Aultman Cancer Symposium: Updates in CNS Radiation Oncology

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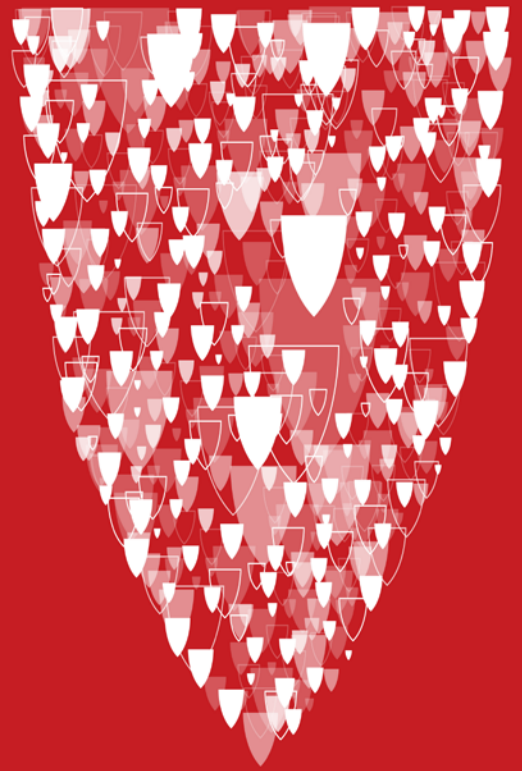

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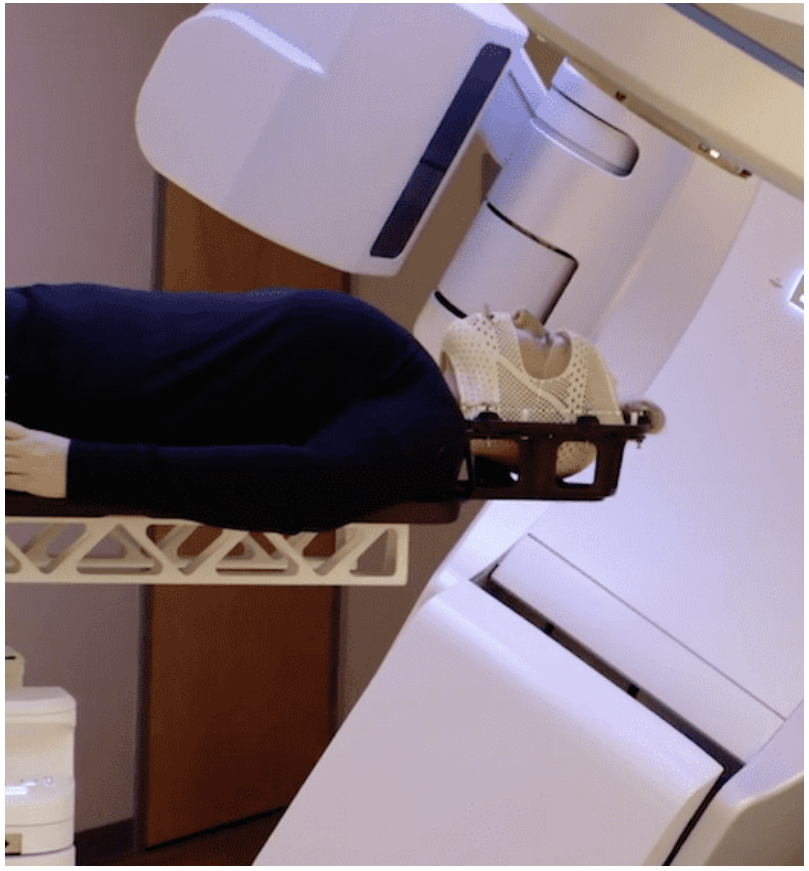
Disclosures

- *None*

Themes for Today

1. **Technology**
2. **Metastatic Disease**
3. **Gliomas**
4. **Everything Else**



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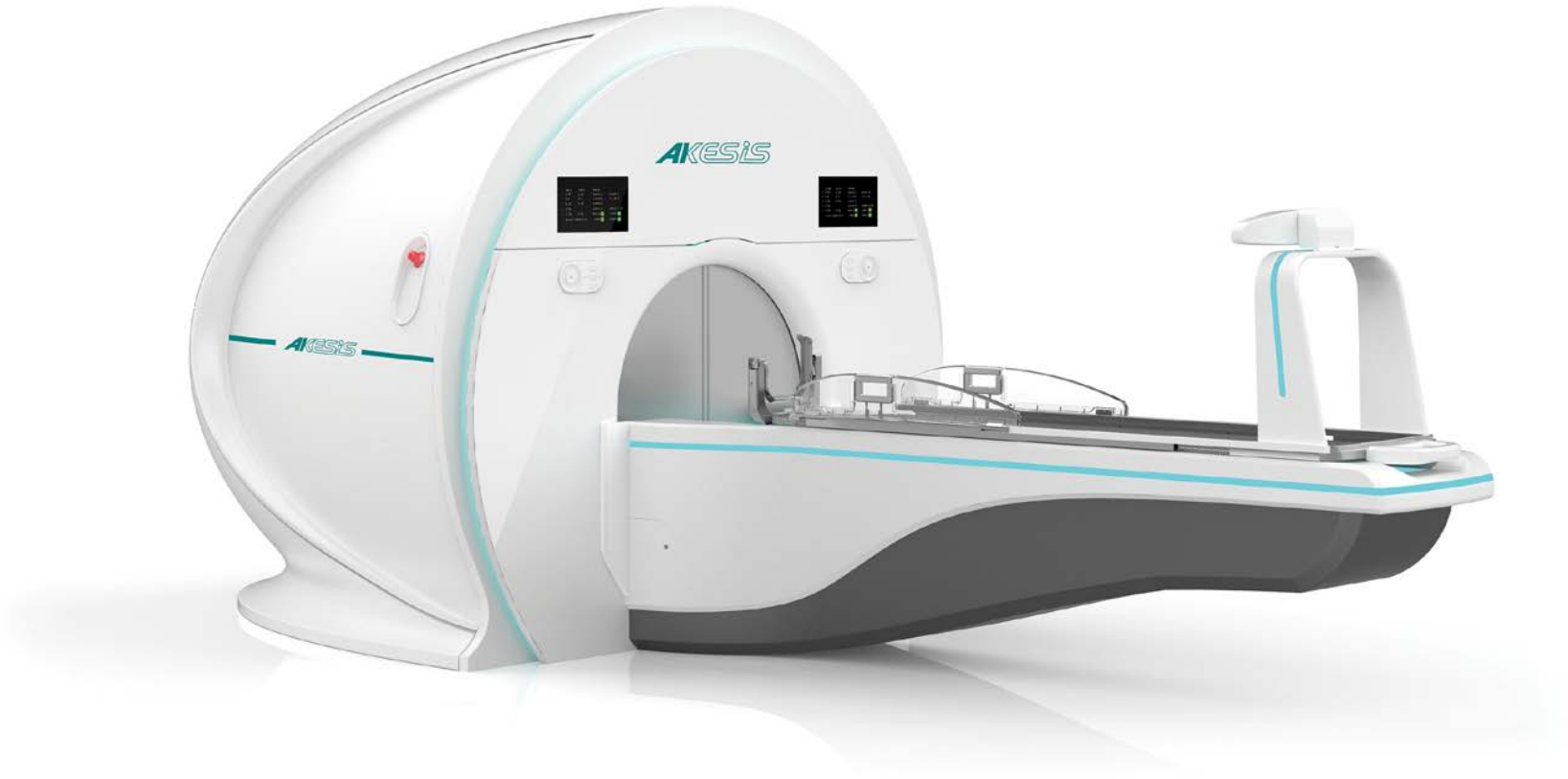
Radiosurgery

- Brain Metastases
- Meningioma’s
- Acoustic Neuroma’s/Vestibular Schwannoma
- Trigeminal Neuralgia
- Arteriovenous Malformation (AVM)
- Paraganglioma/ Glomus tumors

Akesis SRS



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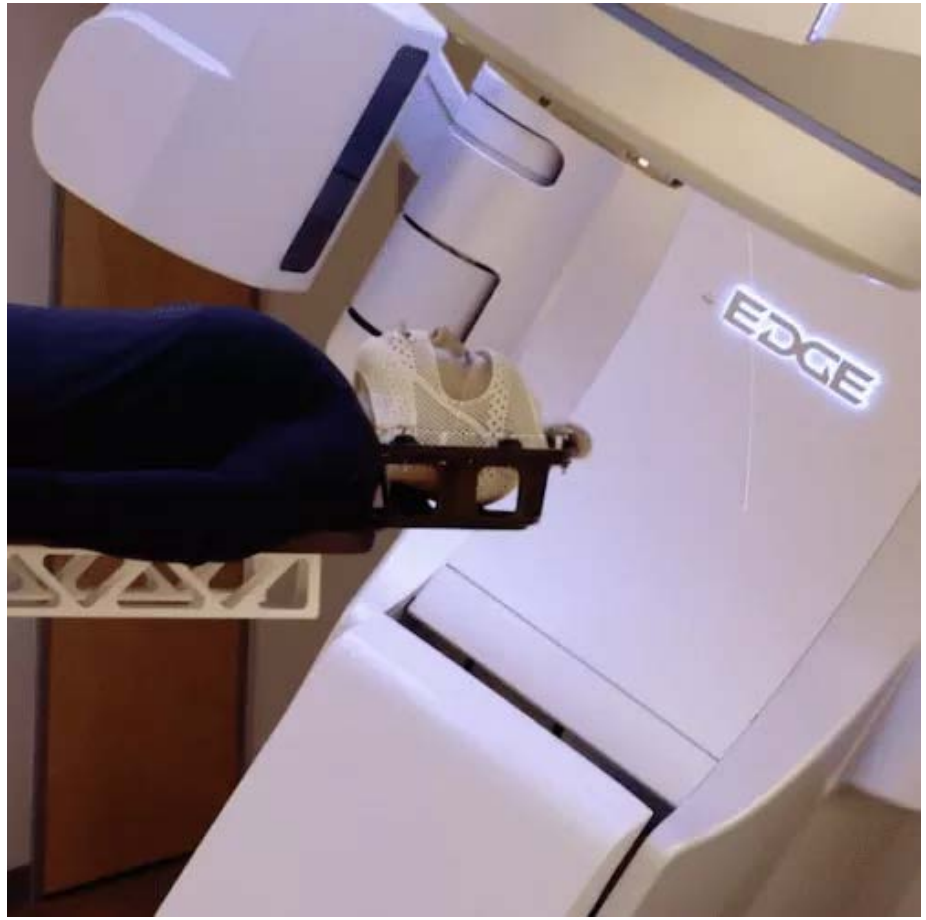
Varian Edge SRS



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Fractionated Radiation Therapy

- Glioblastoma
- Low Grade Glioma
- Large Meningioma
- Brain Metastases
- Pediatric Tumors

Varian Edge

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Proton Therapy

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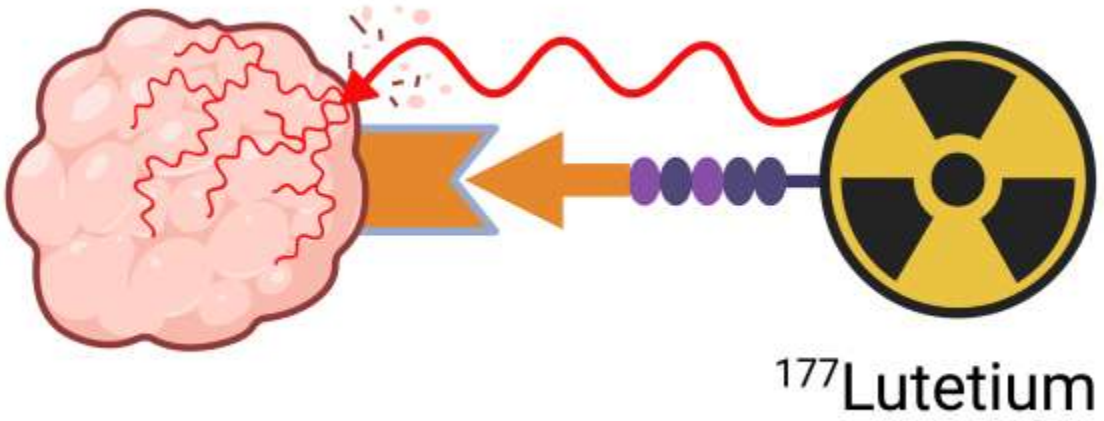
Theranostics

- Investigational
- Novartis trial for primary and recurrent Glioblastoma
- Meningioma (Pending)



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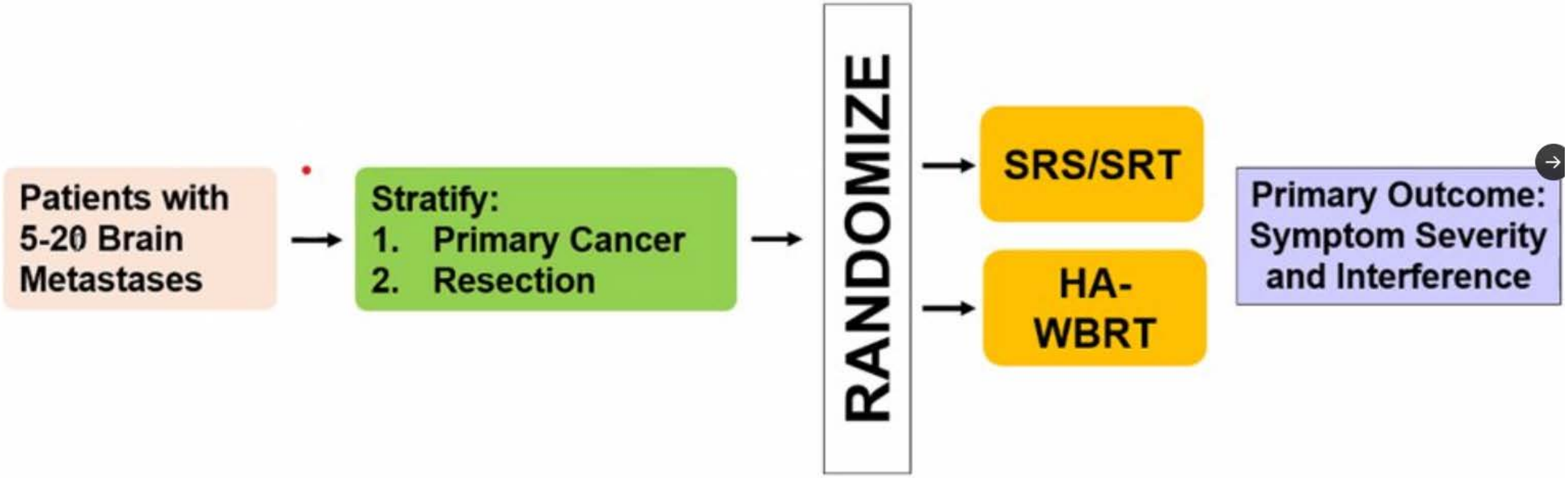
Metastatic Disease

WBRT with hippocampal sparing and memantine versus SRS for 5-20 brain metastases

Aizer A et al., ASCO 2025

Study Design



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Radiation

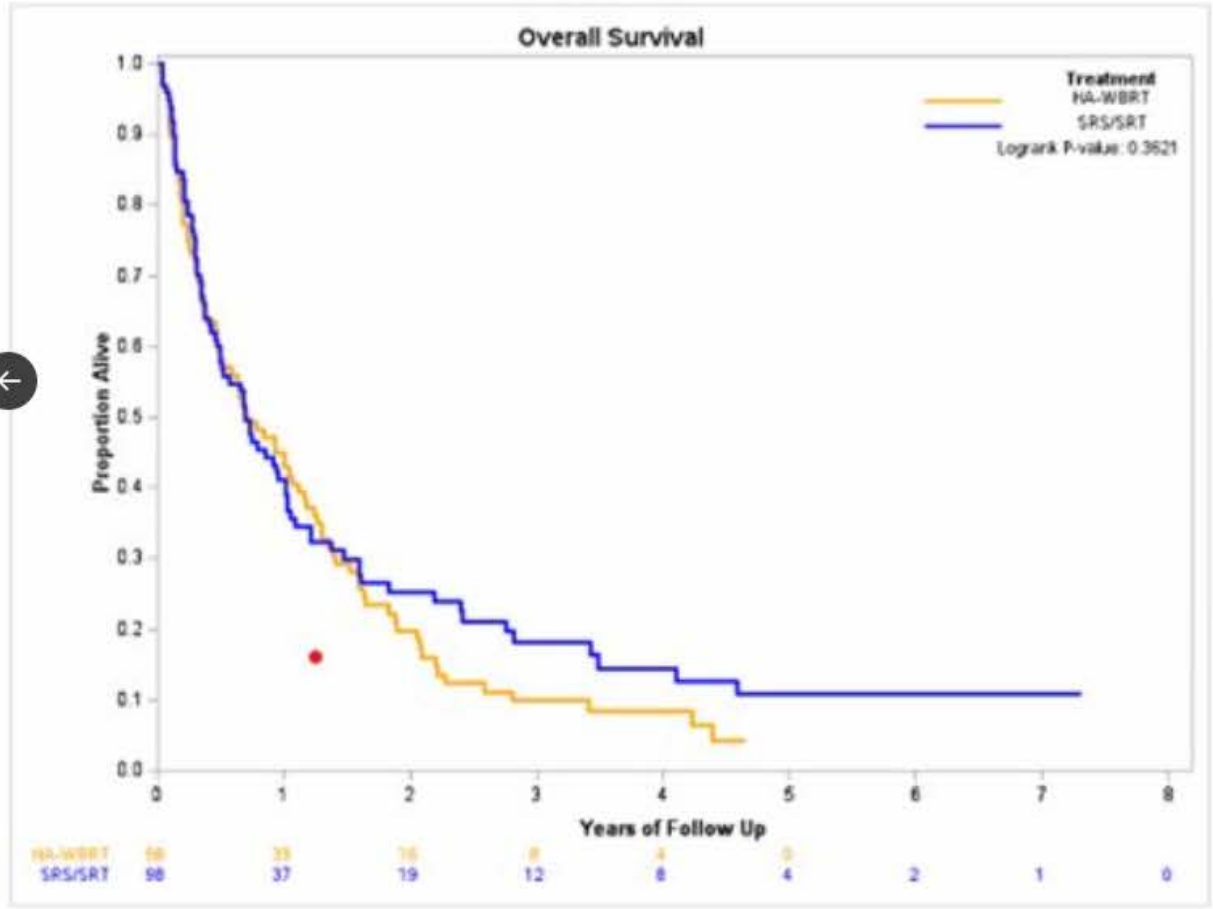
SRS/SRT

- Central credentialing
- VMAT
- 1-3 isocenters
- SRS: 16-20 Gy
  - 96%: 20 Gy
- SRT: 30 Gy in 5 Fx
  - Cavities with GTR: 25 Gy in 5 Fx
  - Dose reduction permitted for tumors near optics or brainstem

HA-WBRT

- Central credentialing
- Similar to CC001
  - 30 Gy in 10 Fx
  - Hippocampal metrics
    - Max ≤ 16 Gy
    - D100% ≤ 9 Gy
  - Except
    - Metastases contoured and dosimetrically evaluated
    - Metastases in/near hippocampi treated, with sparing of remainder of ipsilateral and contralateral hippocampus
- Memantine

Overall Survival



	SRS/SRT	HA-WBRT
Median Survival, mo (95% CI)	8.3 (5.9 -12.3)	8.5 (5.9 - 13.9)
12 Month Survival (95% CI)	41.1% (31.3% - 50.7%)	42.8% (32.7% - 52.6%)

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Results

Category	SRS/SRT Arm	HA-WBRT Arm	Difference (SRS/SRT – HA-WBRT)	p-value
Patients enrolled	98	98	–	–
Median brain metastases (IQR)	14 (11–18)	14 (11–18)	–	–
Baseline MDASI-BT symptom severity	2.2	1.9	0.3	0.20
Post-baseline symptom severity – baseline	-0.03	0.59	-0.62	<0.001
Post-baseline interference – baseline	-0.62	0.89	-1.50	<0.001

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Discussion

- Is SRS the Standard of Care for upto 20 brain metastases?

- Volume of Disease, Brain met velocity vs # of metastases

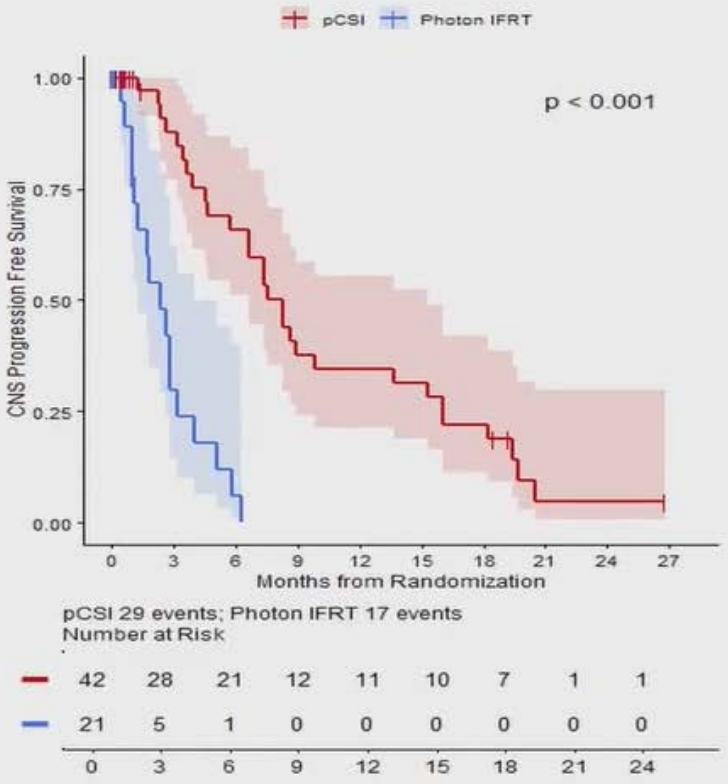
Proton Craniospinal Irradiation for Patients with Solid Tumor Leptomeningeal Metastasis- Final Analysis of a Phase II Study

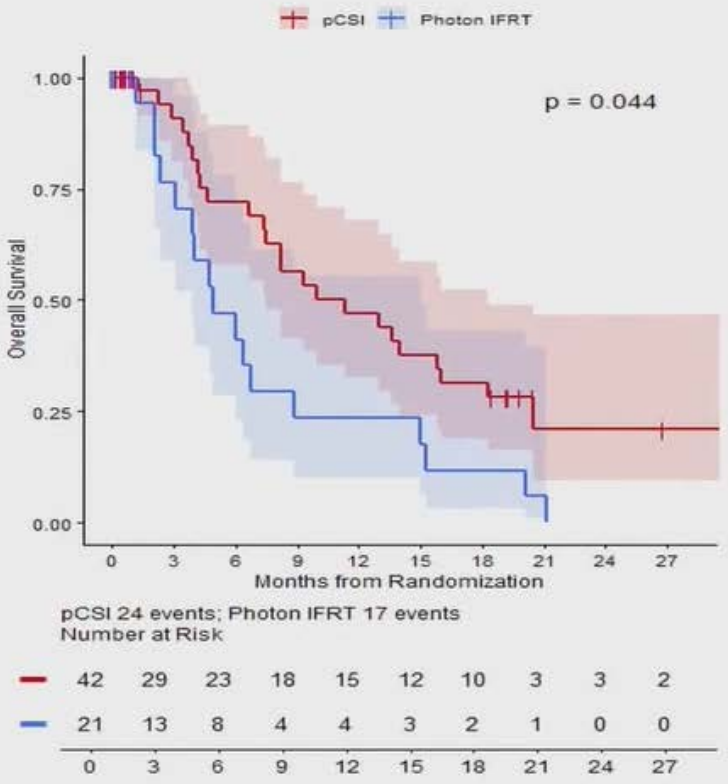
Yang JT et al., JAMA 2025

Study Details

- **Enrollment and Characteristics:**
  - **63 NSCLC and breast patients randomized to pCSI (n=42) vs. photon IFRT (n=21)**
  - **35 patients of other solid tumor histology enrolled completed follow-up at 12 months**
  - **In randomized cohort, 52% of patients had active systemic disease**
  - **Median KPS of 80 (range 60-90)**
  - **Median 2 lines of prior systemic therapy**

Final Analysis Survival Outcomes Randomized Groups





Median CNS PFS: 8.2 vs. 2.3 months, *p*<0.0001

Median OS: 11 vs. 4.9 months, *p*=0.044

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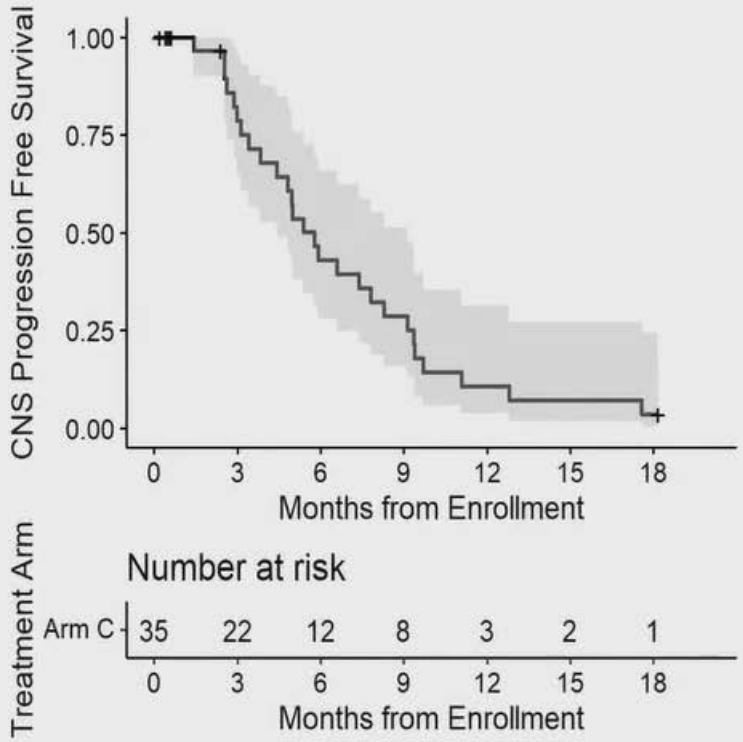
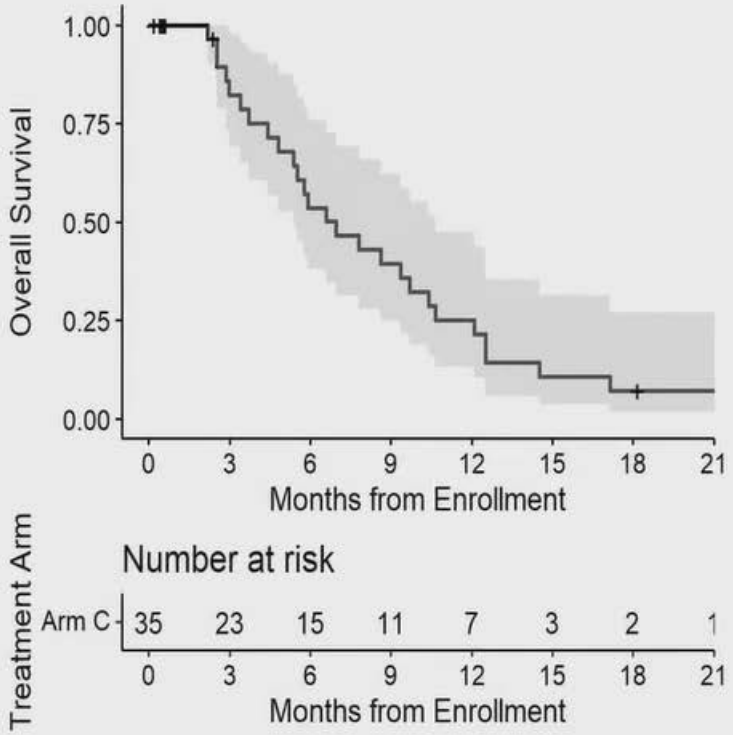
Final Analysis Survival Outcomes Exploratory Group



Median CNS PFS: 5.8 months



Median OS: 7.0 months

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Discussion

- Clear Survival benefit with the Phase 2 trial.

- Currently open NRG-BN014 clinical trial

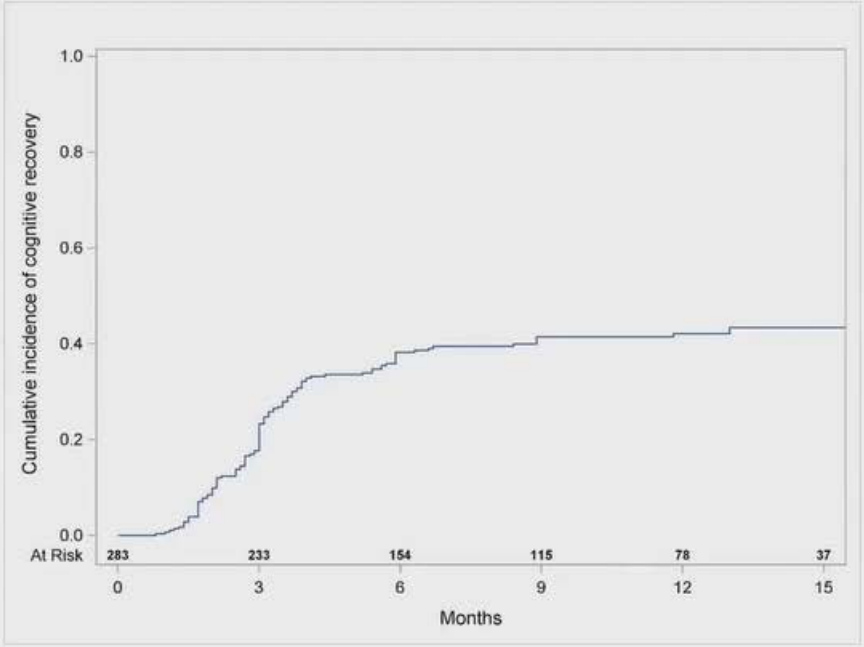
Evaluating Neurocognitive Recovery Following Stereotactic Radiosurgery and Whole Brain Radiation Therapy: Insights from a Pooled Analysis of Three Phase III Trials

Cherng HR et al., ASTRO 2024

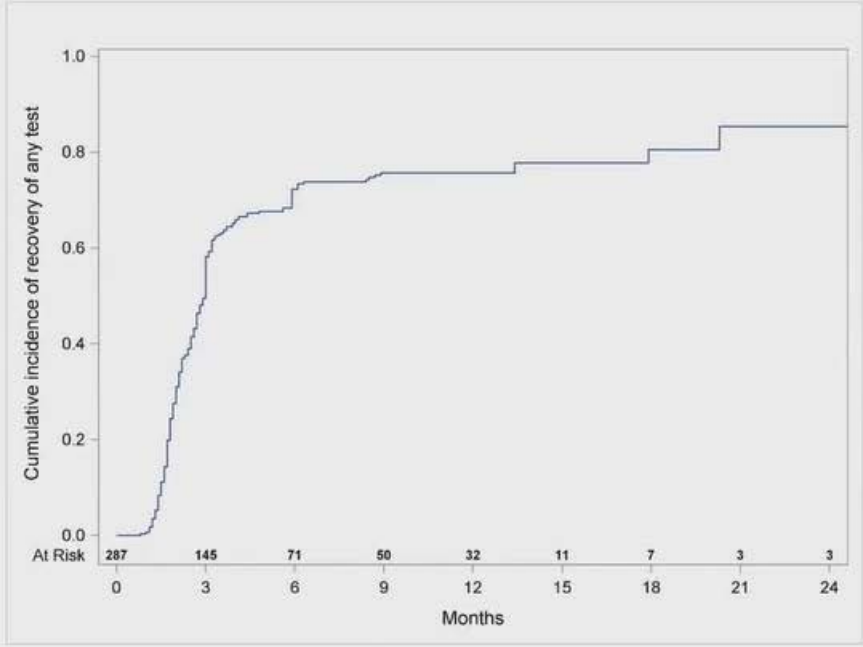
Background

- NCCTG N107C/CEC3: phase 3 RCT comparing post-operative SRS (12-20 Gy) vs WBRT (30Gy/10fx or 37.5Gy/15fx)
- NCCTG N0574: phase 3 RCT comparing SRS (20-24 Gy) vs SRS (18-22 Gy) and WBRT (30Gy/12fx)
- NRG CC001: phase 3 RCT comparing HA-WBRT + memantine vs WBRT + memantine
- Full cognitive recovery: no longer exhibiting 1 or more SD decline
- Recovery on individual test: at least a 1 SD improvement on previously failed test

Results – pooled incidence of cognitive recovery



Cumulative incidence of cognitive recovery



Cumulative incidence of recovery on any cognitive test

- 288 patients who experienced trial-defined neurocognitive function failure were included. Pooled incidence of full CR was 38% and 42% at 6- and 12-months after onset of neurocognitive failure, respectively.

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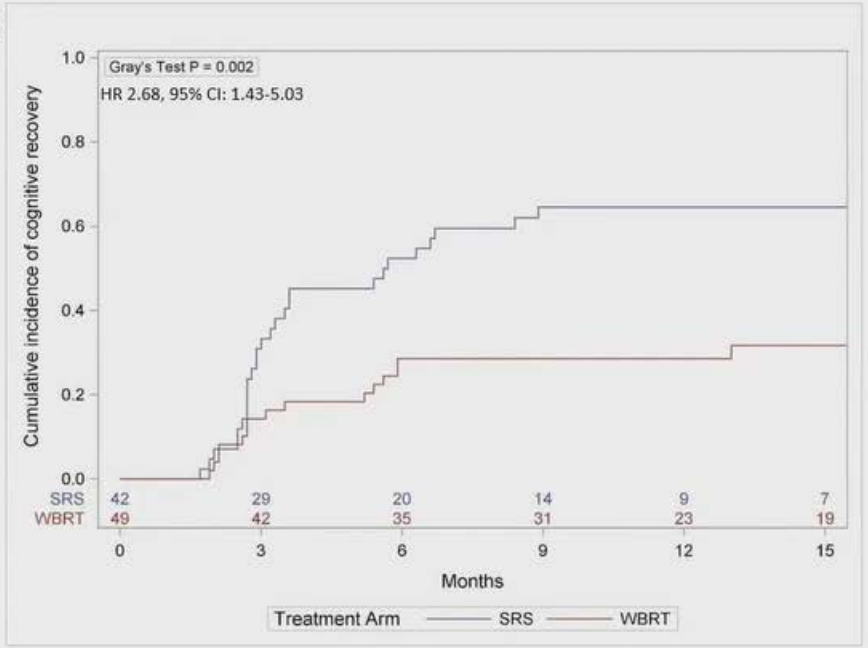
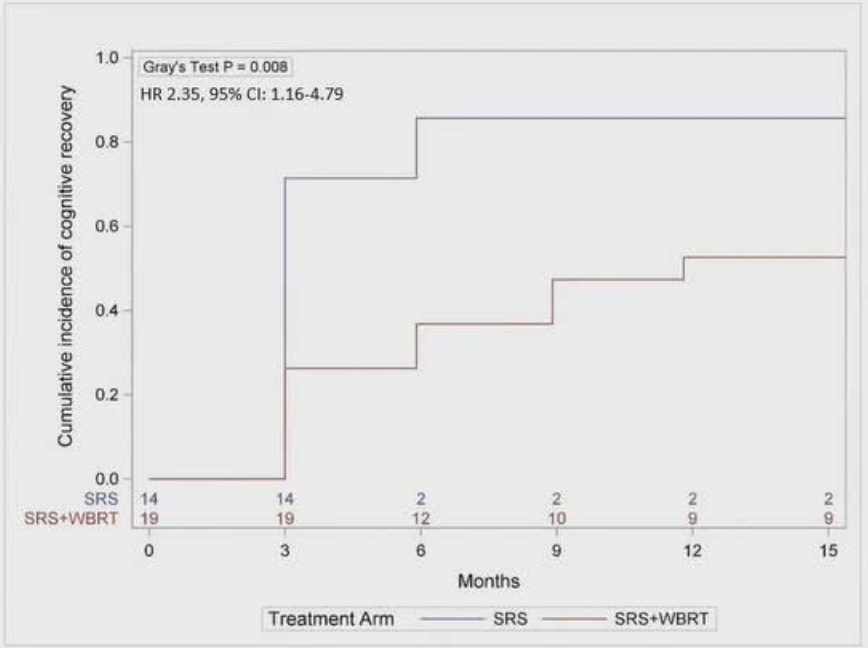
Cognitive Recovery by Trial (N107C and N0574)

N107C



Cumulative incidence of cognitive recovery by arm (postoperative SRS vs WBRT)

N0574



Cumulative incidence of cognitive recovery by arm (SRS vs SRS + WBRT for intact BM)

- Cumulative incidence of full CR was significantly greater with more conformal radiation techniques (SRS vs WBRT, SRS vs. SRS+WBRT)

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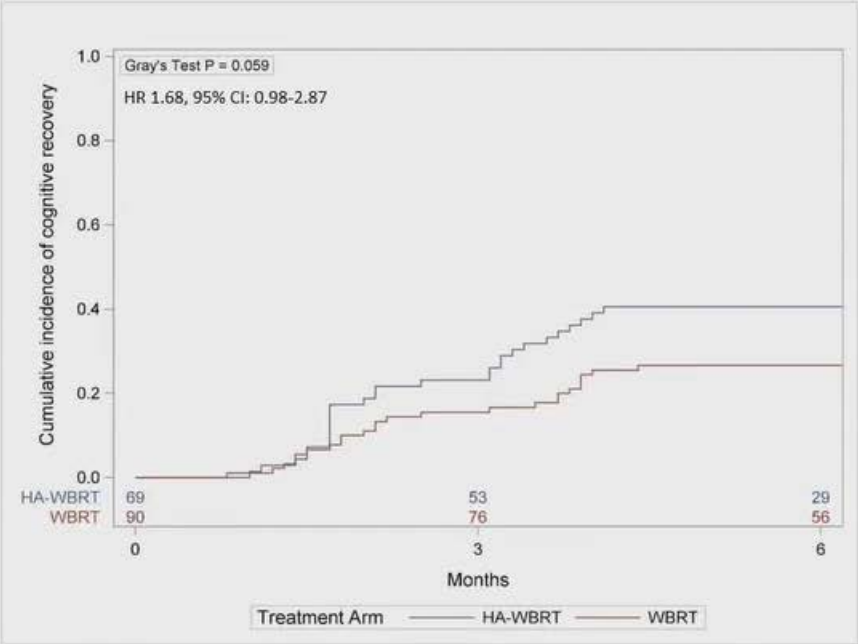
Cognitive Recovery by Trial (CC001)



Cumulative incidence of cognitive recovery by arm in CC001 (HA-WBRT vs WBRT)

- Trends toward significant increase in cumulative incidence of full CR with HA-WBRT vs WBRT

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Discussion

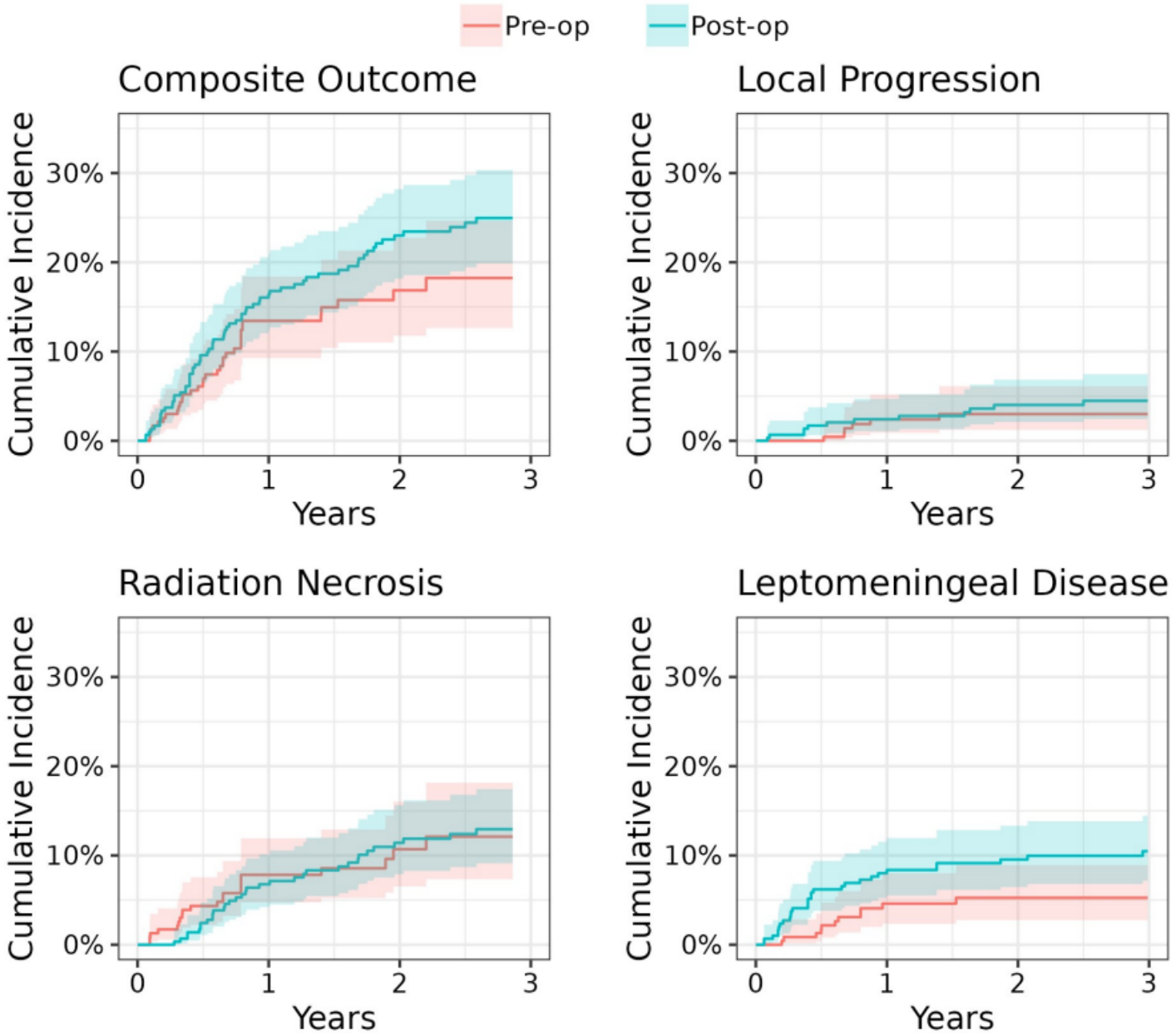
- 2/3 patients with cognitive recovery sustained recovery
- To what degree does radiation impact cognition? For SRS, does it impact cognition at all (factoring in chemotherapy, KPS, age, systemic progression, hospitalizations, etc)
- Are we using the correct definition of cognitive failure if many patients recover?

Pre-Operative vs. Post-Operative Fractionated Stereotactic Radiotherapy: A Single-Institution Analysis of 534 Resected Metastases

Perlow et al., ASTRO 2024

Background

- Patients with large or symptomatic brain metastases typically have surgery followed by post-operative (post-op) stereotactic radiosurgery (SRS).
- SRS leads to elevated rates of radiation necrosis (RN), meningeal disease (MD), and local failure (LF)
- Fractionated stereotactic radiotherapy (FSRT) can deliver a higher biological effective dose and may reduce the risk of LF
- Pre-operative (pre-op) treatments may reduce the risk of RN and MD through treating smaller volumes and tumor sterilization.



Composite Endpoint: G2+ radionecrosis, meningeal disease, or local failure

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Variable	Preoperative FSRT, N = 235	Postoperative FSRT, N = 299	p-value	Overall
Local Progression			0.2	
No	229 (97%)	286 (96%)		515 (96%)
Yes	6 (3%)	13 (4%)		19 (4%)
Radiation Necrosis			0.073	
Grade 2	12 (5%)	14 (5%)		26 (5%)
Grade 3	9 (4%)	24 (9%)		33 (7%)
Grade 4 or Higher	0	0		
Leptomeningeal Disease			0.031	
No	224 (95%)	270 (90%)		494 (92%)
Yes	11 (5%)	29 (10%)		40 (8%)
Type of Leptomeningeal Disease			0.2	
Classic	7 (64%)	15 (52%)		22 (55%)
Nodular	3 (27%)	14 (48%)		17 (43%)
Both	1 (9%)	0 (0%)		1 (3%)
Composite Endpoint			0.005	
No	201 (86%)	226 (76%)		427 (80%)
Yes	34 (14%)	73 (24%)		107 (20%)
Follow Up			0.012	
Censored	103 (44%)	99 (33%)		202 (38%)
Death	132 (56%)	200 (67%)		332 (62%)

Gliomas

Progression-Free and Overall Survival Results of ECOG-ACRIN E3F05: a Phase 3 Intergroup Trial of Radiation +/- Temozolomide for Grade II Gliomas

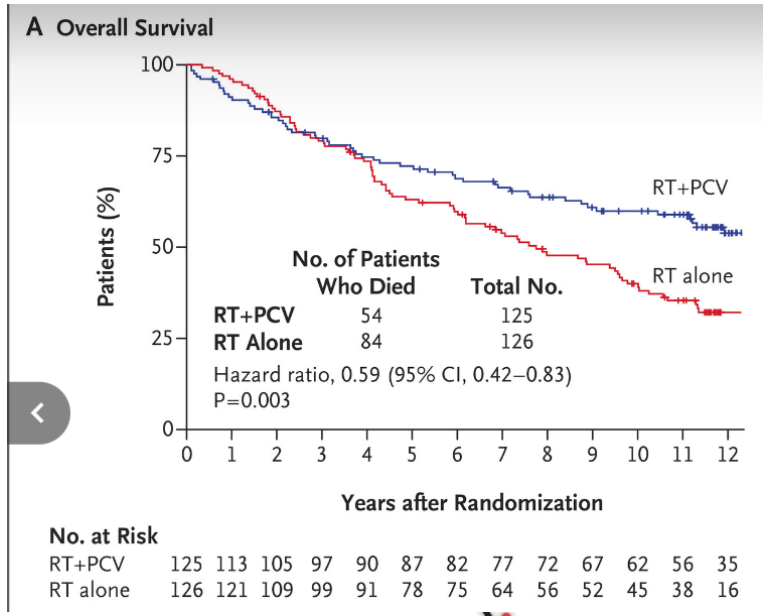
Schiff et al, SNO 2024

E3F05

	10 Yr PFS	10 Yr OS#
LGG* n=172 RANDOMIZE → 50.4 Gy	36%	47%
LGG* n=172 RANDOMIZE → 50.4 Gy+TMZ**	54%	70%

Schiff et al. SNO 2024 *>40, uncontrolled symptoms/seizures, or progression
**Concomitant TMZ + 12 cycles adjuvant. 43% were oligo. #OS benefit both oligo and astro

****Trial stopped after RTOG 9802 showed benefit from addition of PCV chemotherapy to radiation in Grade II gliomas, RTOG 9802 OS below



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Study	Population	Treatment	HR for OS
RTOG 9802	LGG	RT +/- PCV	0.59
CATNON	Gr 3 Astrocytoma	RT +/- adj TMZ	0.64
	IDHmt astrocytomas	RT any TMZ	0.53
RTOG 9402	Gr3 Oligo	RT +/- PCV	0.61
EORTC 26951	Gr3 Oligo	RT +/- PCV	0.6
E3F05	**LGG**	**RT +/- TMZ**	**0.54**

Awaiting results from CODEL trial comparing RT + PCV vs RT + TMZ

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

Mellinghoff et al, NEJM 2023, SNO 2024

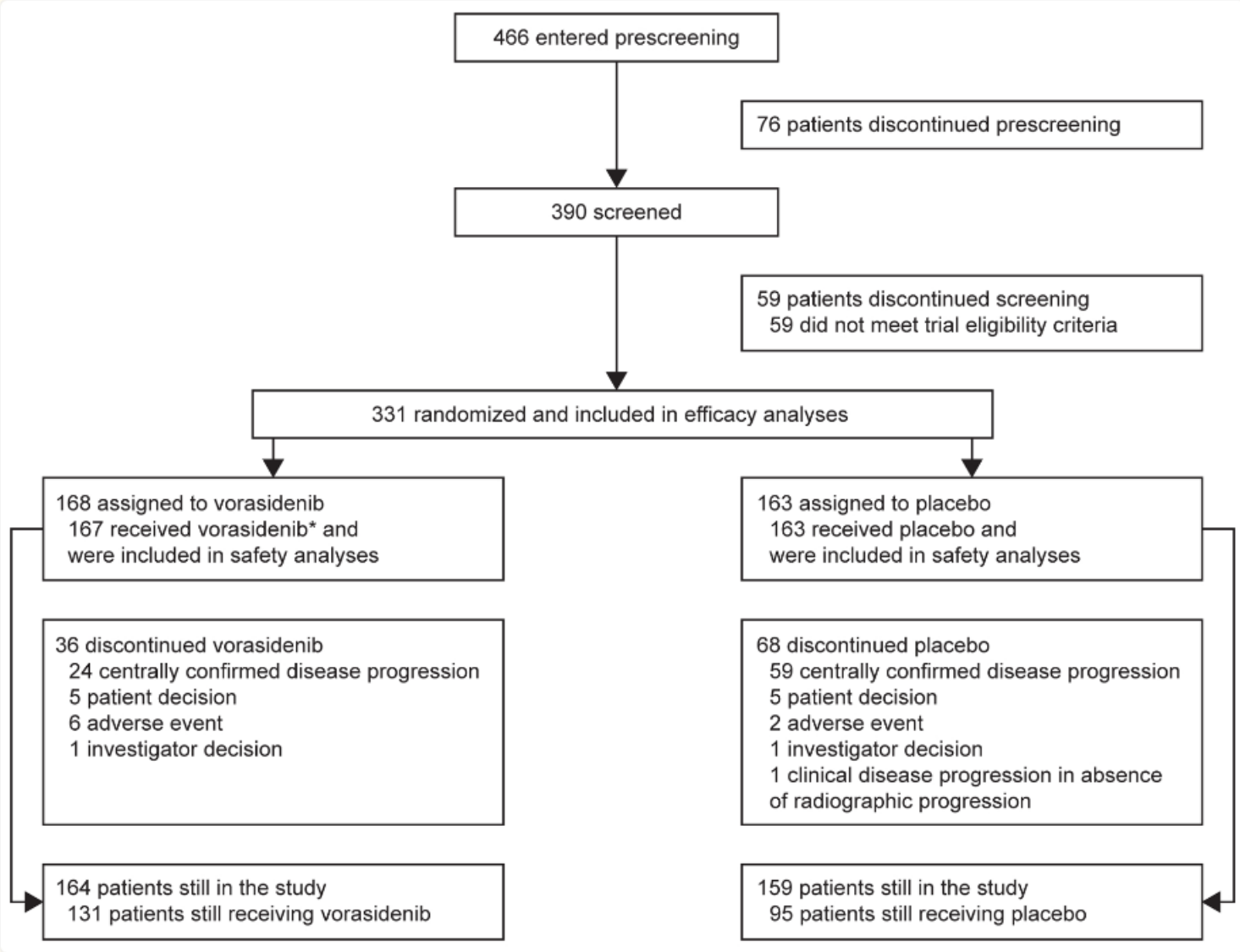

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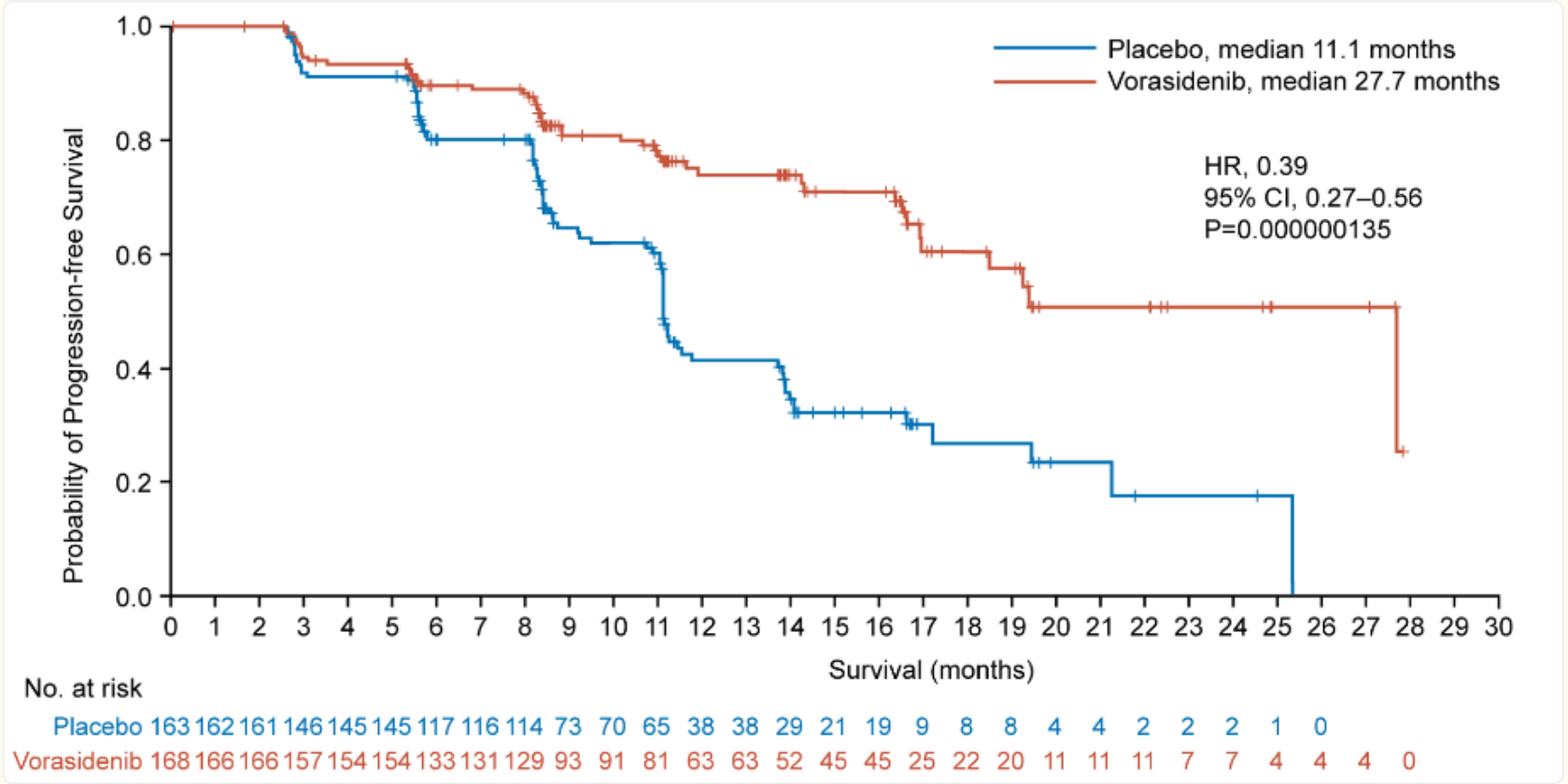
Figure 2. Progression-free Survival and Time to Next Intervention in the Full Analysis Set.



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Discussion

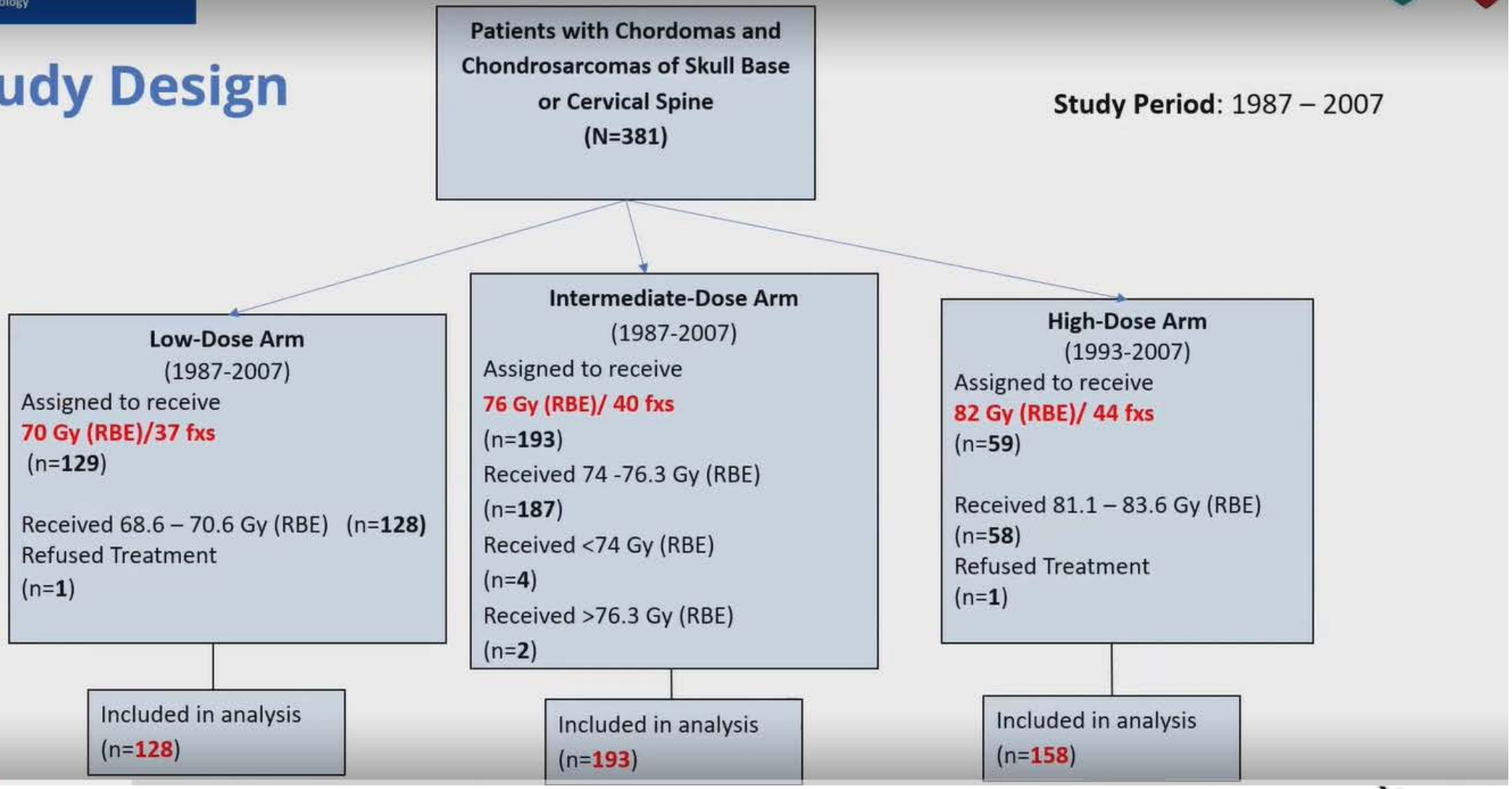
- Proper sequencing of IDH inhibition (as first therapy or adjuvantly after radiation and chemotherapy?)
- Does IDH inhibition cause earlier transformation to HGG?
- Awaiting QOL/neurocognitive data
- Awaiting OS data

Everything Else

Phase I/II Prospective Dose Escalation Trial with Proton-Based Radiation Therapy for Chordomas and Chondrosarcomas of the Skull Base and Cervical Spine: Long-Term Results from Proton Radiation Oncology Group 82-26

Ioakeim-Ioannidou et al, ASTRO 2024

Study Design



Mass General Brigham
Mass General Cancer Center
Radiation Oncology

PROG 85-26

	All Patients (n=379)	70 Gy (RBE) (n=128)	76 Gy (RBE) (n=193)	82 Gy (RBE) (n=58)
Age, years				
Median (range)	42 (18-87)	42 (18-75)	42 (18-87)	41 (20-81)
Gender				
Male	202 (53%)	88 (69%)	100 (52%)	14 (24%)
Female	177 (47%)	40 (31%)	93 (48%)	44 (76%)
Histology				
Chordoma	273 (**72%**)	82 (64%)	134 (69%)	57 (98%)
Chondrosarcoma	106 (28%)	46 (36%)	59 (31%)	1 (2%)
Location				
Skull Base	319 (**86%**)	122 (96%)	157 (84%)	40 (69%)
Cervical Spine	54 (14%)	5 (4%)	31 (16%)	31 (31%)
Extent of resection				
Biopsy	16 (5%)	10 (8%)	4 (2%)	2 (4%)
STR/NTR	320 (**84%**)	108 (84%)	166 (86%)	46 (79%)
GTR	42 (11%)	10 (8%)	22 (11%)	10 (17%)
Pre-RT Tumor Progression				
No	268 (71%)	93 (73%)	136 (70%)	39 (67%)
Yes	110 (**29%**)	35 (27%)	56 (29%)	19 (33%)

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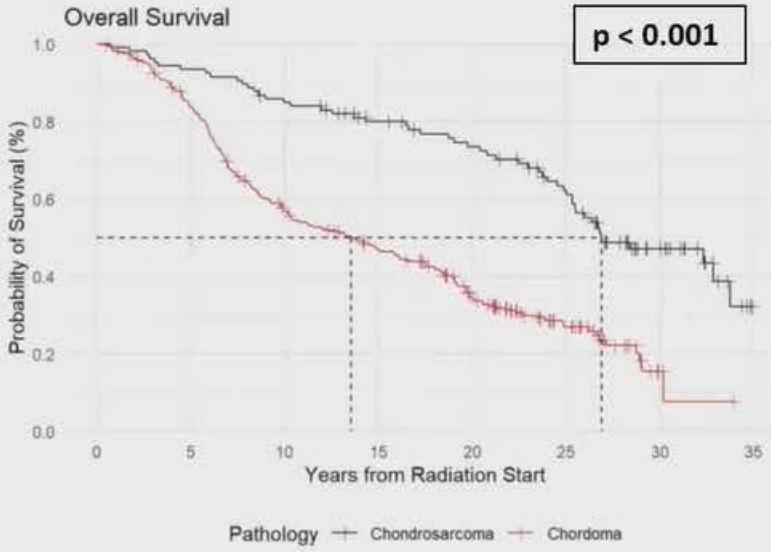
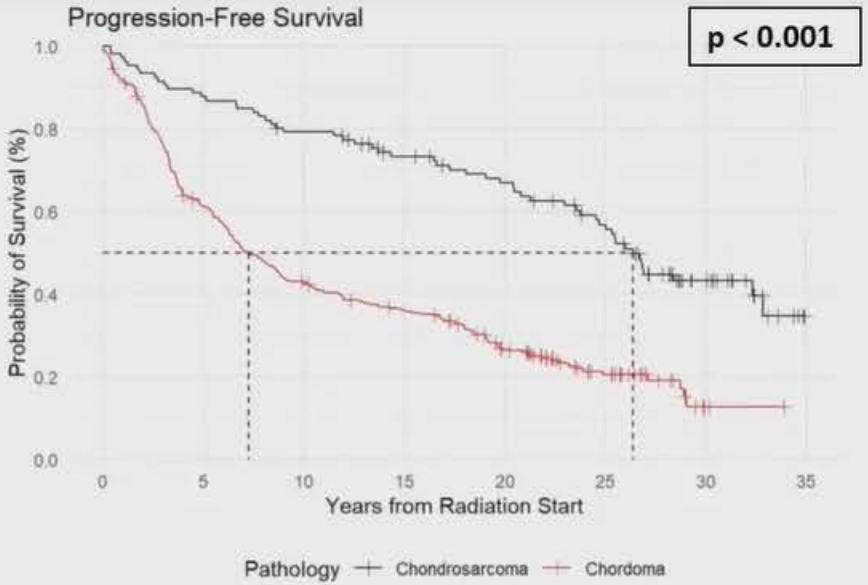
Secondary Endpoints

Overall Survival				
	5-year	10-year	20-year	25-year
All Patients	86.4%	64.7%	45.8%	37.2%
70 Gy (RBE)	87.5%	66.1%	49.5%	39.2%
76 Gy (RBE)	86.9%	64.4%	46.7%	39.6%
82 Gy (RBE)	81.9%	62.8%	34.5%	22.6%

Progression-Free Survival				
	5-year	10-year	20-year	25-year
All Patients	68.6%	53.1%	37.8%	31%
70 Gy (RBE)	74.2%	60%	41.8%	36.5%
76 Gy (RBE)	67.7%	51.1%	39.3%	31.3%
82 Gy (RBE)	59.2%	44.4%	24.1%	16.5%

Secondary Endpoints





Overall Survival				
	5-year	10-year	20-year	25-year
All Patients	86.4%	64.7%	45.8%	37.2%
Chordoma	**83.6%**	56.7%	34.7%	**26.9%**
Chondrosarcoma	93.3%	84.7%	73.2%	61.8%

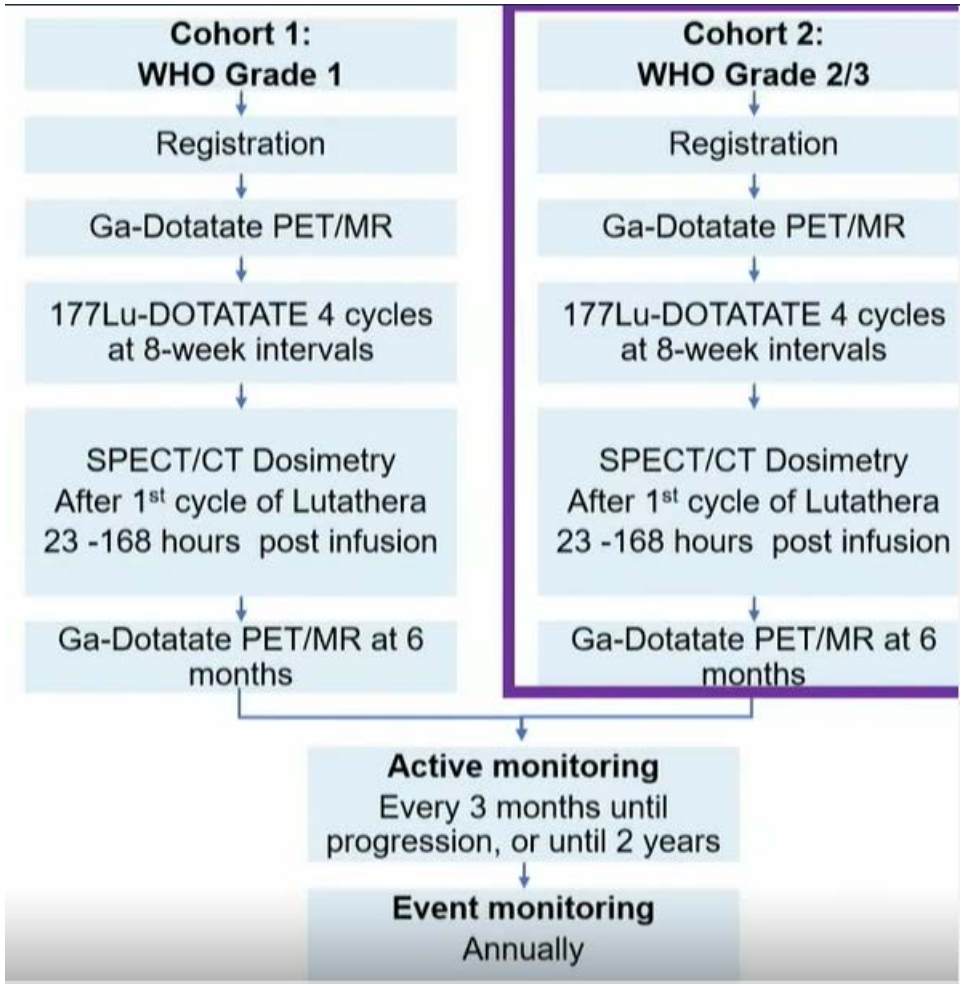
Progression-Free Survival				
	5-year	10-year	20-year	25-year
All Patients	68.6%	53.1%	37.8%	31%
Chordoma	**61.2%**	42.8%	26.4%	**20.6%**
Chondrosarcoma	87.6%	79%	66.5%	56.4%

Discussion

- Chordoma and chondrosarcoma are different diseases
- Does dose escalation matter more for chordoma?
- How would data look in a modern cohort with better imaging and modern photon radiation?

A Prospective, Phase II Study of 177Lu-Dotatate in Patients with Surgery- and Radiation-Refractory Meningioma: Results of the WHO Grade 2 and 3 Cohort

Merrell et al., ASTRO 2024



Tumor and Treatment Characteristics

Variable		Total (N=20)
WHO Grade	2	95%
Krenning Score	2	45%
	>2	55%
Largest Tumor Dimension (cm)	Mean (SD)	3.5 (1.6)
	Range	1.8-7.5
Multifocal Meningioma	Yes	75%
Prior Surgery	Yes	100%
Prior Courses of RT	Median	2
	Range	1-7
Prior Chemotherapy	Yes	15%

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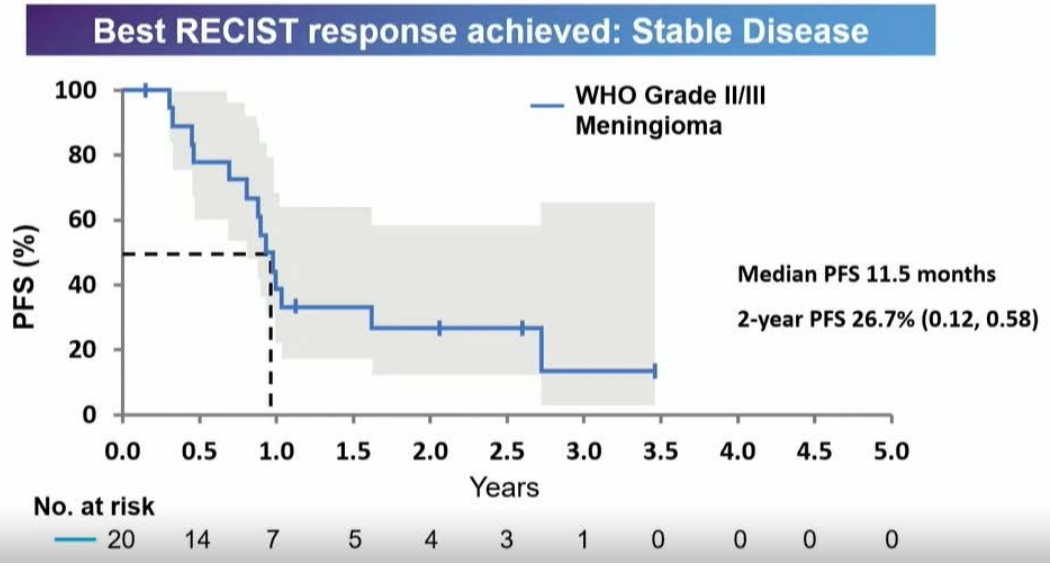
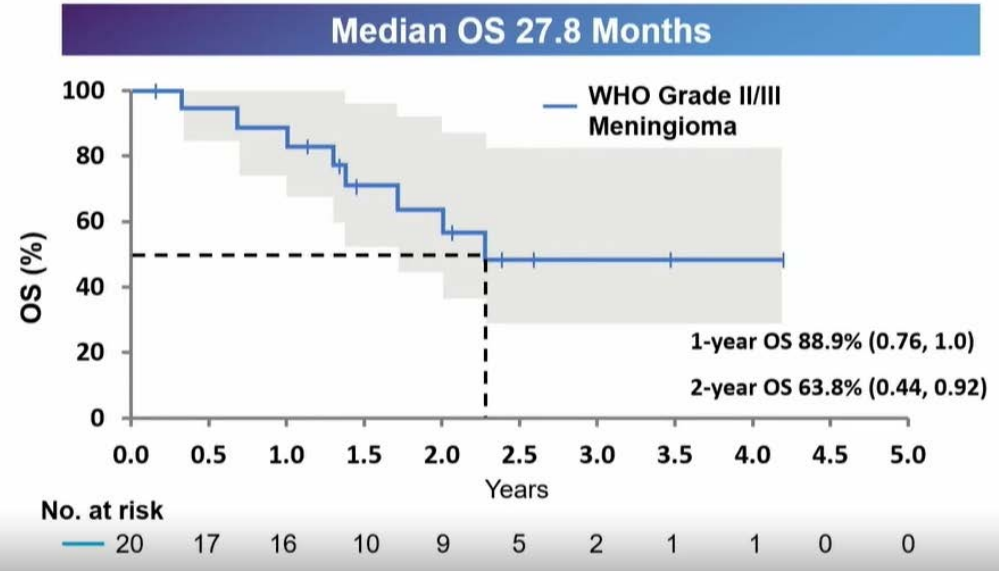
Primary Endpoint Met: PFS-6 of 77.8%



Overall Survival



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Discussion

- Heterogenous group with varying histologies
- Role of targeted gene expression profiling?
- When to switch from focal therapy to Lutathera?

Newly Diagnosed GBM Trials

Trial ID	Description
CASE5320	Phase II: O6-benzylguanine (BG) + Temozolomide (TMZ) with autologous P140KMGMT+ progenitors
NVOX1323	Phase 2 RESTORE study: NanO2™ + radiation and temozolomide
NOVO1324	Phase 3 EF-41/Keynote D58: Optune (TTFields) + Temozolomide
GCAR1319	Innovative Platform Trial in newly diagnosed & recurrent GBM

Recurrent GBM Trials

Trial ID	Description
CASE3316	Phase I/II: LITT + Checkpoint Inhibitor for recurrent GBM
GCAR1319	Innovative Platform Trial in newly diagnosed & recurrent GBM
NOVA1324	Phase Ib [177Lu]Lu-NeoB + RT + TMZ, MGMT methylated/unmethylated

Meningioma Trials

Trial ID	Description
A071701	Genomically-Guided Treatment Trial in Brain Metastasis
RTOG3523	MOMENTUM-1: [177Lu]Lu-DOTATATE in progressive grade 1–3 meningioma

Brain Metastases Trials

Trial ID	Description
A071701	Genomically-Guided Treatment Trial in Brain Metastasis
NRG-CC009	Phase III: SRS vs HA-WBRT for ≤10 brain mets from small cell lung cancer
NRG-BN012	Phase III: Pre-op vs Post-op SRS in resectable brain mets
NRG-BN013	Phase III: Single Fraction SRS vs Fractionated SRS for intact brain mets

Acknowledgements

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Attallah Baydoun, MD, PhD
Daniel Spratt, MD
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RADIATION ONCOLOGY

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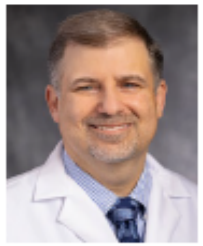

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Thank you!

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