Stereotactic Radiosurgery Versus Whole-brain Radiation Therapy For Patients With 4-15 Brain Metastases: A Phase III Randomized Controlled Trial

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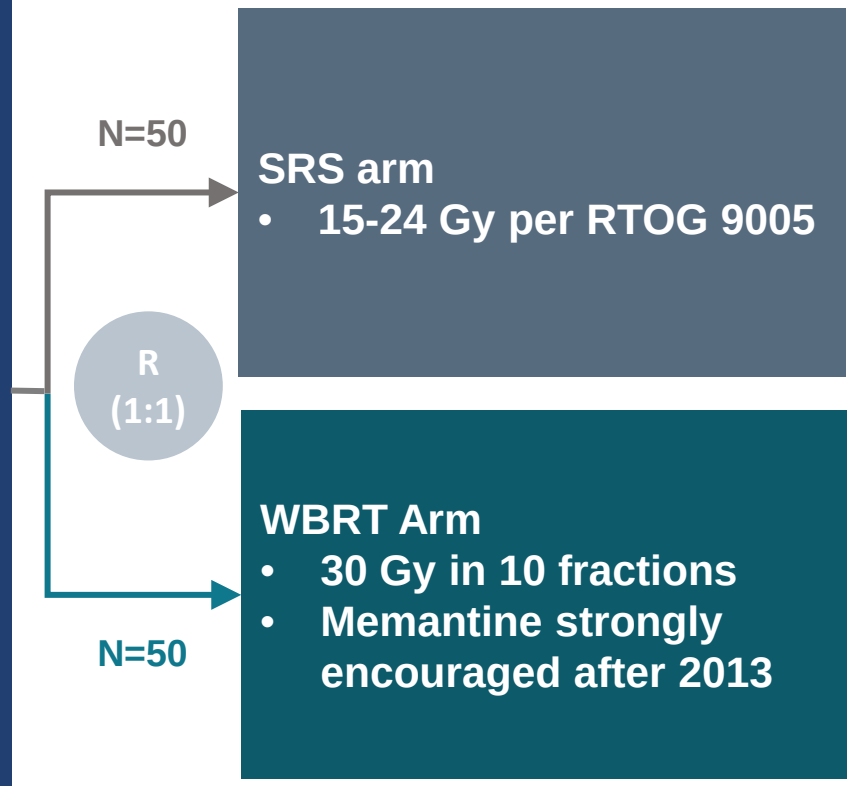
Background

- Up to 30% of cancer patients develop brain metastases
  - Rising incidence due to prolonged survival and better imaging surveillance
  - Historically poor overall survival (~1-4 months)
    - Main treatment modalities: radiation and surgery
    - Whole brain radiation (WBRT) associated with significant cognitive side effects
- In patients with 1-3 (or 4) brain metastases
  - Two Phase III randomized trials established stereotactic radiosurgery (SRS) as the standard care, replacing WBRT, due to better preservation of patients' cognitive function, without compromising overall survival *(Chang EL, Lancet Onc 2009; Brown PD, JAMA 2016)*
- Purpose of the current study
  - To investigate if SRS could replace WBRT in patients with 4-15 brain metastases in a phase III randomized trial

Trial Design (Schema)

Key Eligibility Criteria:

- Adult patient with 4-15 untreated brain mets confirmed by neuroradiology (up to 20 lesions allowed at the time of treatment)
- All lesions amenable to SRS treatment
- KPS >/=70
- No LMD (radiographic or cytological)
- No prior WBRT
- Prior SRS to 1-3 brain mets with > 6 weeks intervals allowed
- Excluded prior surgical resection of brain mets
- Excluded histology: melanoma, small cell carcinoma, lymphoma/leukemia, or germ cell histology
- Systemic therapy allowed at the discretion of treating oncologist

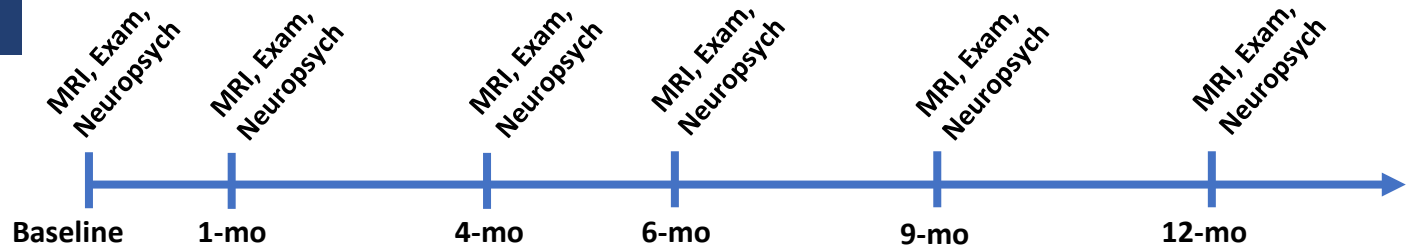


Stratification factors:

- **Histology** (breast vs. other)
- **Age** (18-59 vs. 60 and over)
- **Number of lesions** (4-7 vs. 8-15)
- **KPS** (70-80 vs. 90-100)
- **Extra-cranial disease status** (progressive disease prior to enrollment vs. no progression)
- **Baseline HVLT** (</= 17 vs. >/=28
- **Radiotherapy** (Prior SRS vs. no prior SRS)

Neurocognitive function tests:

- **Memory:** HVLT_R_TR, HVLT_R_DR, HVLT_R Recognition
- **Executive function:** COWA, and Trail Making test Part B (TMTB)
- **Attention Span:** WAIS-III Digit Span
- **Psychomotor Speed:** WAIS-III Digit Symbol, Trail Making test Part A (TMTA)
- **Motor dexterity:** Grooved Pegboard

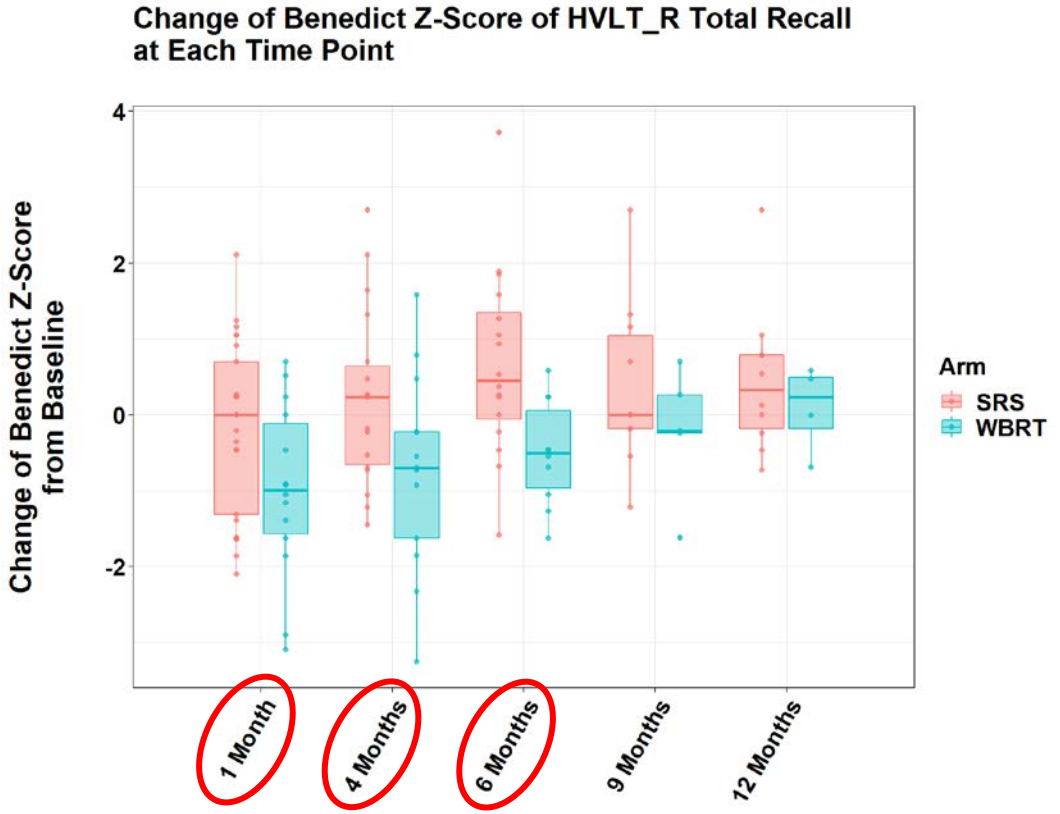


Primary Endpoints

- **Memory function at 4 mo (HVLT_R_TR)**
- **Local control at 4 mo**

Memory Function at 4 Months
-- Primary Endpoint

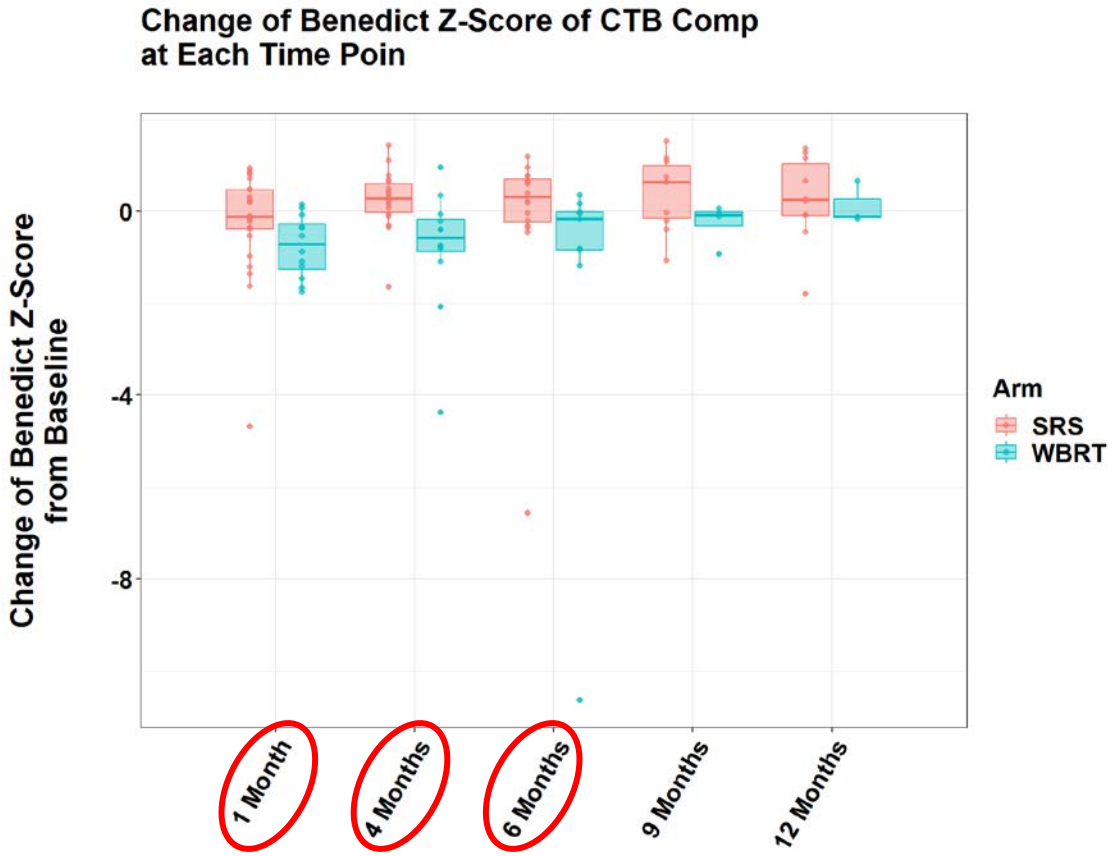
- HVLT_R_TR: change of Z-score from baseline
- **At 4 months**
  - o **SRS:** Increased by 0.21 (SD 1.15) (n=18)
  - o **WBRT:** Decreased by 0.74 (SD 1.31) (n=13)
  - o ***p*=0.041**
- **At 1 month and 6 months**
  - o Clinically meaningful and statistically significant benefit with SRS was also observed at **1 month (*p*= 0.033)** and **6 months (*p*=0.012)**



Global Cognitive Function Measure
(Clinical Trial Battery Composite Score)

- Composite score
  - Mean Z-score from HVLT_R_TR, HVLT_R_DR, and HVLT_R Rec, COWA, TMTA, and TMTB
  - Change from baseline
- **Better cognitive composite scores in SRS arm**
  - **Statistically significant at months 1, 4 and 6**

Follow up Time Point	SRS	WBRT	p
1-mo (median [IQR])	-0.12 [-0.38, 0.47]	-0.71 [-1.26, -0.28]	0.024
4-mo (median [IQR])	0.28 [-0.03, 0.60]	-0.57 [-0.88, -0.17]	0.004
6-mo (median [IQR])	0.31 [-0.23, 0.70]	-0.16 [-0.84, -0.01]	0.027
9-mo (median [IQR])	0.64 [-0.16, 1.00]	-0.08 [-0.32, -0.01]	0.153
12-mo (median [IQR])	0.25 [-0.09, 1.03]	-0.12 [-0.14, 0.27]	0.823



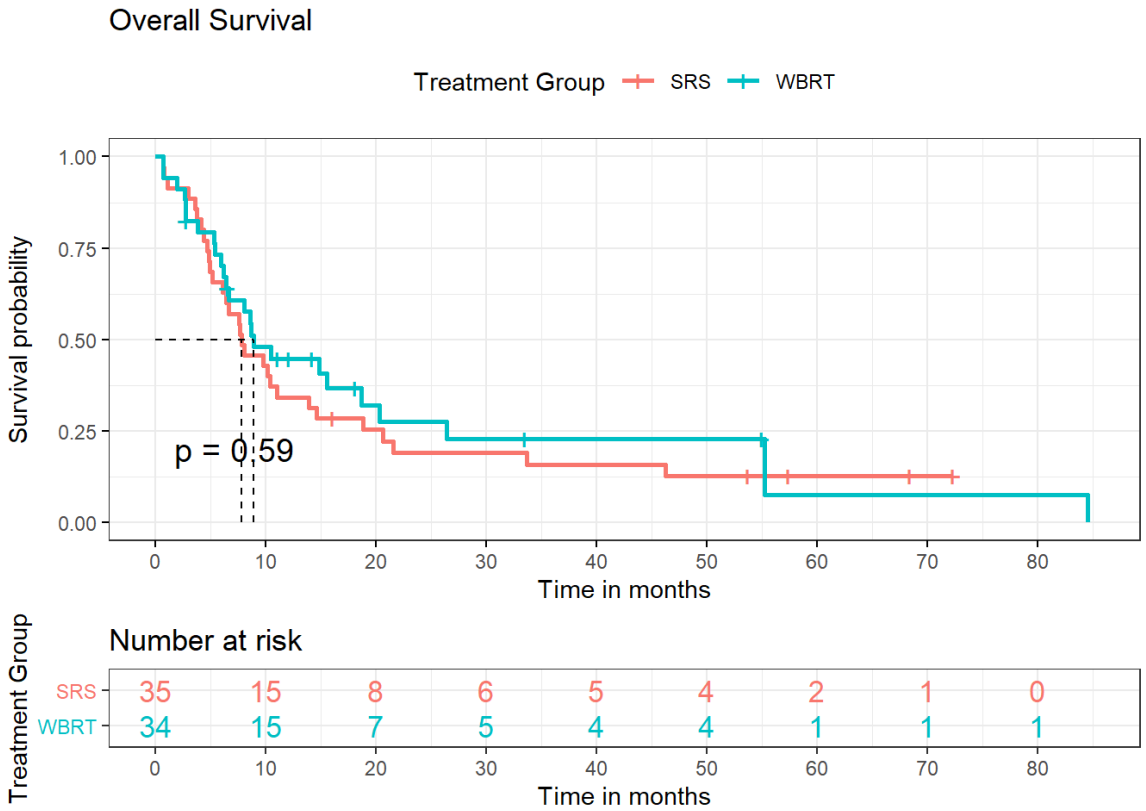
Overall Survival

- **Overall survival by intention-to-treat**
  - o 69 out of 72 pts evaluable for OS
    - o 35 for SRS and 34 for WBRT
  - o Estimate median OS

	N	Events (death)	Median (month)	95% CI (month)
SRS	**35***	**30**	**7.8**	**6.1 – 14.6**
WBRT	**34****	**26**	**8.9**	**6.4 – 26.4**

*Include 6 patients who had more than 20 lesions at time of SRS planning and received WBRT off protocol

** Include 4 patients received SRS and 2 patients received HA-WBRT off protocol



Estimating Overall Survival Curves with the Kaplan-Meier Method by intention-to-treat: *P*= 0.59

Other Results

- Local Control at 4 mo
  - 95% (SRS) vs 87% (WBRT), p-value 0.79
- Distant brain control
  - 60% (SRS) vs 80% (WBRT), p-value 0.37
- **Time to systemic therapy**
  - 1.7 weeks (SRS) vs 4.1 weeks (WBRT), **p-value 0.001**
- Toxicities
  - $\geq$ Grade 3 toxicities 8% (SRS) vs 15% (WBRT)
  - Radiation necrosis: 17% at patient level and 4% at lesion level

Summary

Despite early termination of the trial due to NRG CC001 and use of memantine in 2/3 WBRT patients, in patients with 4-15 brain mets:

- SRS was associated with reduced risk of neurocognitive deterioration compared to WBRT, as demonstrated by a constellation of neurocognitive tests, individually or by composite scores
  - The differences between the two arms were large and clinically meaningful
- No difference in overall survival rates
- SRS was associated with shorter time to systemic therapy

Conclusion

The results from this phase III randomized trial strongly supports the use of SRS in patients with 4-15 brain metastases to better preserve cognitive function and to minimize interruption of systemic therapy, without compromising overall survival.