

ADVANCES IN STEREOTACTIC RADIOTHERAPY OF BRAIN METASTASES

Results of the CYBER-SPACE and ESTRON Trials

UNIVERSITÄTSMEDIZIN
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UMG



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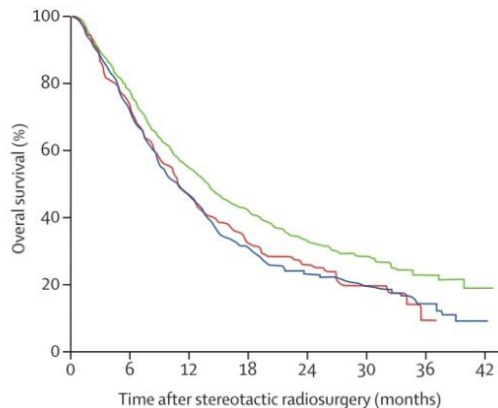
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Radiosurgery of multiple BM

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Masaaki Yamamoto*, Toru Serizawa*, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gonda, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tamoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
— 1 tumour	13.9 (12.0–15.6)	0.76 (0.66–0.88)	0.0004
— 2–4 tumours	10.8 (9.4–12.4)	Reference	
— 5–10 tumours	10.8 (9.1–12.7)	0.97 (0.81–1.18)	0.78



- Prospective cohort of 1194 patients with **1-10 brain metastases**
- **Gamma-Knife SRS** of all lesions
- **No difference in survival between patients with 2-4 vs. 5-10 brain metastases**

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

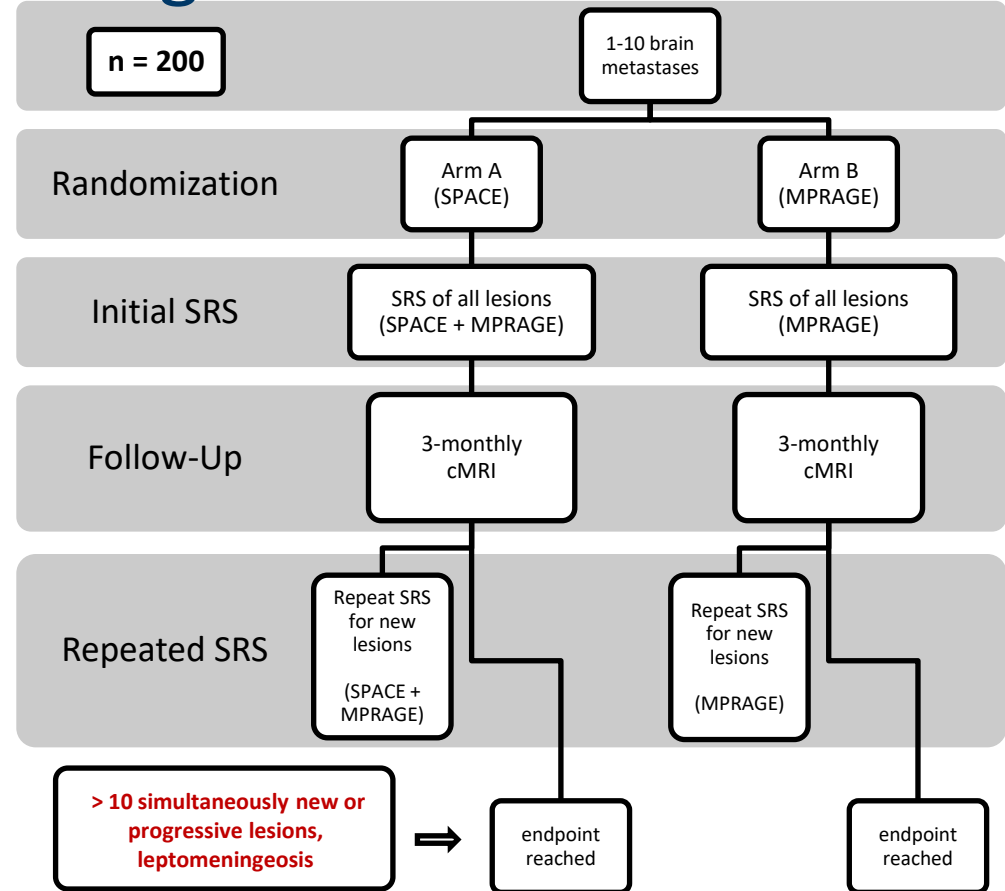
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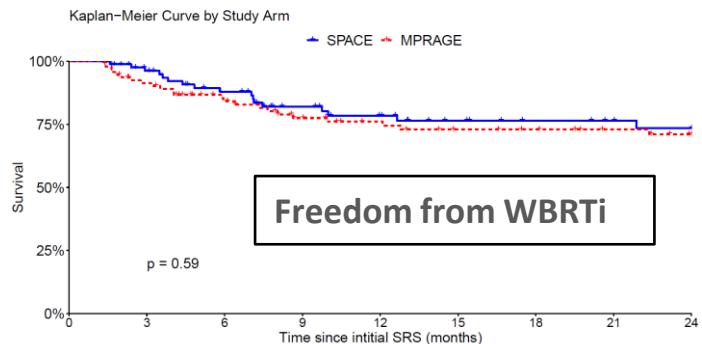
	Total (n=1194)	1 tumour (A) (n=455)	2-4 tumours (B) (n=531)	5-10 tumours (C) (n=208)	p value (B vs C)
Died	850 (71%)	310 (68%)	392 (74%)	148 (71%)	0.46
Neurological death*	71 (8%)	32 (10%)	25 (6%)	14 (9%)	0.27
Deterioration of neurological function	146 (12%)	56 (12%)	62 (12%)	28 (13%)	0.53
Local recurrence†	138 (13%)	65 (16%)	54 (11%)	19 (10%)	0.78
New lesions†	625 (58%)	199 (48%)	297 (63%)	129 (69%)	0.12
Leptomeningeal dissemination†	144 (13%)	48 (12%)	61 (13%)	35 (19%)	0.067
Leukoencephalopathy†	9 (1%)	3 (1%)	4 (1%)	2 (1%)	0.68
Salvage SRS procedures	459 (38%)	148 (33%)	221 (42%)	90 (43%)	0.74
1	256 (21%)	76 (17%)	129 (24%)	51 (25%)	0.92
2	113 (9%)	45 (10%)	47 (9%)	21 (10%)	
≥3	90 (8%)	27 (6%)	45 (8%)	18 (9%)	
Salvage WBRT	107 (9%)	36 (8%)	54 (10%)	17 (8%)	0.48
Salvage surgery	23 (2%)	12 (3%)	8 (2%)	3 (1%)	1.00
Systemic anticancer agents	861 (72%)	308 (68%)	387 (73%)	166 (70%)	0.059
Molecularly targeted agents	356 (30%)	123 (27%)	157 (30%)	76 (37%)	0.078

- Regular **MRI follow-up** and **Salvage-therapy** applied to **49% of patients** for new lesions
- **77%** of salvage treatments in the form of **repeated SRS**

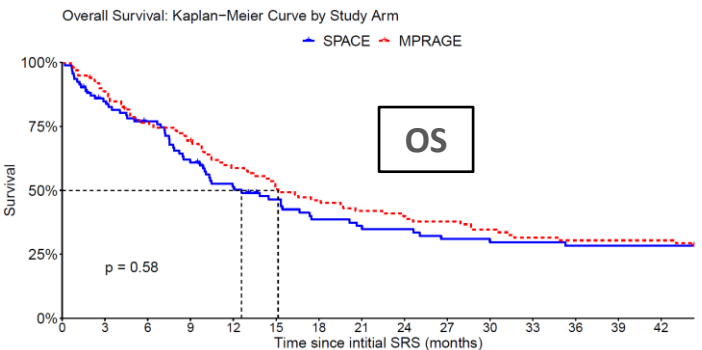
CYBER-SPACE Study Design

- **Single-center randomized phase 2 trial**
- **Heidelberg University Hospital**
- **Targeted patient collective:**
1-10 newly diagnosed BM
- **Rationale:**
Avoidance or delay of WBRT
- **Study intervention:**
 - SRS of all visible BM
 - Repeated SRS upon occurrence of new BM





93	73	62	48	41	34	29	27	25
99	81	66	55	49	44	42	38	34



93	76	67	53	43	36	30	28	27	24	23	23	22	22	22
99	87	74	67	56	48	44	40	38	36	33	30	29	29	29

- **24-mo Freedom from WBRT indication**
 - SPACE arm: 80.6%
 - MPRAGE arm: 76.1%
 - overall cohort: **78.3%**
- **mOS: no sign. difference (p=0.59)**
 - SPACE arm: 10.5 mo
 - MPRAGE arm: 15.2 mo
 - Cause of death: 10% from BM, 68% extracranial causes, 22% unknown
- **Initial number of BM predictive of iffS (HR 3.1, p=0.002 for 5-10 BM), but not of OS**
- **Safety:**
 - no safety signals
 - Grade 3 radionecrosis: 4% vs. 6% (n.s.)

Conclusions:

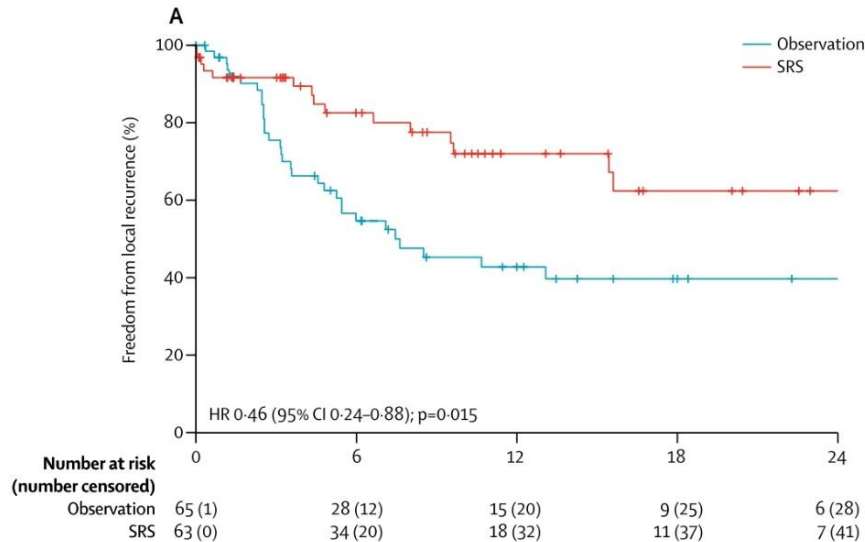
SRS for patients with **1-10 BM avoided the need for WBRT in 78.3% of cases, when repeated** upon occurrence of new lesions

- **First prospective randomized trial** for SRS of up to 10 simultaneous BM
- SRS for patients with **1-10 BM avoided the need for WBRT in 79.2%** of cases, **when repeated** upon occurrence of new lesions.
- **Regular high-sensitivity MRI** is a prerequisite for this strategy.
- **Proactive management** of multiple BM with SRS can greatly **limit the impact of BM** on overall prognosis.
 - Only **10% of deaths** due to BM
- Repeated SRS of multiple BM **is safe** and should be regarded as a **favorable alternative to WBRT**.

Post-operative Cavity SRS

Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

Anita Mahajan, Salmaan Ahmed, Mary Frances McAleer, Jeffrey S Weinberg, Jing Li, Paul D Brown, Stephen Settle, Sujit S Prabhu, Frederick F Lang, Nicholas Levine, Susan McGovern, Erik Sulman, Ian E McCutcheon, Syed Azeem, Daniel Cahill, Claudio Tatsui, Amy B Heimberger, Sherise Ferguson, Amol Ghia, Franco Demonte, Shaan Raza, Nandita Guha-Thakurta, James Yang, Raymond Sawaya, Kenneth R Hess, Ganesh Rao

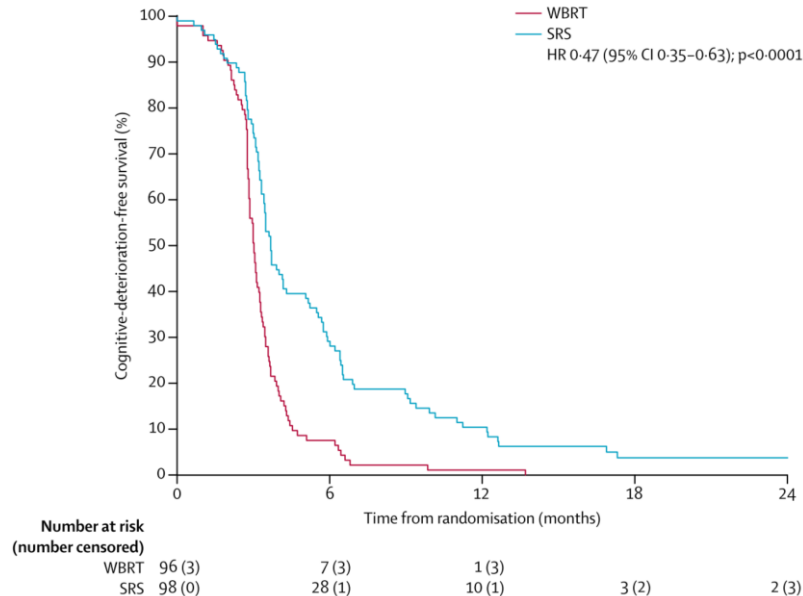


- SRS Improves local control at cavity, compared to observation

SRS of the resection cavity

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial

Paul D Brown, Karla V Ballman, Jane H Cerhan, S Keith Anderson, Xiomara W Carrero, Anthony C Whittom, Jeffrey Greenspoon, Ian F Parney, Nadia N Laack, Jonathan B Ashman, Jean-Paul Bahary, Costas G Hadjipanayis, James J Urbanic, Fred G Barker II, Elana Farace, Deepak Khuntia, Caterina Giannini, Jan C Buckner, Evanthis Galanis, David Roberge



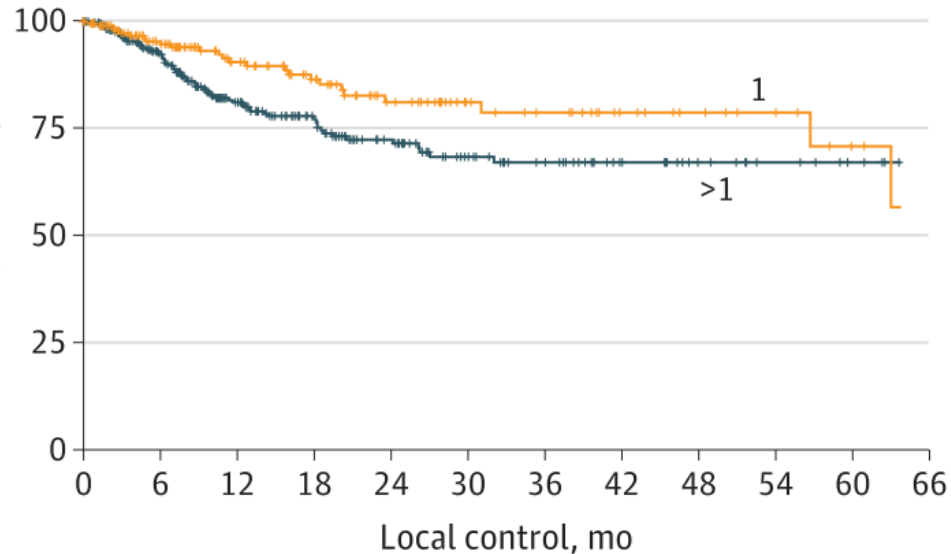
- SRS Improves local control at cavity, compared to observation
- SRS causes less neurocognitive decline, compared to WBRT

BUT ...

- Local control following SRS inferior to WBRT → **60% vs. 72% at 1 year!**

Multi-institutional Analysis of Prognostic Factors and Outcomes after Hypofractionated Stereotactic Radiotherapy to the Resection Cavity in Patients with Brain Metastases

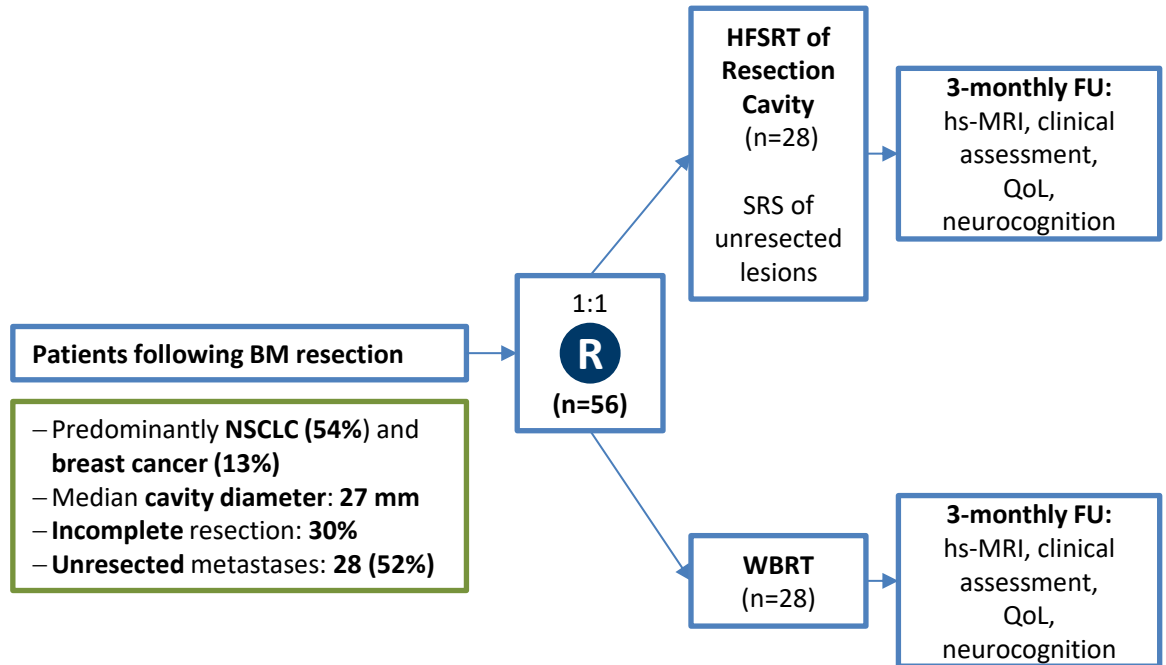
- Retrospective, multicenter database analysis, n=558



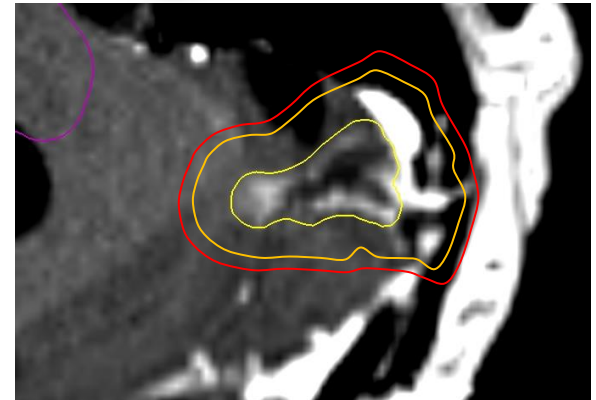
- **Hypofractionated stereotactic radiotherapy, HFSRT (5-7 fractions) delivers higher biologically effective dose (BED) than single-session SRS**
- **HFSRT can achieve 1-year local control rates of up to 84% in pooled retrospective data**

ESTRON – Study Design

- **Single-center randomized phase 2 trial**
- **Heidelberg University Hospital**
- **Targeted patient collective:**
Patients following BM resection
- **Rationale:**
Avoid toxicity of WBRT at comparable intracranial control
- **Study intervention:**
 - HFSRT of resection cavity
 - 7 x 5 Gy with 3-4 mm margin
 - SRS of additional lesions
 - Control: WBRT

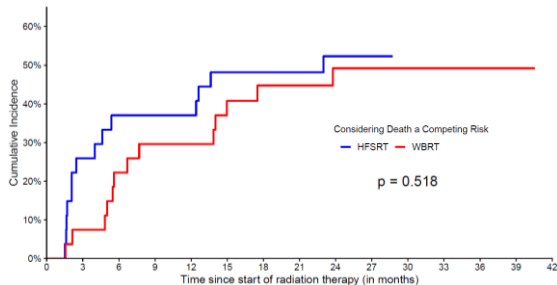


- **Target volumes:**
 - **CTV1:** visible cavity, associated contrast enhancement
 - **CTV2:** CTV1 + 3 mm isotropic expansion, adapted to include meningeal enhancement and resection canal
 - **PTV:** CTV2 + 1 mm isotropic expansion
- **Dose Prescription (@70%-isodose):**
 - **Cavity:** 7 x 5 Gy @70%-isodose (Cavity)
 - **Unresected BM:** 20 Gy (< 2cm), 18 Gy (2-3 cm), 6 x 5 Gy (> 3cm)
- **Treatment Delivery:**
 - Accuray CyberKnife System M6, InCise-2 MLC
 - Stereoscopic X-Ray and intrafractional motion tracking

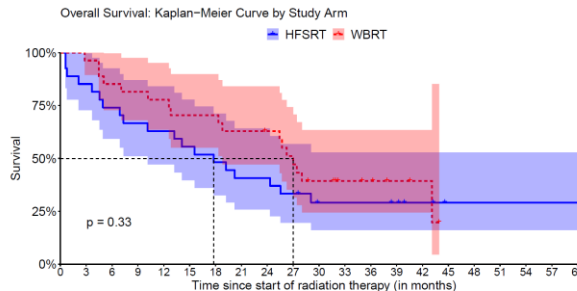


ESTRON – Outcomes

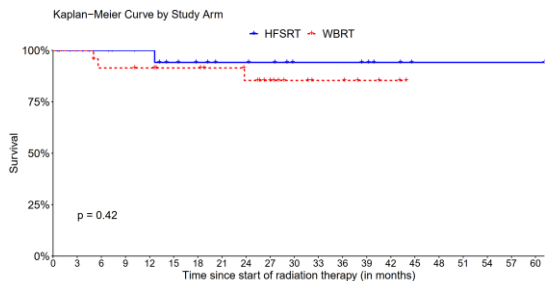
Intracranial control



Overall Survival



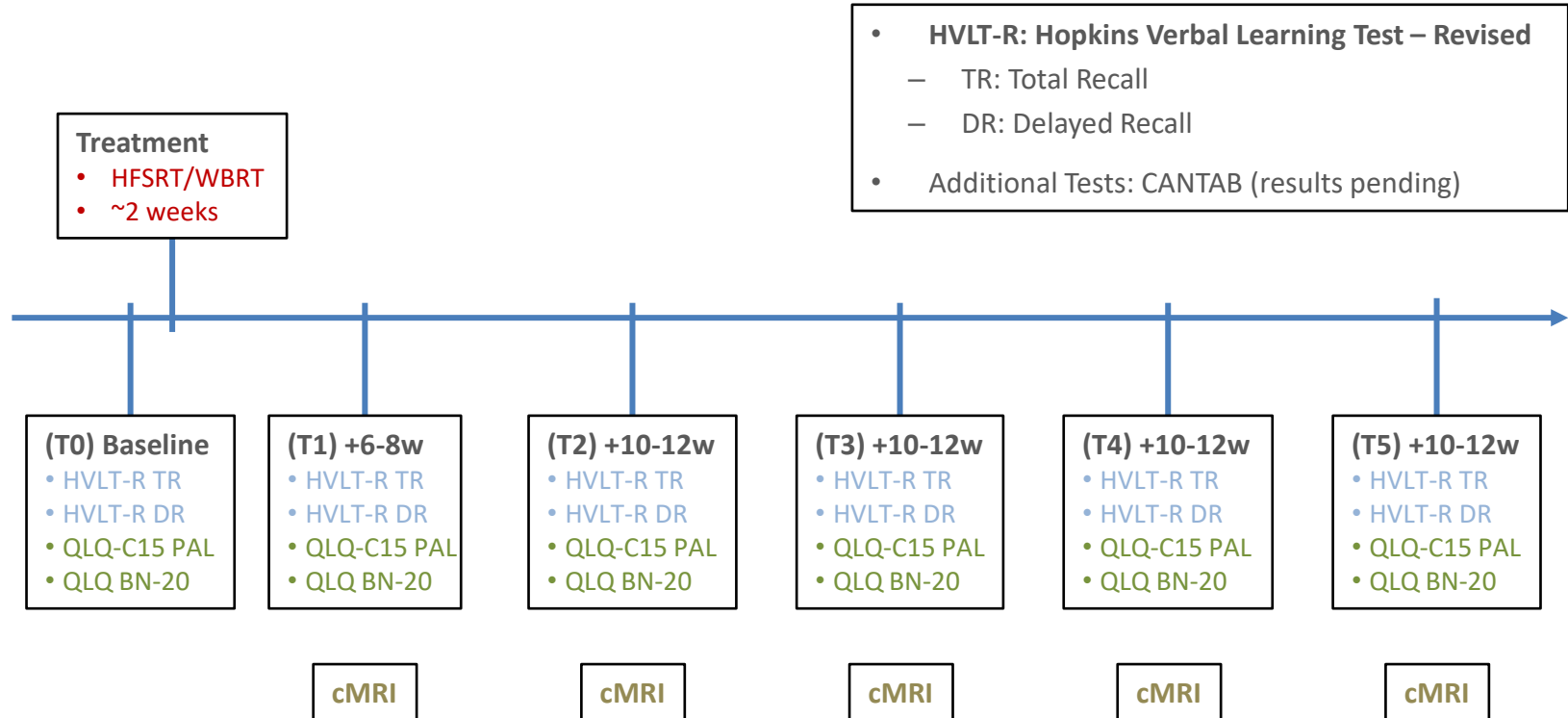
Local Control



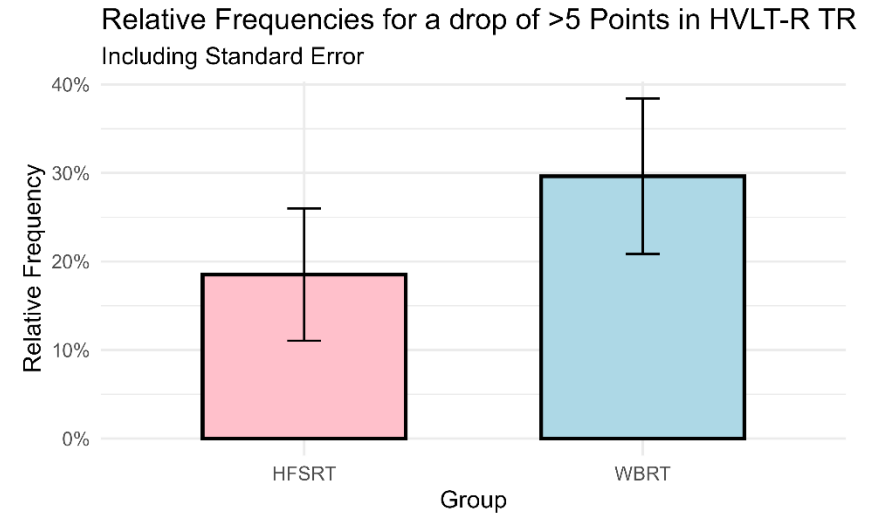
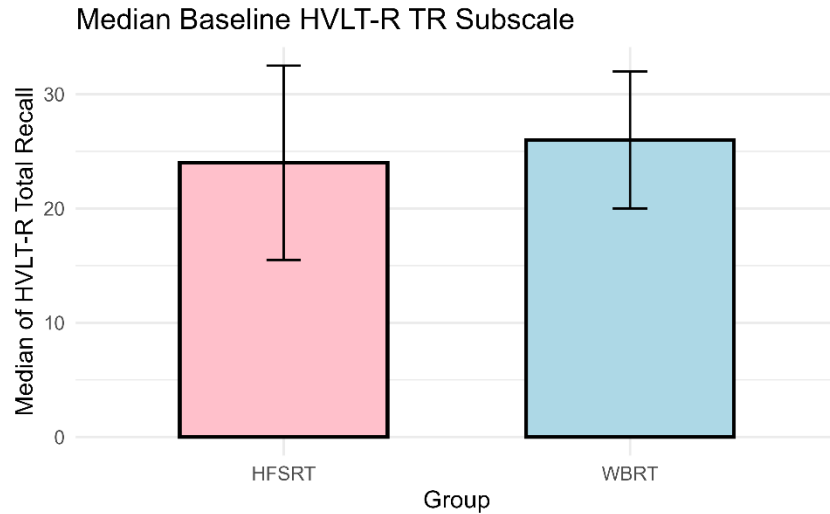
—	27	20	17	13	11	6	6	3	1	1	1
—	27	23	21	19	16	9	5	2	0	0	0

Patterns of failure	HFSRT (n=27)	WBRT (n=27)
Intracranial progression		
• overall	14 (51%)	13 (48%)
• at cavity	1 (7%)	3 (11%)
• distant from cavity	13 (93%)	10 (77%)
Leptomeningeal disease (LMD)		
• overall	7 (26%)	2 (7%)
• at cavity / in field	1 (14%)	1 (50%)
• distant from cavity / out of field	6 (85%)	1 (50%)

- **Intracranial control:**
 - no sign. difference
HR 1.29 (95% CI 0.6-2.7, p=0.518)
- **Local Control:**
 - HFSRT arm: 96%
 - WBRT arm: 89%
- **Patterns of failure:**
 - Relapses **distant from cavity** (both arms)
 - relapses at cavity in WBRT arm ↑ (**11% vs. 7%**)
 - **LMD increased in HFSRT arm (26% vs. 7%)**
 - **LMD almost exclusively distant from cavity in HFSRT arm (6/7 cases)**
- **Safety:**
 - No safety signals
 - sign. less toxicity in HFSRT arm
 - Blood-brain barrier disruption: 15%
- **Conclusion:**
 - HFSRT of the resection cavity provides excellent local control with no increased risk of symptomatic radionecrosis



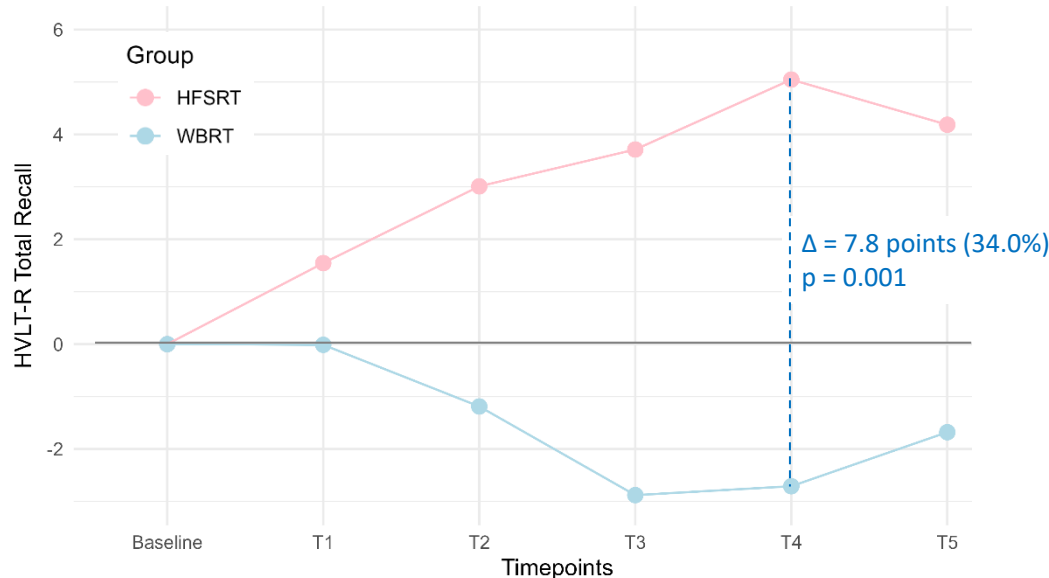
Results – HVLTR-R Total Recall



- **Baseline** HVLTR-R score **slightly lower** in HFSRT group (24 vs. 26 points)
- **Higher** relative frequency of **relevant drop from baseline** in **WBRT** group (18.5% [n=5] vs. 29.6% [n=8])
 - **Risk difference 11%**, 95%-CI [-0.34;0.12], p=0.34

Results – HVLTR Total Recall

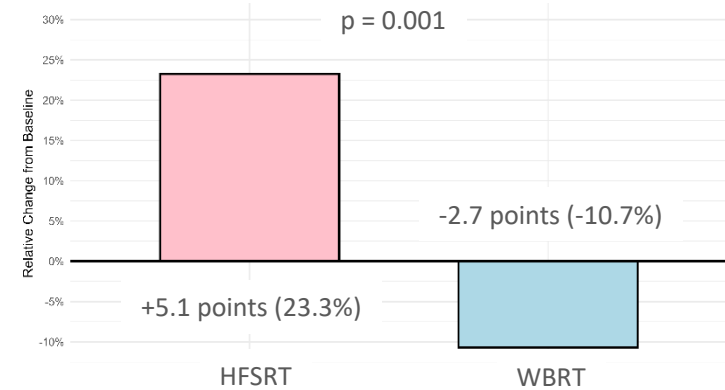
Lineplots of HVLTR Total Recall Means
Adjusted for baseline per group



HFSRT
WBRT

27	20	14	12	12	9
26	24	19	15	11	6

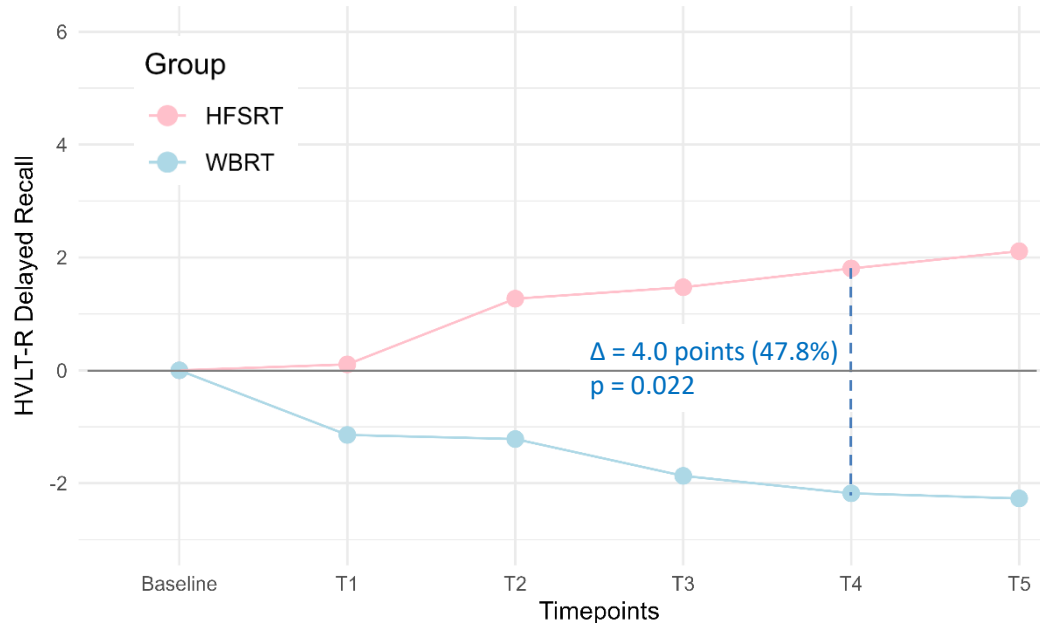
Change from Baseline at ~43 weeks



- **HFSRT:** At no timepoint did the median HVLTR TR score decline from baseline
- **WBRT:** Maximum decline at ~6 months from treatment, followed by partial recovery

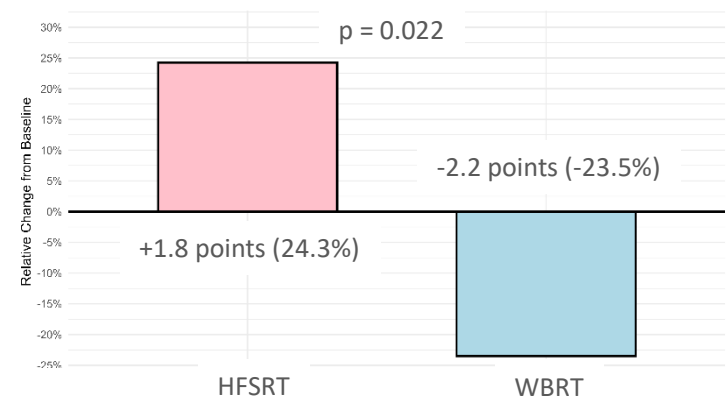
Results – HVLTR Delayed Recall

Lineplots of HVLTR Delayed Recall Means
Adjusted for baseline per group



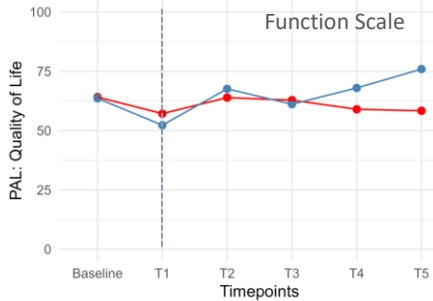
HFSRT	27	20	14	12	12	9
WBRT	26	24	19	15	11	6

Change from Baseline at ~43 weeks



- **HFSRT:** At no timepoint did the median HVLTR TR score decline from baseline
- **WBRT:** Continuous decline from treatment until end of FU (1 year)

Quality of Life – QLQ-C15 PAL



SRS
WBRT

26
27

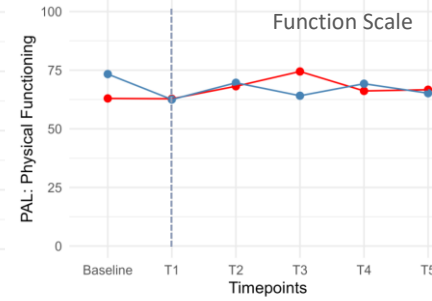
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SRS
WBRT

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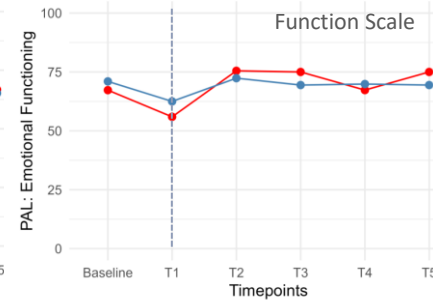
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SRS
WBRT

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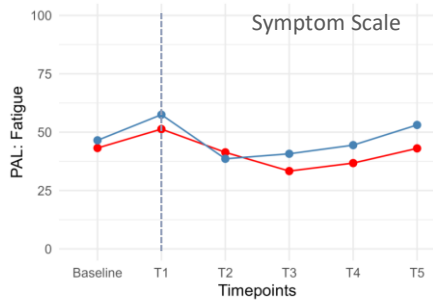
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SRS
WBRT

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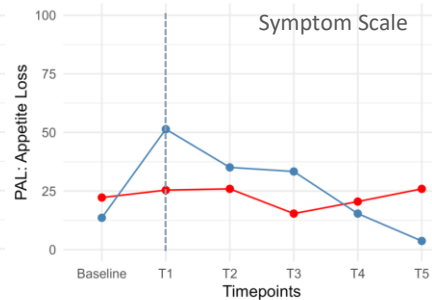
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SRS
WBRT

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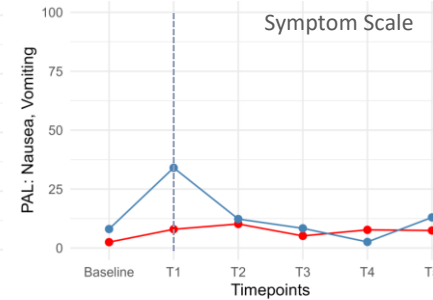
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SRS
WBRT

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- Subscale raw scores converted to value between 0 and 100 according to EORTC QLQ manual
- **Function scales:** greater values = better performance; **Symptom scales:** greater values = increased symptoms

- Overall QoL comparable between groups
 - No difference in **physical and emotional** functioning

- Across subscales: **slight worsening** at 6–8 weeks, followed by recovery
- Subscales with **relevant difference** between groups post-treatment:

- **Appetite loss** (+33.3 pts, SD 13.4, p=0.001)
- **Nausea / vomiting** (+40.3 pts, SD 32.6, p<0.001)

- While providing **excellent local control**, **HFSRT** following BM resection **preserves neurocognition more effectively than WBRT**.
 - **Differences in HVL-R scores most pronounced at 6-8 months** from treatment
 - **No decline from baseline** in HVL-R TR or DR **at any time in HFSRT** group
 - **Descriptive results**, since study was not powered to detect significant difference in neurocognitive testing
- Overall hr-QoL was similar, although **WBRT acutely worsened nausea and appetite loss**.
 - In both groups, symptoms were worst 6-8 weeks post-treatment, followed by recovery.
- **Future questions** in peri-operative radiotherapy of BM:
 - Single-session SRS vs. HFSRT?
 - Pre-operative vs. post-operative SRS/HFSRT?

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patients and their families!**

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