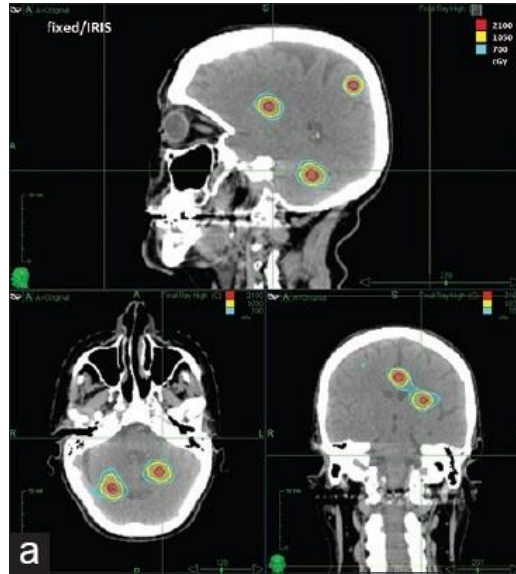
	Fractionated SRS	Pre-operative SRS
Approach	Treat larger area more safely (e.g., dural margin), Treat other macrometastases	Sterilize tumor cells that may be remnant in surgical bed or seeding meningeal/CSF spaces, Treat other macrometastases
Hypothesized to impact surgical bed	Yes	Yes
Hypothesized to impact meningeal surfaces	Yes	Yes
Hypothesized to impact CSF space	No	Yes
Potential Limitations	Longer treatment time; Target delineation remains important	Coordination between RadOnc and Neurosurgery

## Strategies to Improve Outcomes with Focal RT

	Fractionated SRS	Pre-operative SRS	HA-WBRT+Memantine
Approach	Treat larger area more safely (e.g., dural margin), Treat other macrometastases	Sterilize tumor cells that may be remnant in surgical bed or seeding meningeal/CSF spaces, Treat other macrometastases	Treat larger area more safely (e.g., dural margin, intracranial CSF seeding), Treat other macrometastases and micro-metastases
Hypothesized to impact surgical bed	Yes	Yes	Yes
Hypothesized to impact meningeal surfaces	Yes	Yes	Yes
Hypothesized to impact CSF space	No	Yes	Yes (intracranially only)
Potential Limitations	Longer treatment time; Target delineation remains important	Coordination between RadOnc and Neurosurgery	Longer treatment time; Cognition concerns

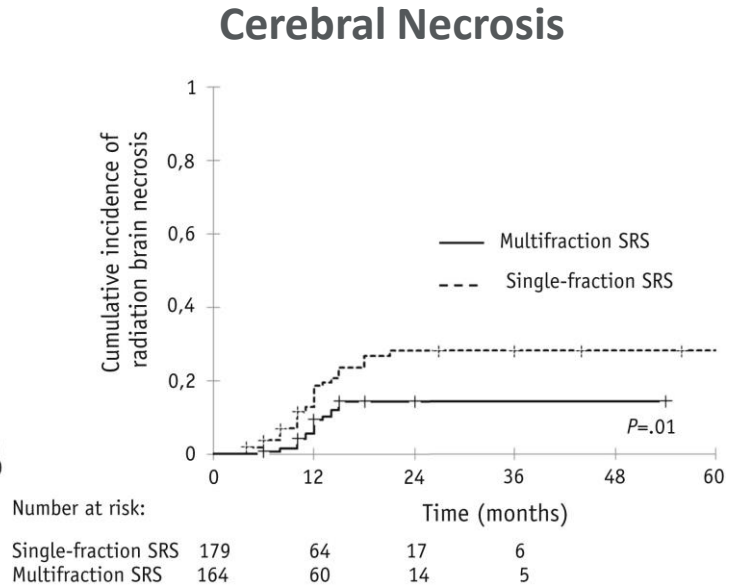
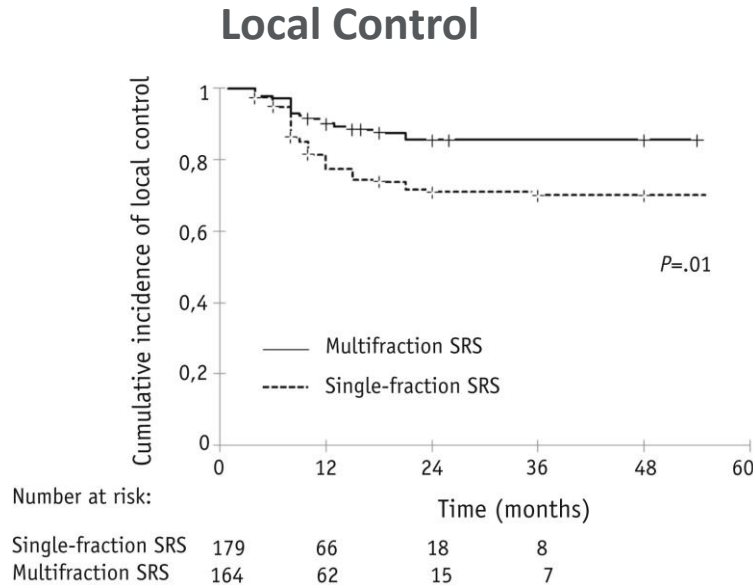
# Advances in Radiosurgery

CyberKnife® Radiosurgery



Multiple metastasis radiosurgery → Cerebral necrosis  
V<sub>12</sub> associated with increased risk of cerebral necrosis  
V<sub>12</sub> associated target volume

# Fractionation in Radiosurgery



**Hypothesis: Fractionation during radiosurgery improves local control and prevents cerebral necrosis**

# NRG BN013: Phase III Trial of Single Fraction SRS vs. Fractionated SRS for Intact Brain Metastases

PI: Rupesh Kotecha (Miami Cancer inst)

<ul style="list-style-type: none"> <li>Solid tumor brain metastases</li> <li>≥1 lesion(s) on diagnostic scan (1-3 cm in size; max of 8 lesions)</li> <li>DS-GPA (≥1.5)</li> <li>ECOG ≤ 2</li> <li>Resection allowed of up to 2 lesions if clinically indicated</li> <li>Absence of leptomeningeal disease</li> <li>No prior radiotherapy</li> </ul>	S T R A T I F Y	<ul style="list-style-type: none"> <li>Symptomatic brain metastases (corticosteroids counted) (Y vs. N)</li> <li>Targeted therapy or Immunotherapy or ADCs ± 4 weeks (Y vs. N)</li> <li>1 vs. 2-4 vs. 5+ metastases</li> </ul>	R A N D O M I Z E (1:1)	<p><u>Arm 1: SRS</u></p> <p>0 – 2 cm: 22 – 24 Gy in 1 fraction</p> <p>2 – 3 cm: 18 – 20 Gy in 1 fraction</p> <p><u>Arm 2: FSRS</u></p> <p>0 – 2 cm: 30 Gy in 3 fractions</p> <p>2 – 3 cm: 27 Gy in 3 fractions</p>	<p><u>Primary Endpoint<sup>4</sup></u></p> <p>1-year LF SRS: 30%</p> <p>1-year LF FSRS: 17%</p> <p>HR: 0.52</p> <p><u>Secondary Endpoints</u></p> <p>Intracranial PFS and OS</p> <p>Time to local tumor failure via central review</p> <p>Patterns of CNS failure</p> <p>Radiation necrosis</p> <p>Time to WBRT</p> <p>Adverse events</p> <p>QOL, emotional wellbeing, functional independence</p>

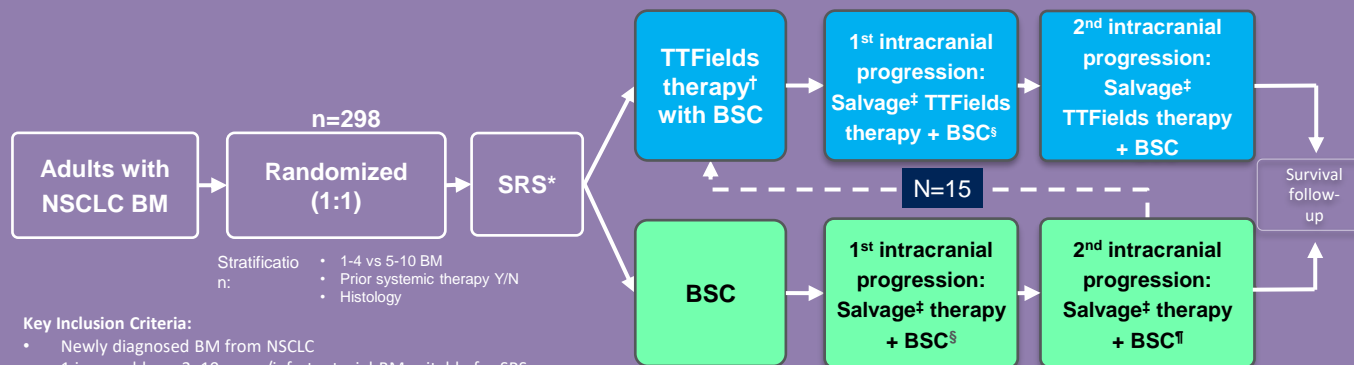
1. Solid tumor histologies include: Non-small cell lung cancer, melanoma, breast cancer, renal cell carcinoma, or gastrointestinal cancer
2. If additional lesions found on treatment planning scan, patient stays on study as long as ≤15 lesions and investigator deems patient to be SRS candidate
3. Brain metastasis must be located ≥5 mm from the optic chiasm and outside of the brainstem
4. Only lesions meeting trial eligibility size criteria will be evaluated for the primary endpoint.

## Topline Results from METIS (EF-25), an International, Multicenter Phase III Randomized Study Evaluating the Efficacy and Safety of Tumor Treating Fields (TTFields) Therapy in Patients With Non-Small Cell Lung Cancer (NSCLC) with Brain Metastases

Minesh P. Mehta,<sup>1</sup> Vinai Gondi,<sup>2</sup> Manmeet S. Ahluwalia,<sup>1</sup> David Roberge,<sup>3</sup> Rosanda Ilic,<sup>4</sup> Terence T. Sio,<sup>5</sup> Daniel M. Trifiletti,<sup>6</sup> Thierry Muanza,<sup>7</sup> Ana M. Krpan,<sup>8</sup> Naren Ramakrishna,<sup>9</sup> John Fiveash,<sup>10</sup> Philippe Metellus,<sup>11</sup> Chiachien J. Wang,<sup>12</sup> Loïc Feuvret,<sup>13</sup> Jinming Yu,<sup>14</sup> Zhengfei Zhu,<sup>15</sup> Christian Freyschlag,<sup>16</sup> Tibor Csősz,<sup>17</sup> Paul D. Brown,<sup>18</sup> Maciej Harat;<sup>19</sup> *on behalf of the METIS study investigators*

<sup>1</sup>Miami Cancer Institute, Miami, FL, US; <sup>2</sup>Northwestern Medicine Cancer Center Warrenville and Northwestern Medicine Proton Center, Warrenville, IL, US; <sup>3</sup>CHUM, Montreal, QC, Canada; <sup>4</sup>Clinical Center of Serbia, Neurosurgery Clinic-Department for Neurooncology, Belgrade, Serbia; <sup>5</sup>Department of Radiation Oncology, Mayo Clinic, Phoenix, AZ, US; <sup>6</sup>Department of Radiation Oncology, Mayo Clinic, Jacksonville, FL, US; <sup>7</sup>Montreal Neurological Institute McGill University, Montreal, Canada; <sup>8</sup>Radiochirurgia Zagreb, Serbia; <sup>9</sup>Orlando Health Cancer Institute, Orlando, FL, US; <sup>10</sup>The University of Alabama at Birmingham, Birmingham, AL, USA; <sup>11</sup>Hôpital Privé Clairval, Marseille, France; <sup>12</sup>Willis Knighton Cancer Center, Shreveport, LA, US; <sup>13</sup>Lyon HCL, Lyon, France; <sup>14</sup>Shandong Cancer Hospital, Jinan, China; <sup>15</sup>Fudan University Shanghai Cancer Center, Shanghai, China; <sup>16</sup>Medizinische Universität Innsbruck, Innsbruck, Austria; <sup>17</sup>Jász-Nagykun-Szolnok Megyei Hetényi Géza Kórház-Rendelőintézet, Szolnok, Hungary; <sup>18</sup>Department of Radiation Oncology, Mayo Clinic, Rochester, MN, US; <sup>19</sup>Department of Neurooncology and Radiosurgery, Francisek Lukaszcyk Memorial Oncology Center, Bydgoszcz, Poland

# METIS Trial: Study Design



## Key Inclusion Criteria:

- Newly diagnosed BM from NSCLC
- 1 inoperable or 2–10 supra/infratentorial BM suitable for SRS
- KPS ≥70
- Receive systemic NSCLC treatment

## Key Exclusion Criteria:

- Known mutations with available targeted agents (ALK, EGFR, ROS-1, and B-RAF genes)
- Prior WBRT
- Leptomeningeal or recurrent BM

**Study sites:** 78 (enrolled; 298 pts randomized)

**Enrollment:** October 2016–March 2023

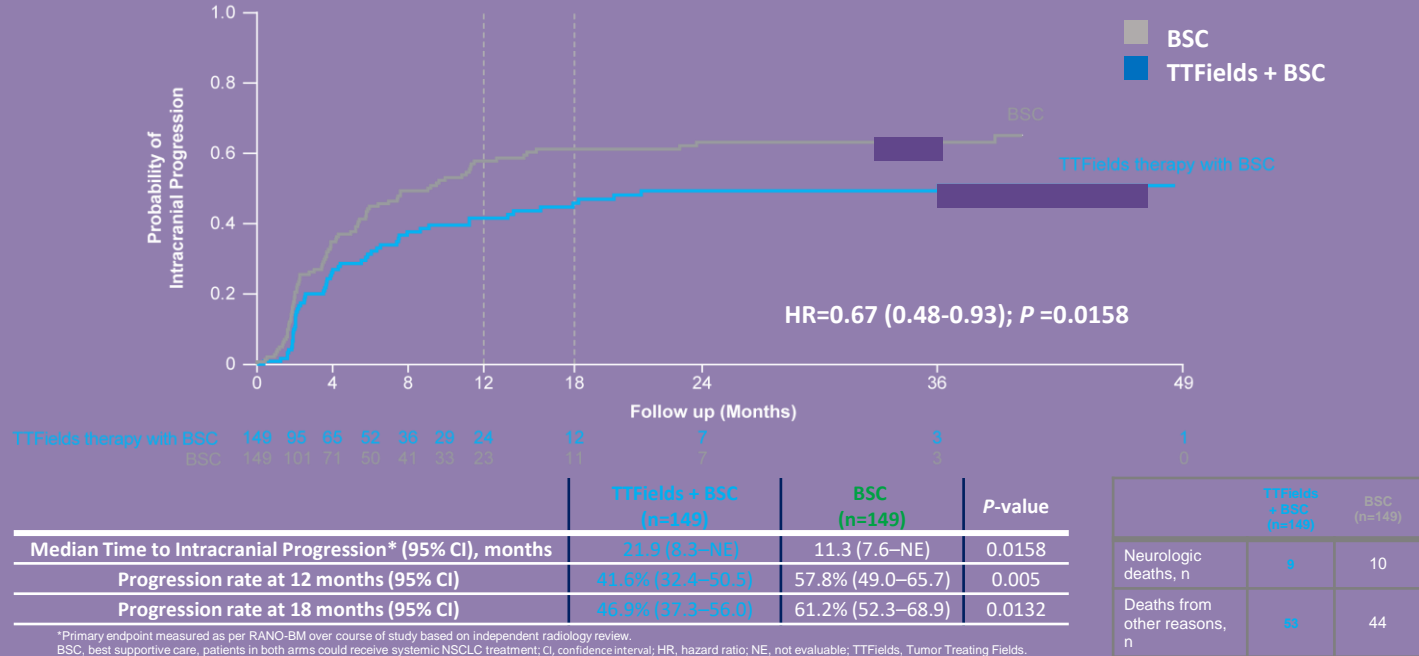
**Data cut off:** 5th December 2023

**Registration number:** NCT02831959

\*SRS or HF-SRS was allowed. TTFields therapy was administered at 150kHz for ≥18 h/day. †Surgery, repeat SRS, WBRT. ‡Follow up and MRI Q&W. §Patients in the control arm were offered to cross over to the TTFields arm and receive TTFields therapy with or without salvage therapy for second intracranial progression. ALK, anaplastic lymphoma kinase; BM, brain metastases; BSC, best supportive care; patients in both arms could receive systemic NSCLC treatment; B-RAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HF-SRS, hypofractionated stereotactic radiosurgery; KPS, Karnofsky Performance Scale; NSCLC, non-small cell lung cancer; pts, patients; ROS-1, ros proto-oncogene 1; SRS, stereotactic radiosurgery; TTFields, Tumor Treating Fields; WBRT, whole brain radiotherapy.

Mehta MP, Gondi V, et al. ASCO 2024

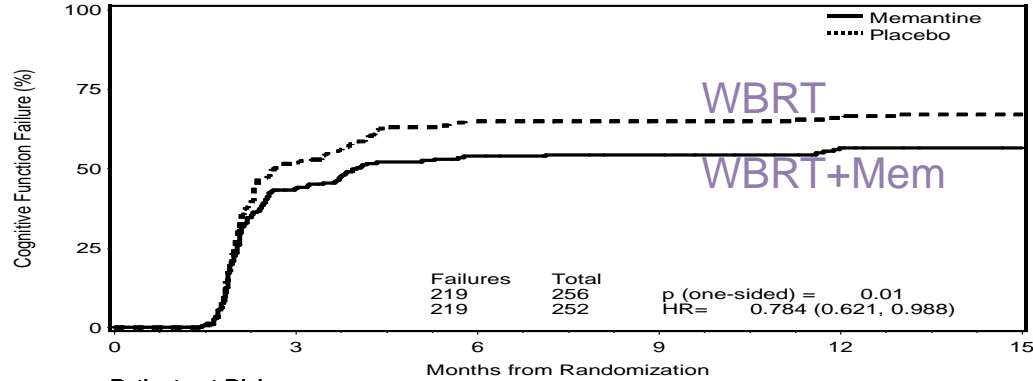
# Primary Endpoint: Time to First Intracranial Progression or Neurologic Death Favors TTFields Arm



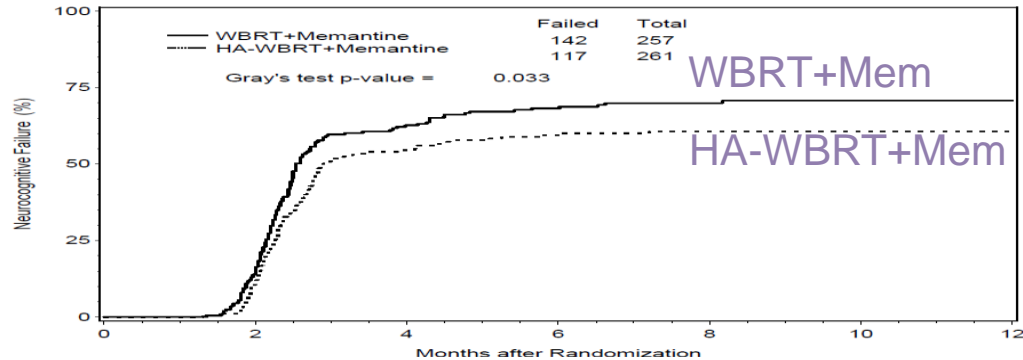
Mehta MP, Gondi V, et al. ASCO 2024



# 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

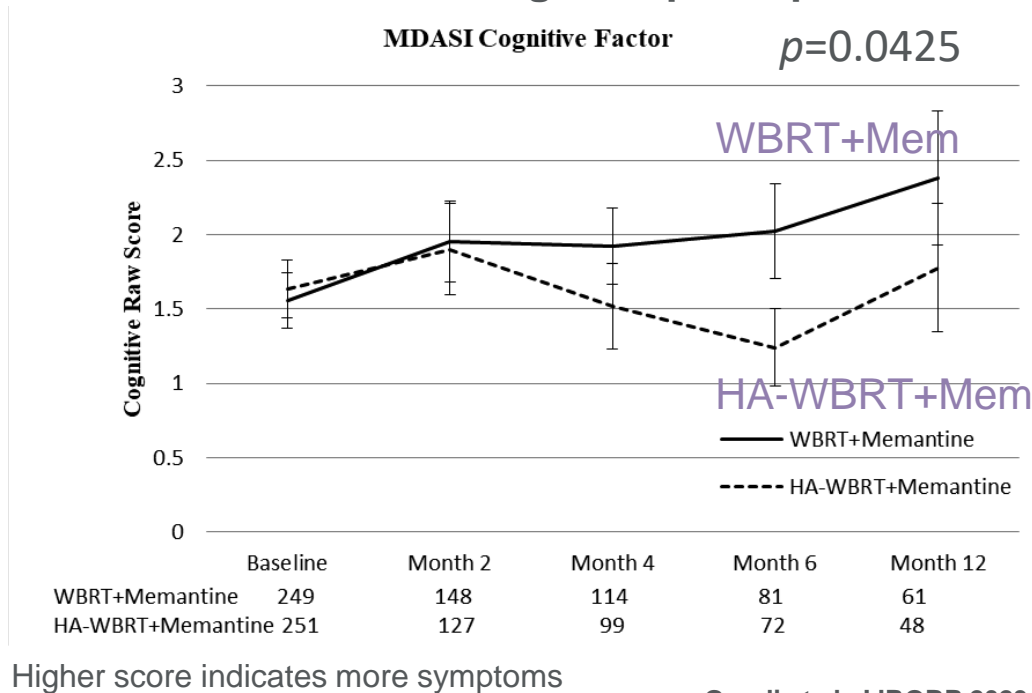
- Reduces deterioration of
  - 4 months: Executive function  
(Trail Making Test B)
  - 6 months: Learning and memory  
(HVLT-R Recognition)
- Preserves all learning and memory domains over time
  - HVLT-R total recall, delayed recall and recognition

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:

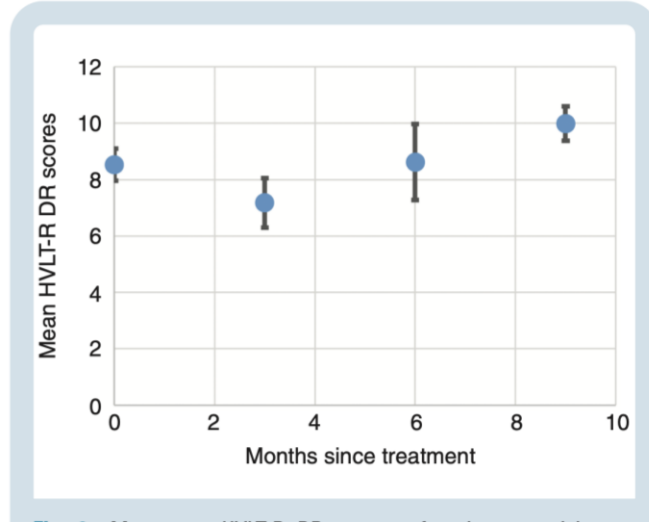
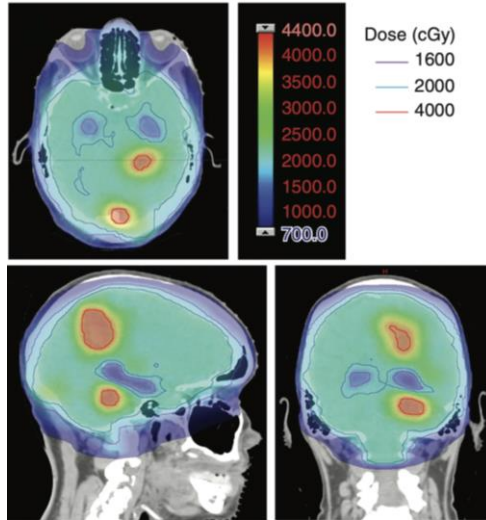


Gondi et al., IJROBP 2023

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

# HA-WBRT with Simultaneous Integrated Boost

UT-Southwestern Phase II Trial

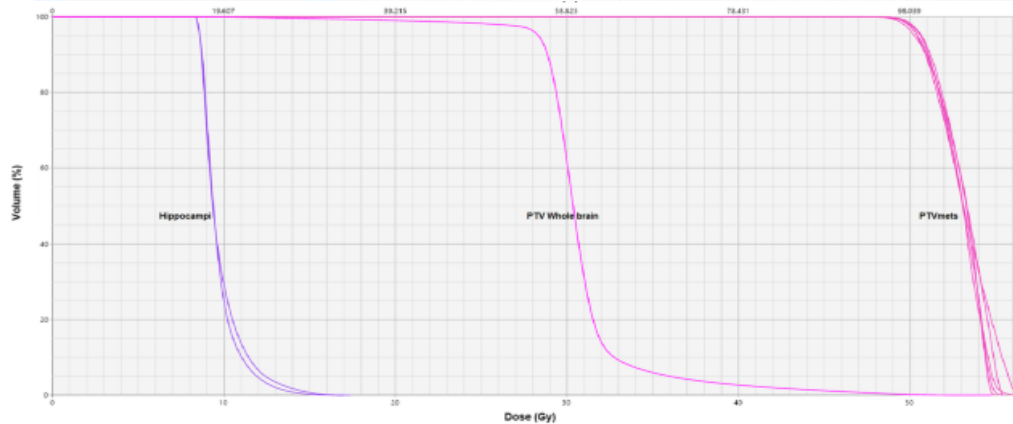
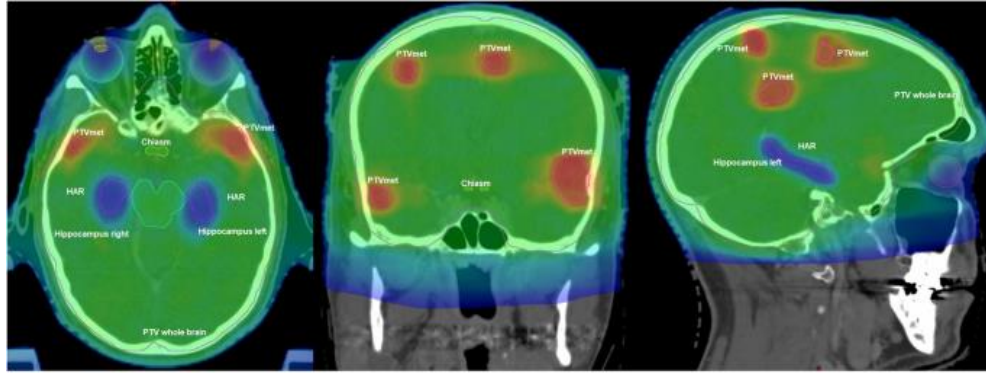


HA-WBRT+SIB had

- Improved HVL1-DR outcomes vs. historical WBRT controls
- Similar intracranial control vs. historical WBRT+SRS controls

# HA-WBRT with Simultaneous Integrated Boost

HIPPORAD



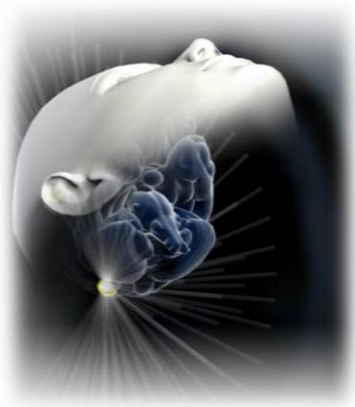
HIPPORAD (NOA-14, ARO 2015-3, DKTK-ROG):

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

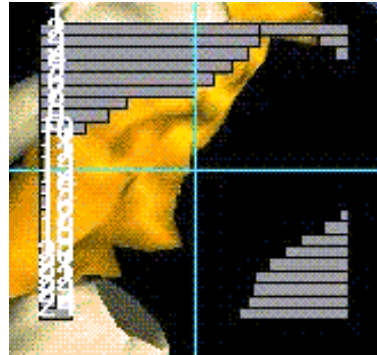
Developing NRG Trial:

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

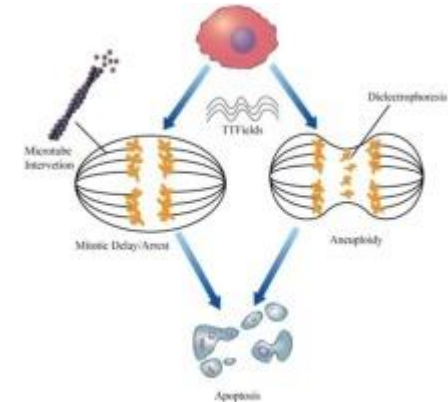
# Innovative Radiotherapy Techniques for Brain Metastases



**Stereotactic  
Radiosurgery**



**Intensity Modulated  
Radiotherapy**



**Tumor-Treating Fields**