Evidence Based Radiation Oncology Fact Sheets
Brain Metastases

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Chapters

Overview

Epidemiology

- Estimated almost 200,000 new cases in US per year.
  - Incidence increasing, likely due to improvements in systemic therapy and greater use of MRI.
  - On autopsy, ~10-30% of cancer patients have brain metastases.
- Brain mets = 1.7 million cases in a year of all cases, about 4x higher than primary brain cancers.
- About 20-40% of all cancer patients will develop brain mets.
- Most common sites are cerebral hemispheres (80%), cerebellum (15%), brainstem (5%).
- Primary tumors that most frequently metastasize to brain are in order of frequency
  - Lung (≥50%), breast (15–25%), melanoma (5–20%) and, less frequently, testis, kidney, colon–rectum, thyroid, but more in general any cancer subtype can metastasize to the brain.
  - In 15% of cases, the primary site is unknown.
- Bleeding brain mets include: RCC, melanoma, choriocarcinoma.

- **Single metastasis** = only one lesion in the brain, regardless of extra-cranial status.
- **Solitary metastasis** = CNS metastasis as the only site of disease.

Imaging

MRI Thickness Study (SRS)
RR: 28 images acquired with a MRI slice thickness of 1 mm resampled to simulate 2- and 3-mm slice thickness.
102 metastases ranging from 0.0030 cc to 5.08 cc (75-percentile 0.36 cc) were contoured on the original images.
All 3 sets of images were recontoured by experienced physicians.

Thrower, IJROBP 2021.
Results: Of lesions detected/contoured on 1 mm… 3% of lesions were missed on the 2 mm images,
13% of lesions were missed on the 3 mm images.
Lesions were contoured 11% larger on the 2 mm images
Lesions were contoured 43% larger on the 3 mm images
Conclusions: Using images with a slice thickness >1 mm effects detection and segmentation of brain lesions, which can have an important effect on patient management and treatment outcomes.

NOTE: Dedicated "thin-slice SRS protocol" scans are required for SRS TX.

NOTE: In terms of MRI resolution, either SPACE or MPRAGE MRI sequences are both acceptable.
The CYBER-SPACE Phase II trial randomized patients with 1-10 brain mets 1:1 on either sequence → SRS for avoiding or delaying WBRT. Results were comparable. **Shafie, Neuro-Oncology 2025**

Prognostic Factors

- Duration of survival with symptomatic mets:
  - 1 month (NO TREATMENT aka natural course), 2 months (with steroids), 4 months (WBRT alone; Patchell).

- **RPA** I 7 mo KPS > 70 + Age < 65 + 1^{o} controlled + no extracranial mets.
  II 4 mo all others
  (e.g. KPS of 80 with recently diagnosed disease falls into this category since 1^{o} not controlled yet)
  III 2 mo KPS < 70

- **GPA** (Graded Prognostic Assessment) → think high school…you want a **4.0**.

GPA Score	Median OS
0-1	2.6 months
1.5-2.5	3.8 months
3.0	6.9 months
3.5-4.0	11.0 month

Sperduto, IJROBP 2009. Retrospective. 4,259 patients from 11 institutions.
Outcome: For NSCLC/SCLC need 4 prognostic factors (age, KPS, ECM, number of brain mets).
For renal cell/melanoma need 2 prognostic factors (KPS/number of brain mets).
For breast/GI need 1 prognostic factor (KPS).
Conclusion: Significant prognostic factors varied by diagnosis.

DS-GPA	0 Points	0.5	1	2	3	4
NSCLC/SCLC						
Age	>60	50-59	<50	-	-	-
KPS	<70	70-80	90-100	-	-	-
No. Cranial Mets	>3	2-3	1	-	-	-
Extra-cranial Mets	Present	-	Absent	-	-	-
Renal/Melanoma						
KPS	<70	-	70-80	90-100	-	-
No. Cranial Mets	>3	-	2-3	1	-	-
Breast/GI						
KPS	<70	-	70	80	90	100

PA Score	Overall Survival (months)					
	NSCLC	SCLC	Melanoma	Renal cell	Breast	GI
0-1	3.0	2.8	3.4	3.3	6.1	3.1
1.5-2.5	6.5	5.3	4.7	7.3	9.4	4.4
3.0	11.3	9.6	8.8	11.3	16.9	6.9
3.5-4.0	14.8	17.0	13.2	14.8	18.7	13.5
Overall	7.0	4.9	6.7	9.6	11.9	5.4

Sperudto, JCO 2020 **https://brainmetgpa.com/#start**
Retrospective, 6,984 patients with newly diagnosed brain metastases.
Conclusion
Median survival varies widely and our ability to estimate survival for patients with brain metastases has improved. The updated GPA (available free at brainmetgpa.com) provides an accurate tool with which to estimate survival, individualize treatment, and stratify clinical trials. Instead of excluding patients with brain metastases, enrollment should be encouraged and those trials should be stratified by the GPA to ensure those trials make appropriate comparisons. Furthermore, we recommend the expansion of eligibility to allow for the enrollment of patients with previously treated brain metastases who have a 50% or greater probability of an additional year of survival (eligibility quotient > 0.50).

NOTE: BMs from patients having BM treated with SRS from GI primaries N=102 (vs. Non-GI primaries N=1281) have a significantly poorer outcome despite excellent local control from SRS (2%). Qazi et. al. (Adv Radiat Oncol 2025) showed:
Intracranial PFS Median 6.2 months vs. 12.3 months
OS Median 5.4 months vs. 10.6 months
And, GI patients are younger (mean 59.1 vs 63.5 years, *P* = .001), male (56.9% vs 44.3%, *P* = 0.014), received systemic therapy (73.5% vs 63.9%, *P* = .049), and have resection of BM (45.1% vs 25.0%, *P* < .001) prior to radiosurgery.

Radiation Technique

CT Sim

- CT w/ contrast (thin slice SRS Protocol)
- Face Mask (short): can also consider frameless SRS Protocol
- Fusion: Thin-slice MRI, high-resolution T1 scans w/ contrast: e.g. MPRAGE
  - For Post-op Cavity Treatment: Pre-op and Post-op MRI Sequences

- **NOTE**: While thin slice MRI is a must, either SPACE or MPRAGE MRI sequences have 1-year WBRTi-free survival ~ 77%.
  - CYBER-SPACE Phase II trial randomized patients with 1-10 brain mets 1:1 on either sequence + SRS for avoiding or delaying WBRT. **Shafie, Neuro-Oncology 2025**

- **NOTE**: A single isocenter SRS plan can be used to treat many lesions.
  - Local Failure is not associated with distance to isocenter.
  - Local Failure can be associated with size (Kraft Study below) and certainly dose.

Sample SRS (Gamma Knife) Procedure:

- Arrive by 6 am.
- Local anesthesia by neurosurgeon and application of stereotactic GK frame.
- SRS MRI protocol 1 mm thin slices with IV contrast.
- Import and discuss with neurosurgeon which lesions to ID and treat.
- Contour all lesions.
- Place shots.
- Plan evaluation and QA (for collision > 4 mm)
- Consider dexamethasone short course before SRS.

Fun Facts! GK contains 192 individual sources of cobalt-60.

Single-isocenter multiple-target (SIMT) Study
RR 140 patients and 708 patients treated with SIMT SRT.
Evaluation of LR based on distance to isocenter.
LR compared to patients treated with single-isocenter-single-target (SIST) approach.

Kraft, Radiotherapy & Oncology 2021 Median FU 13.9 mo SIMT, 11.9 mo SIST.
1-year FFLR 94% SIMT vs. 87% SIST.
Median distance to isocenter (DTI) was 4.7 cm (range 0.2–10.5) in the SIMT group.
Local recurrence-free interval was not associated with the distance to the isocenter in univariable or multivariable Cox-regression analysis. Multivariable analysis revealed only **volume** as an independent significant predictor for local failure (*p*-value <0.05).
Conclusion SRS/SRT using single-isocenter VMAT for multiple targets achieved high local metastases control rates irrespective of distance to the isocenter, supporting efficacy of single-isocenter stereotactic radiation therapy for multiple brain metastases.

Some important technical considerations:

ISRS Technical Guidelines for Stereotactic Radiosurgery: Treatment of Small Brain Metastases (≤1 cm in Diameter)
Grishchuk, PRO 2022

Immobilization device	Device characteristics
Gamma Knife Leksell G frame	IGRT: CBCT (starting from Icon model) Patient positioning accuracy: (0.44 ± 0.19) mm (mean ± SD) – film measurements inside phantom[72] (0.48 ± 0.23) mm (mean ± SD) - film measurements inside phantom[73] Positioning tracking: No Intrafraction motion: Translation: X (0.05 ± 0.04) mm Y (0.03 ± 0.02) mm Z (0.08 ± 0.07) mm Rotation: X (0.03 ± 0.03)° Y (0.07 ± 0.07)° Z (0.07 ± 0.13)° (ref. [74]) Values relate to: Difference between patient's pre- and post-treatment CBCT
LINAC frame	IGRT: Orthogonal x-rays, CBCT Patient positioning accuracy: (1.0 ± 0.5) mm - orthogonal x-rays (ExacTrac) patient measurements[63] Positioning tracking: No Intrafraction motion: (0.40 ± 0.3) mm - ExacTrac patient measurements[63] (0.30 ± 0.21) mm - ExacTrac patient measurements[75] Values relate to: ExacTrac patient measurements
Gamma Knife SRS mask	IGRT: CBCT Patient positioning accuracy: (0.5 ± 0.6) mm[76] Positioning tracking: HDMM system (tracking accuracy 0.15 mm)[76] Intrafraction motion: (0.62 ± 0.25) mm after correction based on pre-treatment CBCT[77] Values relate to: Observed movements during treatment based on HDMM marker position (used a displacement HDMM threshold of 1.5 mm)
Actina PinPoint bite-block system	IGRT: CBCT + 6-DoF robotic couch (HexaPod) Patient positioning accuracy: 6-DoF robotic couch positioning accuracy ± 0.3 mm and ± 0.2° (ref. 76) Positioning tracking: Alarm if vacuum is lost[75] Intrafraction motion: (0.45 ± 0.33) mm – difference between pre- and posttreatment patient's CBCT[75]
Brainlab mask	IGRT: Orthogonal x-rays + 6-DoF robotic couch Patient positioning accuracy: (0.7 ± 0.3) mm – hidden target test[63] Positioning tracking: Infrared optical-tracking system for couch Intrafraction motion: (0.35 ± 0.21) mm – patient's pre- and posttreatment x-ray[78] (0.7 ± 0.5) mm – patient's pre- and post-treatment x-ray[63]
CyberKnife mask	IGRT: Orthogonal x-rays + 6-joint robotic treatment couch (RoboCouch, Accuray, Inc)[79] Positioning tracking: Repeated x-ray image acquisitions at a user-defined frequency (typically every 30-60 s) Intrafraction motion: Translation: X (0.27 ± 0.61) mm Y (0.24 ± 0.62) mm Z (0.14 ± 0.24) mm Rotation: X (0.13 ± 0.21)° Y (0.18 ± 0.25)° Z (0.28 ± 0.44)° (ref. [80]) Based on patient measurements during treatment with 6D-skull tracking
SGRT open masks	IGRT: CBCT Patient positioning accuracy: Not published Positioning tracking: Tracking 1D accuracy 0.1 ± 0.1 mm[81]

SRS Contour and Eval

(Per ALLIANCE and Institutional Protocols) **NOTE:** C.I. (conformity index) = Prescription IDL Volume (PIV) / PTV

- Intact Lesions:
  - PTV = GTV (C.I. ~ ≤ 1.2 ideally, ≤ 1.5 accepted)
  - Many centers consider a margin, PTV = GTV + 0.1 cm (~C.I. 1.0).
  - **NOTE**: In theory, a C.I. > 1.0 functions effectively as a contoured margin.
    This above can be demonstrated in a simple evaluation:

    A spherical 2.0 cm diameter lesion would yield a 4.19 cc volume of GTV ($V = 4/3\,\pi\,r^3$).
    Plan A (1 mm margin): PTV = GTV + 0.1 cm (C.I.~1.0) → PIV = 5.58 cc x 1.0 = 5.58 cc (= PTV)
    Plan B (0 mm margin): PTV + GTV + 0.0 cm (C.I. ~1.2) → PIV = 4.19 cc x 1.2 = 5.03 cc (> PTV)

    In both plans, the PIVs are more than the contoured GTV (as expected).
    Regarding the actual "additional % of coverage outside GTV," which is *not exactly* the definition of C.I…
    Plan A: 5.58 cc / 4.19 cc = 1.33 ~ 33% more GTV volume treated.
    Plan B: Depending on CI 1.2 – 1.5 ~ 20% - 50% more GTV volume treated.
  - **NOTE**: In complex plans (multi-target, post-surgical, non-spherical, single isocenter), the usefulness of a C.I. is diminished compared to a single spherical lesion.

- Post-op Cavities (ALLIANCE Protocol)
  - GTV = POST-OP MRI C+ T1.
  - CTV = GTV + 2mm PTV = CTV
  - ARM A Single fraction
  - ARM B Multi fraction if < 30 cc = 9 Gy x 3 if > 30 cc = 6 Gy x 5

Excellent Review: Minniti Radiat Oncol 2021 https://www.biomedcentral.com/epdf/10.1186/s13014-021-01802-9
Current status and recent advances in **resection cavity irradiation** of brain metastases

Table 4 Summary of imaging modalities for target volumes delineation and dose/fractionations for postoperative resection cavity of brain metastases

Imaging for target delineation	Isotropic post-contrast-enhanced 3D T1-weighted MRI sequences with 1 mm thick slices and T2-weighted images. Additional images include preoperative contrast-enhanced T1-weighted MRI sequences to identify the preoperative tumor extent and dural involvement
Gross Tumor Volume (GTV)	Surgical cavity on postoperative contrast-enhanced T1-weighted MR images (typically represented by the rim of enhancement at the edge of the resection cavity) with inclusion of any residual nodular enhancement
Clinical Tumor Volume (CTV)	The CTV is defined as the GTV plus 0–1 mm margins constrained at anatomical barriers such as the skull. GTV-to-CTV margins up to 5–10 mm are applied along the bone flap/meningeal margin, with larger margins used for tumors in contact with the dura preoperatively. Vasogenic edema and surgical corridor (for deep lesions) are not usually included
Planning Target Volume (PTV)	A margin of up to 3 mm is usually added to the CTV to generate the PTV, depending on the radiation technique. For frame-based SRS, no additional safety margin is necessary; with frameless SRS and SRT, a GTV-to-PTV safety margin of 1–3 mm is usually applied according to Institutional practice
Timing of treatment	There is a general consensus to perform postoperative SRS/HSRT to the resection cavity within 4 weeks after surgery with planning MRI acquired < 7 days before treatment to limit negative impact of cavity changes on clinical outcomes
Dose and fractionation	12–18 Gy using single-fraction SRS; 24–27 Gy in 3 fractions and 30–35 Gy in 5 fractions using HSRT, typically for larger resection cavity; less commonly 30–40 Gy in 10 fractions

SRS, stereotactic radiosurgery; HSRT, hypofractionated stereotactic radiation therapy; MRI, magnetic resonance imaging; 3D, 3-dimensional

NOTE: Singh PRO 2025 ←M→ evaluated the Impact of PTV Margins on LC and RN (Radionecrosis) in SRS for Brain Metastases. Median SRS 21 Gy in 1 fraction. 7 studies, 1360 lesions SRS no margin and 3684 SRS with a margin.

1-year LC	**margin** vs. no margin	**88.4%** vs. 83.0% ($P = 0.28$).
Radiographic RN after SRS		9.2% vs. 7.0% ($P = 0.56$)
Symptomatic RN after SRS		4.1% vs. 8.6% ($P = .24$).

Note: Gamma Knife **Gradient Index** = Volume of 50% of Prescription IDL / **Chosen Prescription IDL**

*Recall: **R50%** = Volume of 50% of Prescription IDL / **PTV***

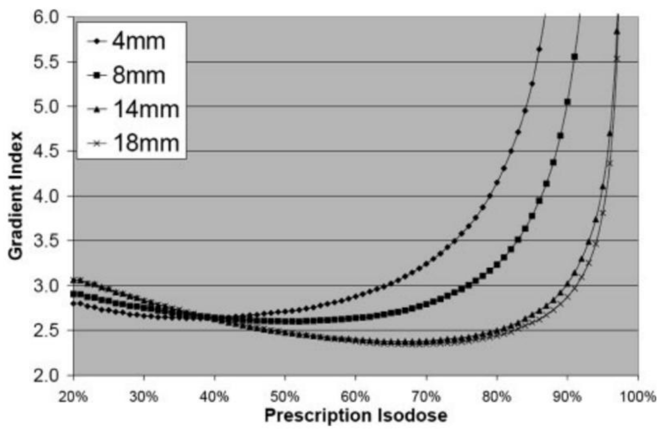


FIG. 4. Graph showing the variation of the proposed GI against the prescription isodose line for individual collimators.

For a plan normalized to the 50% IDL, it is the ratio of the 25% isodose volume (PIV25%) to the 50% isodose volume (PIV50%), whereas for a plan normalized to the 60% isodose line, it is PIV60%/PIV30%.

TABLE 3

Summary of data contained in Fig. 4

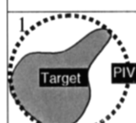
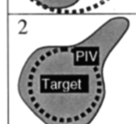
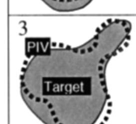
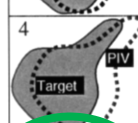
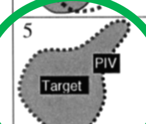
Factor	Value			
collimator size (mm)	4	8	14	18
GI for 50% prescription isodose	2.71	2.71	2.52	2.51
optimal prescription isodose (%)	38	52	66	68
GI for optimal prescription isodose	2.63	2.60	2.37	2.34
percent difference between GI for 50% & optimal GI (%)	3.0	4.1	6.0	6.8

Definitions:

PITV	Conformity Index
PIV	Prescription Isodose Volume
TV	Target Volume
PITV = C.I. = PTV / TV	
TVR	Inverse of PITV or C.I.
TV_{PIV}	TV covered by PIV

Paddick recommends a new index, P. CI = TV_{PIV}^2 / (TV x PIV).

Note: Isodose plans 3 and 4 are exactly why we cannot simply rely on a C.I. without properly evaluating the plan slice per slice and evaluating the DVH coverage.

Isodose Plan	Parameters	PITV $\frac{PIV}{TV}$	RCI_i $\frac{TV_{PIV}}{TV}$	Proposed Index $\frac{TV_{PIV}^2}{TV \times PIV}$
1 	$TV = 5cm^3$ $TV_{PIV} = 5cm^3$ $PIV = 10cm^3$	2.00	**1.00**	0.50
2 	$TV = 5cm^3$ $TV_{PIV} = 3cm^3$ $PIV = 3cm^3$	0.60	0.60	0.60
3 	$TV = 5cm^3$ $TV_{PIV} = 4cm^3$ $PIV = 5cm^3$	**1.00**	0.80	0.64
4 	$TV = 5cm^3$ $TV_{PIV} = 3cm^3$ $PIV = 5cm^3$	**1.00**	0.60	0.36
5 	$TV = 5cm^3$ $TV_{PIV} = 5cm^3$ $PIV = 5cm^3$	1.00	1.00	1.00

Retrospective Margin Conformity Matters
RR 72 patients with 76 cavities SRS median marginal dose of 18.6 Gy (range, 15–30 Gy) targeting an average tumor volume of 9.8 cc.

Soltys, IJROBP 2008.
Actuarial LC at 6 and 12 months were 88% and 79%, respectively.

Table 2. Analysis of the additional margin of the PIV on the TIV per CI quartile if volumes are converted to an idealized spherical volume (4/3 π radius^3)

CI quartile	Median CI per quartile	Median volumes per quartile (cm^3)	Corresponding radius of idealized spherical volume (mm)	Additional margin of PIV on TIV (mm)	Local control per quartile (%)
Most conformal	1.22	TIV = 8.50	12.7	0.8	43
		PIV = 10.37	13.5		
	1.37	TIV = 10.80	13.7	1.5	52
		PIV = 14.80	15.2		
	1.50	TIV = 7.20	12.0	1.7	78
		PIV = 10.80	13.7		
Least conformal	1.76	TIV = 5.80	11.1	2.4	100
		PIV = 10.21	13.5		

Abbreviations: TIV = target isodose volume; PIV = prescription isodose volume; CI = conformality index.

Conclusions
In this retrospective series, SRS administered to the resection cavity of brain metastases resulted in a 79% local control rate at 12 months. This value compares favorably with historic results with observation alone (54%) and postoperative WBI (80–90%). Given the improved local control seen with less conformal plans, **we recommend inclusion of a 2-mm margin around the resection cavity when using this technique**.

Soliman Contouring CONSENSUS, IJROBP 2018.
SUMMARY 3 considerations: 1. Surgical Cavity/Tract 2. Bone Flap 3. Sinus.
1. CTV include the entire contrast-enhancing surgical cavity (use T1 gadC+ axial MRI scan).
2. Excluding edema
3. CTV should include entire surgical tract seen on postoperative CT or MRI
4. If tumor was in contact with the dura preoperatively, CTV should include a 5- to **10-mm margin** along the bone flap beyond the initial region of preoperative tumor contact
5. If the tumor was not in contact with the dura, CTV should include a margin of 1 to **5 mm** along the bone flap
6. If the tumor was in contact with a venous sinus preoperatively, CTV should include a margin of 1 to **5 mm** along the sinus

SRS Dose

- Intact lesions and Post-op Cavities are treated similarly per volume.

- Diameter

≤ 2.0 cm	21-24 Gy in 1 fraction		
2.0-2.5 cm	18 Gy in 1 fraction		
2.5- 3.0 cm	27 Gy in 3 fractions	or	30 Gy in 5 fractions
≥ 3.0 cm / 30 cc (volume)	30 Gy in 5 fractions		

NOTE: A sphere with 4 cm diameter → volume = 33.5 cc.

Recall:

20 Gy in 1 fraction	EQD2 50.00 Gy	BED_{10} 60.0 Gy
18 Gy in 1 fraction	EQD2 42.00 Gy	BED_{10} 50.4 Gy
17 Gy in 1 fraction	**EQD2 38.25 Gy**	**BED_{10} 45.9 Gy**
15 Gy in 1 fraction	EQD2 31.25 Gy	BED_{10} 37.5 Gy
14 Gy in 1 fraction	EQD2 28.00 Gy	BED_{10} 33.6 Gy
27 Gy in 3 fraction	EQD2 42.75 Gy	BED_{10} 51.3 Gy
30 Gy in 5 fraction	EQD2 40.00 Gy	BED_{10} 48.0 Gy

Prescription Specification: The dose should be prescribed to the highest isodose line encompassing the PTV which can range from 45% to 95% of the maximum dose. Steep dose falloff is necessary.

UAB Hypofractionated Dose Study
RR 251 patients with 1215 brain tumors receiving either 9 Gy x 3 fx or 6 Gy x 5 fx fSRS.
All single Isocenter VMAT. Exclusion: recurrent tumors and post-operative cavities.
LF = 25% ↑ in max tumor diameter (minimum 3 mm) or more than scant tumor cells at time of salvage surgery.

	Total	9 Gy x 3 fx	6 Gy x 5 fx
Number of tumors	1215	256	959
< 2 cm	977	226	751
2 – 4 cm	230	**30**	**200**
> 4 cm	16	8	8

Moradi, Advances in Radiation Oncology 2025

Overall LC	1-year LC 93%		
	2-years LC 88%.		
Per Fraction LC	1-year LC	All Sizes	3-fraction 97% vs. 5-fraction 91% (*p* = 0.001)
		Due to Median tumor diameter (cm) 0.77 vs. 0.98 (p= <0.001)	
Per Size LC	1-year LC	Tumors <2	3-fraction 99% vs. 5-fraction 95% (*p* = 0.004)
		Tumors 2–4 cm	2-years 60-65% NS

One-year freedom from grade 3+ toxicity was similar between regimens (99% for 3-fx vs. 96% for 5-fx, *p* = 0.097).
Conclusions
In this study, 9 Gy x 3 fx for brain metastases had ↑ tumor control and comparable toxicity to 6 Gy x 5, particularly among tumors < 2cm. 9 Gy x 3 fx may be the preferred regimen when treating multiple tumors with one prescription using single isocenter radiosurgery as it improves efficiency and LC while having similar toxicity.

NOTE: Often, tumors < 2 cm are treated institutionally with 1 fraction SRS only. Larger tumors > 2 cm are treated either 3 fractions or 5 fractions per institution guidelines.

RTOG 90-05 Dose escalation study.
Phase I/II 156 patients.
Recurrent primary brain tumors (36%) or metastases (64%) ≤ 4 cm after receiving previously treated RT ≥ 3 months prior.
Maximum results tolerated Gray were 24, (≤ 2cm) 18 (2.1-3 cm), 15 (3.1-4cm).

Shaw, IJROBP 2000
Radionecrosis 11% at 2 years.
Note: Study does not determine max tolerated dose.
At 24 Gy with excellent LC, there was no need to risk ↑ dose and ↑ toxicity.
Grade 3-5 neuro toxicity associated with tumor size, dose, and KPS.
Tumor diameter > 3 cm had a much higher risk of toxicity on multivariate analysis compared to smaller tumors.
Compared to tumors < 20 mm in max diameter, tumors 21–30 OR 7.3 risk of unacceptable CNS toxicity.
Tumors 31–40 mm had OR 16.0.
Conclusions: The maximum tolerated doses of single fraction radiosurgery were defined for this population of patients as 24 Gy, 18 Gy, and 15 Gy for tumors ≤ 20 mm, 21–30 mm, and 31–40 mm in maximum diameter. Unacceptable CNS toxicity was more likely in patients with larger tumors, whereas local tumor control was most dependent on the type of recurrent tumor and the treatment unit.

Dose Constraints

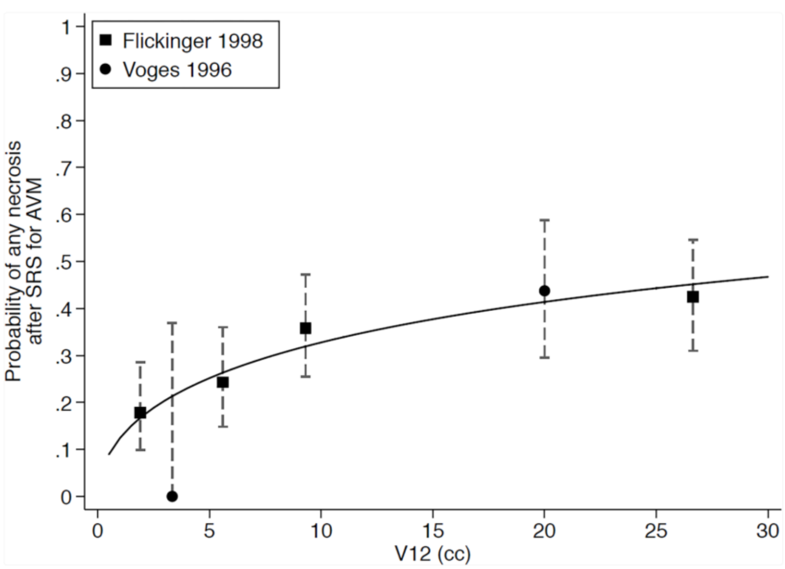
CNS SRS Guidelines

TG 101 Single Fraction

Optic Nerve	< 0.2 cc	8 Gy	Dmax 10	Institutional Dmax 8
Cochlea			Dmax 9	Institutional Dmax 4.2 (Recall: Dmax conventional is 40)
Brainstem	< 0.5 cc	10 Gy	Dmax 15	Institutional V12 < 1cc
Cord/Medulla	< 0.35cc	10 Gy	Dmax 14	
	< 1.2 cc	7 Gy		
Cord Sub-volume 5-6 mm ↑↓	< 10%	10 Gy	Dmax 14	
Cauda/sacral plexus	< 5 cc	14 Gy	Dmax 16	
Brachial plexus	< 3 cc	14 Gy	Dmax 17.5	
	Blonigen, IJROBP 2010			
Brain	**V10 < 10 cc or**		**V12 < 8 cc**	If exceeds → Must hypofractionate. Institutional: minimize 12 Gy line.

Studies with Multi Fractions

	Minniti, IJROBP 2013			
Brain – GTV	3-fractions	V24 > 16.8 cc	16%	radionecrosis
		V24 < 16.8n cc	2%	radionecrosis
	Milano, IJROBP 2021 (Below)			
Brain + Target Volume	3-fractions	V 20 < 20 cc	<10%	necrosis or edema
	5-fractions	V 24 < 20 cc	<4%	radionecrosis require resection



HyTEC Milano, IJROBP 2021
NOTE: For single-fraction SRS to brain metastases… Tissue volumes (including target volumes) receiving 12 Gy (V12) of 5 cm^3, 10 cm^3, or >15 cm^3 were associated with risks of symptomatic radionecrosis of approximately 10%, 15%, and 20%, respectively.

SRS for AVM was associated with lower rates of symptomatic radionecrosis for equivalent V12.

For brain metastases, brain plus target volume V20 (3-fractions) or V24 (5-fractions) <20 cm^3 was associated with <10% risk of any necrosis or edema, and <4% risk of radionecrosis requiring resection.

https://pubmed.ncbi.nlm.nih.gov/32921513/

SAFESTEREO Table 2

Table 2 Organs at risk dose constraints

	1 fraction (Gy)		3 fractions (Gy)		5 fractions (Gy)	
	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory
Brainstem Dmax	10	18	24	27	23	30
Cochlea Dmean	4	9	17	20	22	25
Chiasm Dmax	8	10	15	23	20	25
Lens Dmax	1	3	2	4	3	5
Optic nerves Dmax	8	10	15	23	22	25
Pituary gland Dmean	8	10	15	23	22	25

Dmax Maximum dose, *Dmean* Mean dose

UK SABR Constraints: https://pubmed.ncbi.nlm.nih.gov/29033164/

Constraints only exist for 1 fraction SRS	Normal Brain	D10 cc < 12 Gy	**No 5 fx SRS normal brain limits**
	WB – GTV	D 50% < 5 Gy	

Cochelea Studies (Ishak, PRO 2024)

	Conventional RT	Single fraction SRS	Fractionated SRS[5]
Mean dose	<35 Gy (<45 Gy acceptable)	<4 Gy[5]	<17.1 Gy per fraction (3 fractions) <25 Gy (5 fractions)
Max Dose	<60 Gy	4 Gy to cochlea modiolus[2]	

Timmerman Tables 2021

https://www.redjournal.org/article/S0360-3016(21)02831-5/fulltext

Table 2 Timmerman tables, 1 fraction—Timmerman, 8-2021

Serial tissue	Volume, cm3	Volume max (Gy)	Max point dose (Gy)*	Endpoint (grade ≥3)
Optic pathway	<0.2	8	10	Neuritis
Cochlea			9	Hearing loss
Brain stem (not medulla)	<0.5	10	15	Cranial neuropathy
Spinal cord and medulla	<0.35	10	14	Myelitis
Cauda equina	<5	14	16	Neuritis
Sacral plexus	<5	14.4	16	Neuropathy
Esophagus†	<5	20	24	Esophagitis
Brachial plexus	<3	13.6	16.4	Neuropathy
Peripheral (named) nerve	<2 cm length	16	20	Neuropathy
Heart/pericardium	<15	16	22	Pericarditis
Great vessels	<10	31	37	Aneurysm
Trachea and large bronchus†	<4	27.5	30	Impairment of pulmonary toilet
Bronchus, smaller airways	<0.5	17.4	20.2	Stenosis with atelectasis
Rib	<5	28	33	Pain or fracture
Skin	<10	25.5	27.5	Ulceration
Stomach	<5	17.4	22	Ulceration/fistula
Bile duct			30	Stenosis
Duodenum†	<5	17.4	22	Ulceration
Jejunum/ileum†	<30	17.6	20	Enteritis/obstruction
Colon†	<20	20.5	31	Colitis/fistula
Rectum†	<3.5 <20	30 23	33.7	Proctitis/fistula
Ureter			35	Stenosis
Bladder wall	<15	12	25	Cystitis/fistula
Penile bulb	<3	16		Erectile dysfunction
Femoral heads	<10	15		Necrosis
Renal hilum/vascular trunk	15	14		Malignant hypertension
Parallel tissue	**Critical volume (cm^3)**	**Critical volume dose max (Gy)**	**Max point dose (Gy)***	**Endpoint (grade ≥3)**
Lung (right and left)	1500 for males and 950 for females†	7.2		Basic lung function
Lung (right and left)			V-8 Gy <37%	Radiation pneumonitis
Liver	700‡	11.6		Basic liver function
Renal cortex (right and left)	200‡	9.5		Basic renal function

* "Point" defined as ≤0.035 cm^3.
† Avoid circumferential irradiation.
‡ One-third of the "native" total organ volume (before any resection or volume reducing disease), whichever is greater.

Table 4 Timmerman tables, 3 fractions—Timmerman, 8-2021

Serial tissue	Volume	Volume max (Gy)	Max point dose (Gy)*	Endpoint (grade ≥3)
Optic pathway	<0.2 cm^3	15.3	17.4	Neuritis
Cochlea			14.4	Hearing loss
Brain stem (not medulla)	<0.5 cm^3	15.9	23.1	Cranial neuropathy
Spinal cord and medulla	<0.35 cm^3	15.9	22.5	Myelitis
Cauda equina	<5 cm^3	21.9	25.5	Neuritis
Sacral plexus	<5 cm^3	22.5	25.5	Neuropathy
Esophagus†	<5 cm^3	27.9	32.4	Esophagitis
Brachial plexus	<3 cm^3	22	26	Neuropathy
Peripheral (named) nerve	<2 cm length	25.5	30.6	Neuropathy
Heart/pericardium	<15 cm^3	24	30	Pericarditis
Great vessels	<10 cm^3	39	45	Aneurysm
Trachea and large bronchus†	<5 cm^3	39	43	Impairment of pulmonary toilet
Bronchus, smaller airways	<0.5 cm^3	25.8	30	Stenosis with atelectasis
Rib	<5 cm^3	40	50	Pain or fracture
Skin	<10 cm^3	31	33	Ulceration
Stomach	<5 cm^3	22.5	30	Ulceration/fistula
Bile duct			36	Stenosis
Duodenum†	<5 cm^3	22.5	30	Ulceration
Jejunum/ileum†	<30 cm^3	20.7	28.5	Enteritis/obstruction
Colon†	<20 cm^3	28.8	45	Colitis/fistula
Rectum†	<3.5 cm^3	43	47	Proctitis/fistula
	<20 cm^3	30.3		
Ureter			40	Stenosis
Bladder wall	<15 cm^3	17	33	Cystitis/fistula
Penile bulb	<3 cm^3	25		Erectile dysfunction
Femoral heads	<10 cm^3	24		Necrosis
Renal hilum/vascular trunk	15 cm^3	19.5		Malignant hypertension
Parallel tissue	**Critical volume (cm^3)**	**Critical volume dose max (Gy)**		**Endpoint (grade ≥3)**
Lung (right and left)	1500 for males and 950 for females†	10.8		Basic lung function
Lung (right and left)			V-11.4 Gy <37%	Pneumonitis
Liver	700‡	17.7		Basic liver function
Renal cortex (right and left)	200‡	14.7		Basic renal function

* "Point" defined as ≤0.035 cm^3.
† Avoid circumferential irradiation.
‡ One-third of the "native" total organ volume (before any resection or volume reducing disease), whichever is greater.

Table 6 Timmerman tables, 5 fractions—Timmerman, 8-2021

Serial tissue	Volume	Volume max (Gy)	Max point dose (Gy)*	Endpoint (grade ≥3)
Optic pathway	<0.2 cm^3	23	25	Neuritis
Cochlea			22	Hearing loss
Brain stem (not medulla)	<0.5 cm^3	23	31	Cranial neuropathy
Spinal cord and medulla	<0.35 cm^3	22	28	Myelitis
Cauda equina	<5 cm^3	30	31.5	Neuritis
Sacral plexus	<5 cm^3	30	32	Neuropathy
Esophagus†	<5 cm^3	32.5	38	Esophagitis
Brachial plexus	<3 cm^3	27	32.5	Neuropathy
Peripheral (named) nerve	<2 cm length	31.5	38	Neuropathy
Heart/pericardium	<15 cm^3	32	38	Pericarditis
Great vessels	<10 cm^3	47	53	Aneurysm
Trachea and large bronchus†	<5 cm^3	45	50	Impairment of pulmonary toilet
Bronchus, smaller airways	<0.5 cm^3	32	40	Stenosis with atelectasis
Rib	<5 cm^3	45	57	Pain or fracture
Skin	<10 cm^3	36.5	38.5	Ulceration
Stomach	<5 cm^3	26.5	35	Ulceration/fistula
Bile duct			41	Stenosis
Duodenum†	<5 cm^3	26.5	35	Ulceration
Jejunum/ileum†	<30 cm^3	24	34.5	Enteritis/obstruction
Colon†	<20 cm^3	32.5	52.5	Colitis/fistula
Rectum†	<3.5 cm^3	50	55	Proctitis/fistula
	<20 cm^3	37.5		
Ureter			45	Stenosis
Bladder wall	<15 cm^3	20	38	Cystitis/fistula
Penile bulb	<3 cm^3	30		Erectile dysfunction
Femoral heads	<10 cm^3	30		Necrosis
Renal hilum/vascular trunk	15 cm^3	23		Malignant hypertension
Parallel tissue	**Critical volume (cm^3)**	**Critical volume dose max (Gy)**	**Max point dose (Gy)***	**Endpoint (grade ≥3)**
Lung (right and left)	1500 for males and 950 for females‡	12.5		Basic lung function
Lung (right and left)			V-13.5 Gy <37%	Pneumonitis
Liver	700‡	21.5		Basic liver function
Renal cortex (right and left)	200‡	17.5		Basic renal function

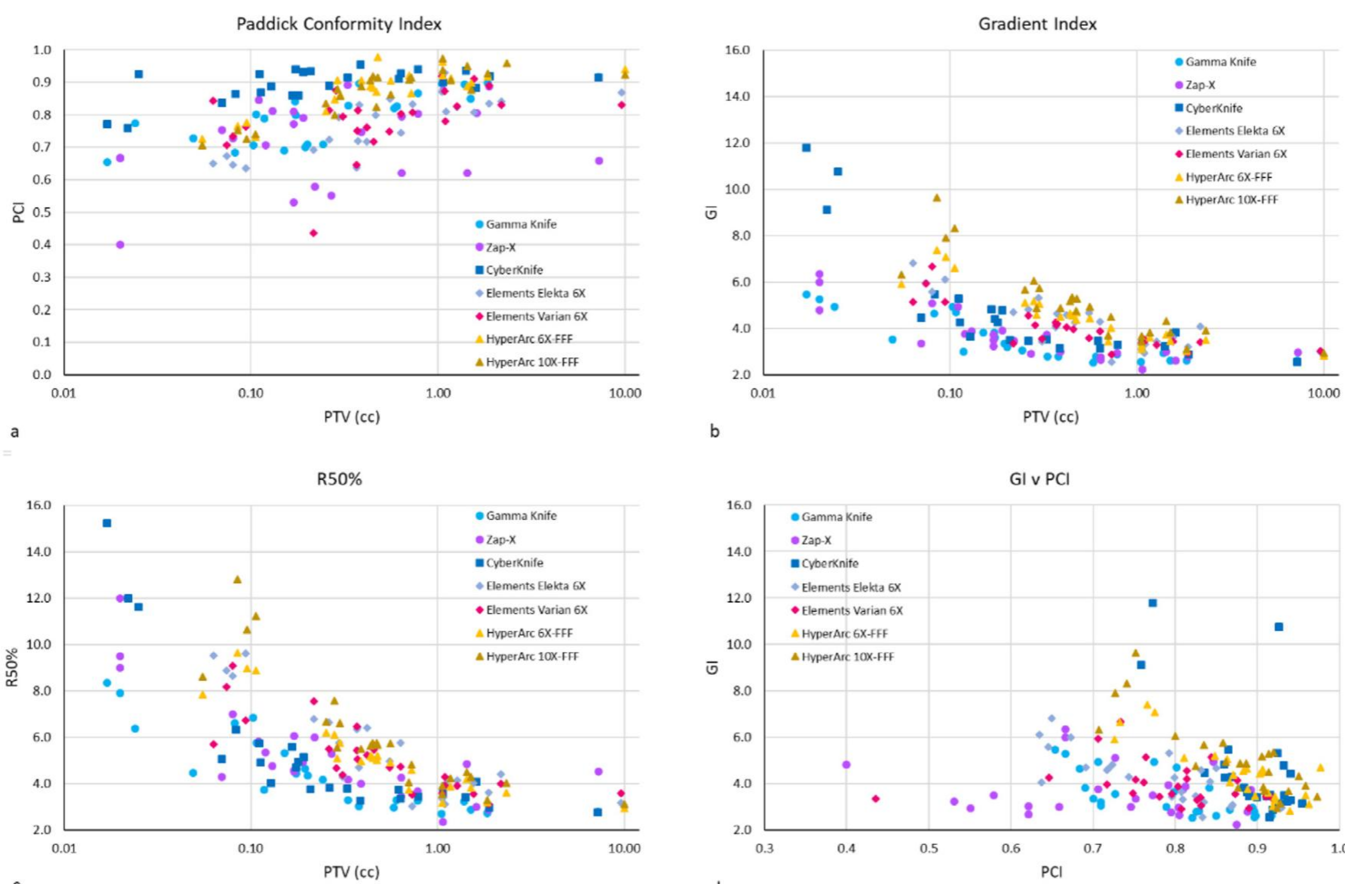
* "Point" defined as ≤0.035 cm^3.
† Avoid circumferential irradiation.
‡ One-third of the "native" total organ volume (before any resection or volume reducing disease), whichever is greater.

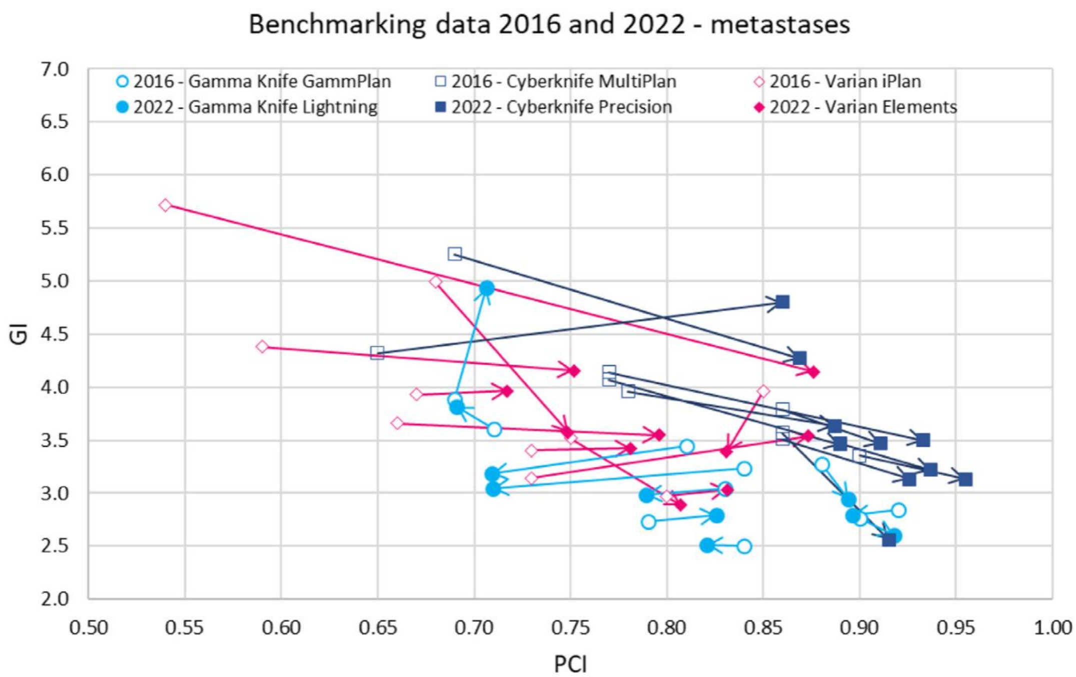
Paddick, PRO 2023 Based on Machine and Technique:

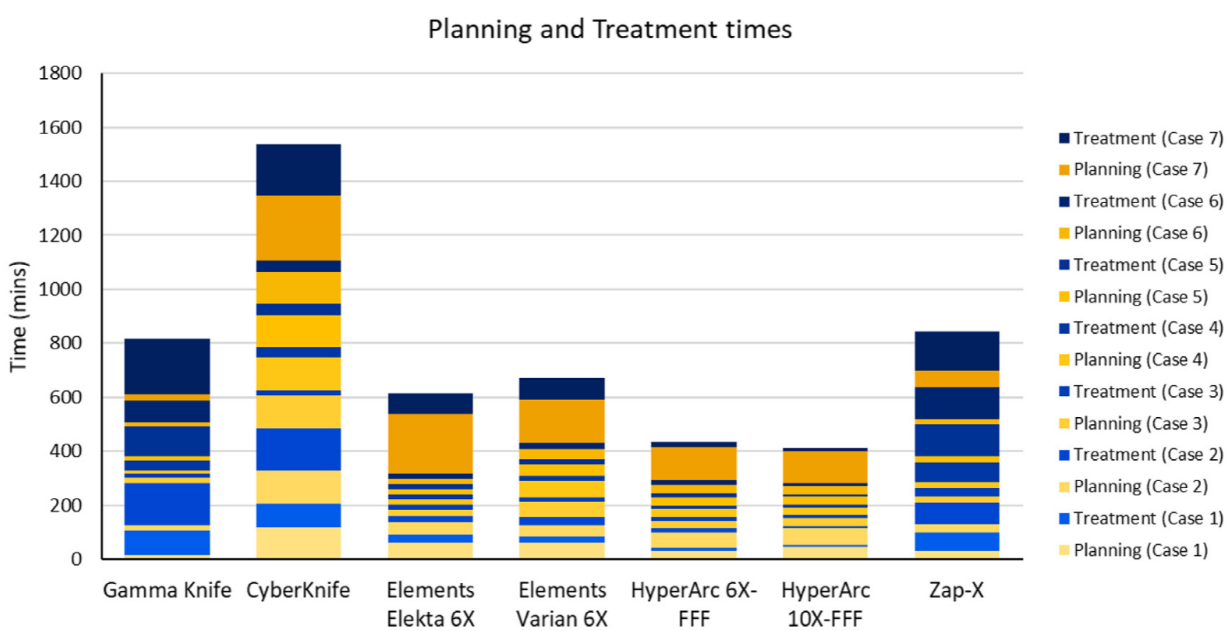
Table 1 Coverage, selectivity, PCI, GI, and R50% for each platform, averaged for benign and metastases separately.

Plan Parameter	Gamma Knife	Zap-X	CyberKnife	Elements Elekta 6X-FFF	Elements Varian 6X	HyperArc 6X-FFF	HyperArc 10X-FFF
				Benign lesions			
Coverage	96.7%	96.2%	97.1%	96.1%	97.5%	98.9%	99.1%
selectivity	0.871	0.862	0.911	0.822	0.914	0.886	0.878
PCI	0.843	0.830	0.885	0.790	0.891	0.876	0.871
GI	2.83	2.74	3.64	4.18	3.72	3.87	4.17
R50%	3.19	3.12	3.91	5.13	3.99	4.50	4.93
				Metastases* (volume averaged)			
Coverage	99.0% (98.8)	100.0% (99.9)	99.7% (99.4)	98.2% (98.3)	99.1% (99.0)	99.8% (99.7)	99.6% (99.6)
Selectivity	0.787 (0.862)	0.700 (0.745)	0.899 (0.928)	0.784 (0.841)	0.773 (0.818)	0.878 (0.913)	0.873 (0.919)
PCI	0.779 (0.852)	0.700 (0.744)	0.896 (0.922)	0.768 (0.825)	0.766 (0.809)	0.877 (0.911)	0.870 (0.915)
P value†	-	.019‡	<.001‡	.420	.490	<.001‡	<.001‡
GI	3.66 (2.91)	3.83 (3.18)	4.89 (3.37)	4.31 (3.49)	4.05 (3.48)	4.63 (3.71)	5.27 (4.11)
P value†	-	.249	.036‡	.030‡	.057	.009‡	<.001‡
R50%	4.74 (3.38)	5.69 (4.31)	5.57 (3.63)	5.60 (4.21)	5.32 (4.28)	5.37 (4.10)	6.19 (4.50)
P value†	-	.040‡	.299	.086	.074	.104	.027‡

Abbreviations: FFF = flattening filter-free; GI = gradient index; PCI = Paddick conformity index.
* Metastases 4, 5, 9, and 10 of case 7 were excluded from the analysis.
† Row data has statistical significance relative to values from the Gamma Knife.
‡ *P* values < .05.
For the metastasis cases, volume averaged data are shown in parentheses.




Benchmarking data 2016 and 2022 - metastases
2016 - Gamma Knife GammPlan
2016 - Cyberknife MultiPlan
2016 - Varian iPlan
2022 - Gamma Knife Lightning
2022 - Cyberknife Precision
2022 - Varian Elements
GI
PCI
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
0.50
0.55
0.60
0.65
0.70
0.75
0.80
0.85
0.90
0.95
1.00


Planning and Treatment times
Time (mins)
1800
1600
1400
1200
1000
800
600
400
200
0
Gamma Knife
CyberKnife
Elements Elekta 6X
Elements Varian 6X
HyperArc 6X-FFF
HyperArc 10X-FFF
Zap-X
Treatment (Case 7)
Planning (Case 7)
Treatment (Case 6)
Planning (Case 6)
Treatment (Case 5)
Planning (Case 5)
Treatment (Case 4)
Planning (Case 4)
Treatment (Case 3)
Planning (Case 3)
Treatment (Case 2)
Planning (Case 2)
Treatment (Case 1)
Planning (Case 1)

Intrafraction Motion Study
RR 55 SRS patients monitored when receiving surface-guided RT (SGRT) between 2017 – 2020.
SRS dose 15 – 21 Gy in 1 fraction and 27 Gy in 3 fractions.
PTV margins were 0 – 3 mm.
If SGRT detected motion >1 mm or a 1 degree of rotation, imaging was repeated and the necessary shifts were made before continuing treatment.
For the 25 patients with intrafraction 3D vector shifts of ≥1 mm, we moved the isocenter in the planning system using the translational shifts from the repeat imaging and recalculated the plans to determine the dosimetric effect of the shifts.

Foster, Advances in Radiation Oncology 2022
Without correcting for motion, GTV minimum dose ↓ 15.8% (SS) and PTV coverage ↓ 10.2% (SS).
Also, GTV minimum dose would have decreased by 3 Gy.

Dosimetric indices	Actual	Simulated	Median difference (actual - simulated)	*P* value*
V12 (cc), median (range)	2.78 (0.32-151.25)	3.02 (0.33-151.32)	−0.01 (−1.5-0.09)	.006
GTV minimum dose (%), median (range)	102.80 (91.70-118.60)	93.80 (15.00-106.00)	15.8 (−1.9-86.08)	<.001
PTV coverage %, median (range)	98.10 (98.00-99.00)	87.89 (36.60-99.56)	10.24 (−1.56-61.40)	<.001
GTV minimum dose (cGy), median (range)	2225.0 (1376.0-2719.0)	1901.8 (271.1-2752.3)	308.2 (−52.3-1548.3)	<.001

Conclusions
SGRT detected clinically meaningful intrafraction motion during frameless SRS, which could lead to large underdoses and increased normal brain dose if uncorrected.

GK vs. LINAC Multiple Brain Met Study
RR 391 patients treated in 537 courses with 2699 lesions (LINAC 1014, GK 1685).
Eligibility: Treated to ≥ 2 lesions.
LINAC single isocenter multitarget technique. 1-2 mm definitive, 2-3 mm margins post-op.
GK single or multi-iso techniques prescribing to 50% IDL. No no margin definitive or post-op.

Sebastain, Radiotherapy & Oncology 2020
GK (vs. LINAC) had similar OS (HR 0.86, p=0.41) but **↑ radionecrosis (HR 3.83, p=0.002)**.
In a secondary propensity score matched analysis comparing radionecrosis in **single**-fraction LINAC and GK, GK remained associated with higher incidence of radionecrosis (HR = 4.42; 95% CI 1.28–15.29; *p* = 0.019).
Conclusions
In this multi-institutional study, we found similar overall survival with lower incidence of radionecrosis in patients treated with LINAC compared to GK SRS. These findings are hypothesis generating and should be validated in an independent cohort.

Treatment Overview

ASTRO Guidelines

Gondi, PRO 2022

KQ 1: Indications for SRS alone for patients with intact brain metastases (Table 3)

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1.For patients with an ECOG performance status of 0-2 and up to 4 intact brain metastases, SRS is recommended.	Strong	High[13-18]
2. For patients with an ECOG performance status of 0-2 and 5-10 intact brain metastases, SRS is conditionally recommended.	Conditional	Low[19-21]
3. For patients with intact brain metastases measuring <2 cm in diameter, single-fraction SRS with a dose of 2000-2400 cGy is recommended. Implementation remark: If multifraction SRS were chosen (eg, V12 Gy >10 cm^3 [see KQ4]), options include 2700 cGy in 3 fractions or 3000 cGy in 5 fractions.	Strong	Moderate[5,13,16,19,22]
4. For patients with intact brain metastases measuring ≥2 to <3 cm in diameter, single-fraction SRS using 1800 cGy or multifraction SRS (eg, 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended (see KQ4).	Conditional	Low [22-24]
5. For patients with intact brain metastases measuring ≥3 to 4 cm in diameter, multifraction SRS (eg, 2700 cGy in 3 fractions or 3000 cGy in 5 fractions) is conditionally recommended. Implementation remarks: If single-fraction SRS were chosen, doses up to 1500 cGy may be used (see KQ4). Multidisciplinary discussion with neurosurgery to consider surgical resection is suggested for all tumors causing mass effect, irrespective of tumor size.	Conditional	Low[23,24]
6. For patients with intact brain metastases measuring >4 cm in diameter, surgery is conditionally recommended, and if not feasible, multifraction SRS is preferred over single-fraction SRS. Implementation remark: Given limited evidence, SRS for tumor size >6 cm is discouraged.	Conditional	Low[19,22-24]
7. For patients with *symptomatic* brain metastases who are candidates for local therapy and CNS-active systemic therapy, upfront local therapy is recommended.	Strong	Low[25,26]
8. For patients with *asymptomatic* brain metastases eligible for CNS-active systemic therapy, multidisciplinary and patient-centered decision making is conditionally recommended to determine whether local therapy may be safely deferred. Implementation remark: The decision to defer local therapy should consider factors such as brain metastasis size, parenchymal brain location, number of metastases, likelihood of response to specific systemic therapy, access to close neuro-oncologic surveillance, and availability of salvage therapies.	Conditional	Expert opinion

KQ2: Indications for observation, preoperative SRS, or postoperative SRS or WBRT in patients with resected brain metastases (Table 4)

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with resected brain metastases, radiation therapy (SRS or WBRT) is recommended to improve intracranial disease control.	Strong	High[13,50,51]
2. For patients with resected brain metastases and limited additional brain metastases, SRS is recommended over WBRT to preserve neurocognitive function and patient-reported QoL.	Strong	Moderate[52]
3. For patients whose brain metastasis is planned for resection, preoperative SRS is conditionally recommended as a potential alternative to postoperative SRS.	Conditional	Low[53,54]

KQ3: What are the indications for WBRT for patients with intact brain metastases? (Table 6)

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with favorable prognosis (estimated using a validated brain metastasis prognostic index) and brain metastases ineligible for surgery and/or SRS, WBRT (eg, 3000 cGy in 10 fractions) is recommended as primary treatment. (See KQ1, recommendations 7 and 8 for consideration of systemic therapy.)	Strong	High[64-67]
2. For patients with favorable prognosis and brain metastases receiving WBRT, hippocampal avoidance is recommended. Implementation remark: Hippocampal avoidance is not appropriate in cases of brain metastases in close proximity to the hippocampi or in cases of leptomeningeal disease.	Strong	High[4,68-70]
3. For patients with favorable prognosis and brain metastases receiving WBRT or hippocampal avoidance WBRT, addition of memantine is recommended.	Strong	Low[71]
4. For patients with favorable prognosis and limited brain metastases, routine adjuvant WBRT added to SRS is not recommended. Implementation remark: To maximize intracranial control and/or when close imaging surveillance with additional salvage therapy is not feasible, adjuvant WBRT may be offered in addition to SRS.	Strong	High[16,17,72]
5. For patients with poor prognosis and brain metastases, early introduction of palliative care for symptom management and caregiver support are recommended. Implementation remarks: Supportive care only (with omission of WBRT) should be considered. If WBRT is used, brief schedules (eg, 5 fractions) are preferred.	Strong	Moderate[73,74]

KQ4: Risks of symptomatic radionecrosis with WBRT and/or SRS for patients with brain metastases (Table 7)

KQ4 Recommendation	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with brain metastases, limiting the single-fraction V_{12Gy} to brain tissue (normal brain *plus* target volumes) to ≤10 cm^3 is conditionally recommended. Implementation remark: Any brain metastasis with an associated tissue V_{12Gy} >10 cm^3 may be considered for fractionated SRS to reduce risk of radionecrosis (see KQ1).	Conditional	Low[12,88]

ASCO Summary 2021

Surgery

1.1 What are the benefits and harms of surgery in adult patients with brain metastases?

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).

Systemic therapy

2.1 What systemic therapy (chemotherapy, immunotherapy, and targeted agents) options, alone or in combination, have demonstrated clinical benefits in adults with brain metastases?

Patients with symptomatic brain metastases should be offered local therapy (radiosurgery and/or radiation therapy and/or surgery) as recommended in this guideline regardless of the systemic therapy used for the systemic disease.
(Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

Radiation therapy

3.1 Radiation therapy should **not be offered** to patients with asymptomatic brain metastases who have:

Performance status Karnofsky Performance Status (KPS) ≤ 50 or less, *or*
Performance status KPS < 70 and no systemic therapy options
(Type: evidence-based; Evidence quality: low; Strength of recommendation: moderate).

3.2 SRS alone (as opposed to WBRT or combination of WBRT and SRS) should be offered to patients with one to four unresected brain metastases, excluding small-cell carcinoma.

Qualifying Statement: The inclusion criteria of the randomized trials that underly this recommendation were generally tumors of less than 3 or 4 cm in diameter and did not include radioprotectant strategies of memantine or hippocampal avoidance
(Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

3.3 SRS alone should be offered to patients with one to two resected brain metastases if the surgical cavity can be safely treated and considering the extent of remaining intracranial disease.

Qualifying Statement: The randomized trials upon which this recommendation is based were of single-fraction SRS and conventional WBRT (without radioprotectant strategies of memantine or hippocampal avoidance).
(Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).

3.4. SRS, WBRT, and the combination of SRS plus WBRT are all reasonable options for patients with more than four unresected or more than two resected brain metastases and better performance status (eg, KPS ≥ 70). SRS may be preferred for patients with better prognosis or where systemic therapy that is known to be active in the CNS is available
(Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

3.5. Memantine and hippocampal avoidance should be offered to patients who will receive WBRT and have no hippocampal lesions and 4 months or more expected survival.
(Type: evidence-based; Evidence quality: high; Strength of recommendation: strong).

3.6. Radiation-sensitizing agents should not be offered to patients.
(Type: Evidence-based; Evidence quality: low; Strength of recommendation: strong).

Timing

4.1. For patients who will receive both radiation therapy and surgery, no recommendation regarding the specific sequence of therapy can be made (Type: informal consensus; Evidence quality: low; Strength of recommendation: none).

Basic Notes

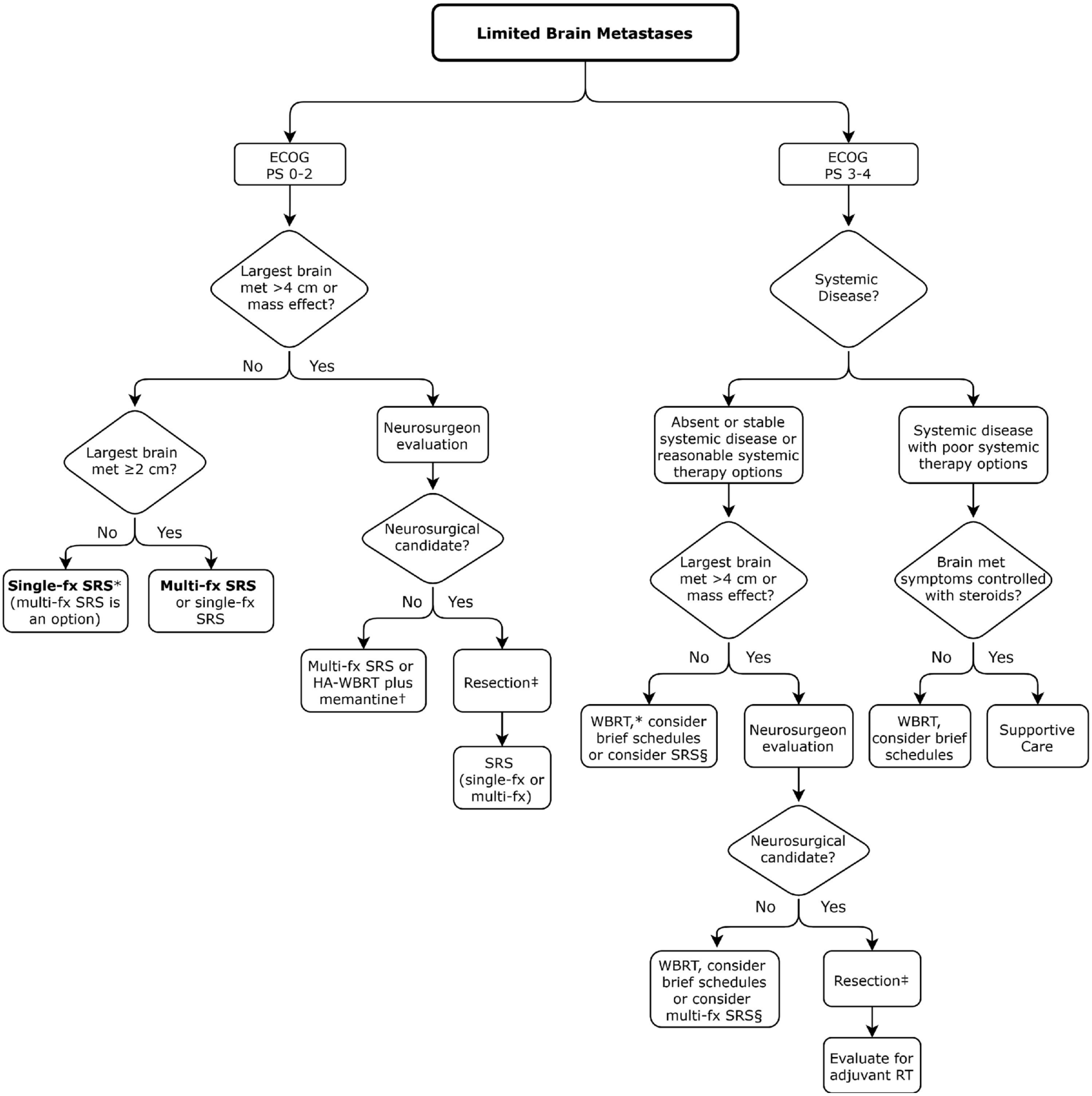
- **Steroids:**
  - Corticosteroids should be used at onset for all symptomatic patients
  - Two dosing schedules to consider:
    - Consider 2 mg BID for mildly symptomatic cases.
    - Consider 4 mg BID for considerably symptomatic cases.
    - Historically, many considered 8mg BID, begin taper during Week 2 of RT by 2-4mg every fifth day.
      - If symptoms (tumor or steroid withdrawal), go back up a level for 4-8 days, then restart taper.
      - If symptoms increase after steroids discontinued, restart full regimen (Posner JB, Neurologic Complications of Cancer, Philadelphia: FA Davis, 1995:37, 77, 311)
  - High doses of steroids can ↓ sleep (take 8 am and 3 pm, not at night).
  - Requires PPI (omeprazole 20 mg daily).
  - Lengthened time > 1 month requires PCP prophylaxis.

- **Seizures:**
  - Prophylaxis against seizures is not recommended.
  - A Meta-Analaysis showed lack of efficacy for seizure prophylaxis in patients without a history of seizures. PMID 15595331, 2004 — "Seizure prophylaxis in patients with brain tumors: a meta-analysis." Mayo Clin Proc. 2004 Dec;79(12):1489-94.
  - 2010 AANS/CNS Guidelines do not recommend routine prophylactic use of anticonvulsants (PMID 19957015)

- **When not to Treat?**
  - Consider no RT if expected survival < 30 days and KPS ≤ 60
  - Expected median survival <3 months.
    - Prostate: hormone-resistant
    - Breast: failure of 3rd line chemotherapy
    - Lung: failure of 1st line chemotherapy.
    - Colon: ascites or liver failure, Liver mets and doubling LFTs q month.
    - SVC syndrome, hypercalcemia, HIV with CD4 <25 and RNA >100K, CHF Class IV with EF <20%
    - Creatinine >8, pO2 <55 and pCO2 >50.

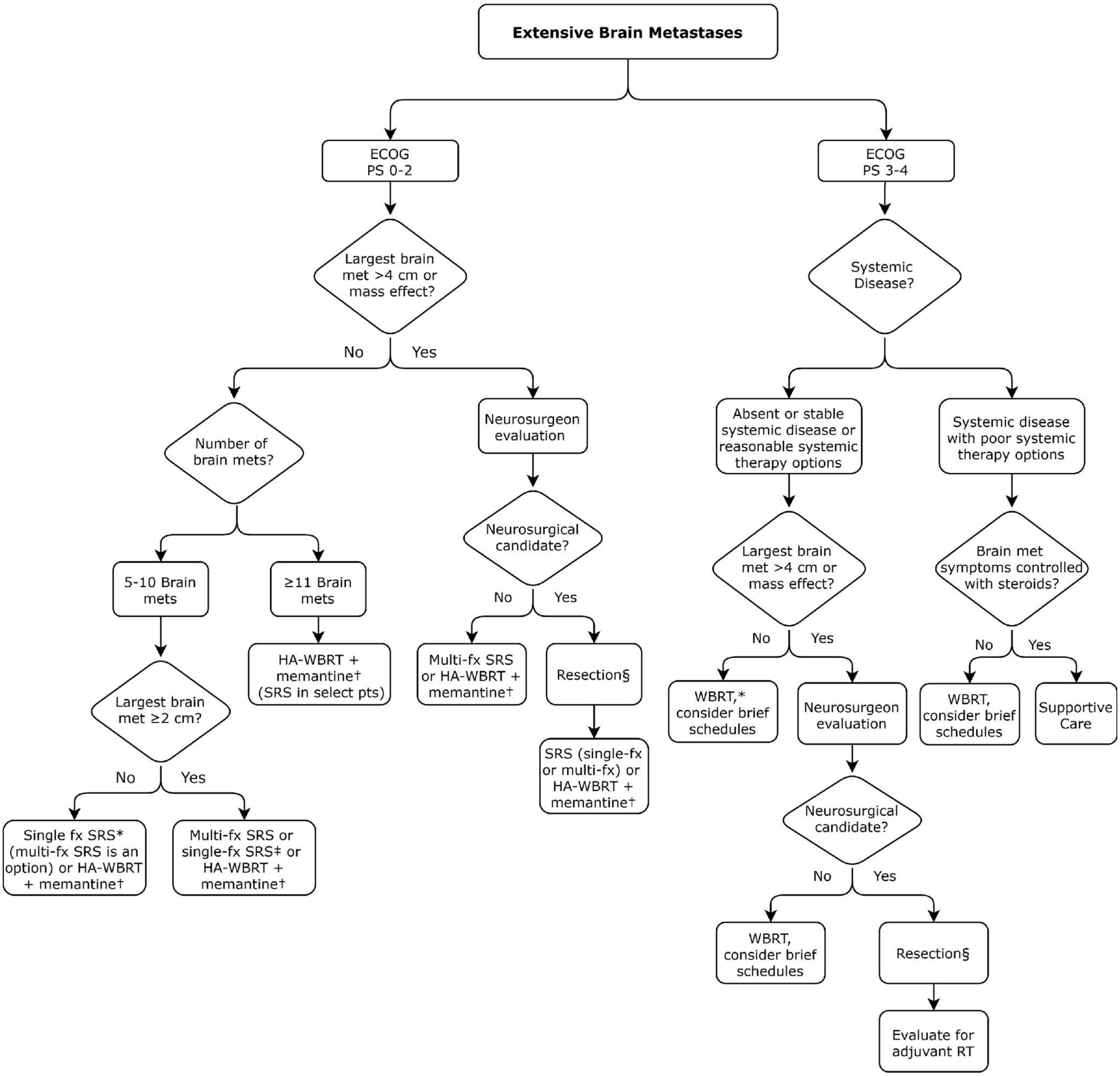
Limited Mets Flowchart

ASTRO Guidelines 2022



Extensive Mets Flowchart

ASTRO Guidelines 2022



WORKUP | **DIAGNOSIS** | **RISK STATUS**

Signs and symptoms suggestive of leptomeningeal disease[a]

→

- Physical exam with careful neurologic evaluation
- Brain and spine MRI if patient is a candidate for active treatment[b,c]
- CSF analysis[d,e,f,g]

→

CSF positive for tumor cells
or
Positive radiologic findings with supportive clinical findings
or
Signs and symptoms with suggestive CSF[h] in a patient known to have a malignancy

→

Good risk:
- KPS ≥60
- No major neurologic deficits
- Minimal systemic disease
- Reasonable systemic treatment options, if needed

→ Treatment (LEPT-2)

Poor risk[i]:
- KPS <60
- Multiple, serious, major neurologic deficits
- Extensive systemic disease with few treatment options
- Bulky CNS disease
- Encephalopathy

→ Treatment (LEPT-2)

RISK STATUS | **TREATMENT**

Good risk:
- KPS ≥60
- No major neurologic deficits
- Minimal systemic disease
- Reasonable systemic treatment options, if needed

→

Systemic therapy[j]

- Intra-CSF therapy[j,k]
  - If symptoms or imaging suggest CSF flow blockage, perform a CSF flow scan prior to starting intra-CSF therapy
    If flow abnormalities confirmed:
    - ◊ Fractionated EBRT[l] to metastatic or painful sites of obstruction and repeat CSF flow scan to see if flow abnormalities have resolved
      or
    - ◊ High-dose methotrexate if breast cancer or lymphoma

- RT[l]
  - Consider involved-field RT (eg, partial or WBRT, skull base RT, focal spine RT) to bulky disease for focal disease control and to neurologically symptomatic or painful sites
  - Consider craniospinal irradiation (CSI)[m] for CNS and CSF disease control in select patients with or without symptoms

→ Assessment of response (LEPT-3)

Poor risk:[i]
- KPS <60
- Multiple, serious, major neurologic deficits
- Extensive systemic disease with few treatment options
- Bulky CNS disease
- Encephalopathy

→

Palliative/best supportive care
and
Consider involved-field RTl to neurologically symptomatic or painful sites for palliation (including spine and intracranial disease)

TREATMENT

CSF cytology negative[n,o]

→

Continue on current therapy (systemic or intra-CSF) and re-evaluate CSF cytology every 4–8 weeks

→

Maintenance therapy[j] and Monitor CSF cytology every 4–8 weeks

CSF cytology positive

→

Patient clinically stable or improving and there is no evidence of radiologic progression of leptomeningeal disease

→

Continue current therapy[j] (systemic or intra-CSF) for 4 weeks
or
Consider switching therapy and treat for 4 weeks before re-evaluating CSF cytology

→

Negative cytology or persistent positive cytology, but patient is clinically stable → Maintenance therapy[j] and Monitor CSF cytology every 4–8 weeks

Principles of Brain and Spine Imaging (BRAIN-A)

Cytology continually positive and evidence of clinical or radiologic progression of leptomeningeal disease → Standard RT[l] to symptomatic sites or Palliative/best supportive care

→

Evidence of clinical or radiologic progression of leptomeningeal disease

→

Consider switching therapy (systemic or intra-CSF)

→

Standard RT[l] to symptomatic sites
or
Palliative/best supportive care

WBRT Studies

Recent

Imaging Based Evaluation of WBRT
Retrospective 4220 subjects (4148 healthy controls and 72 patients with brain metastasis). MRI brain
Median RT Dose 30 Gy (range 25-37.5 Gy).
Examination of MRI brain anatomic surface data before and after WBRT → validated graph convolutional neural network model to estimate patient's "brain age". We further developed a mixed-effects linear model to compare the estimated age of the whole brain and substructures before and after WBRT.

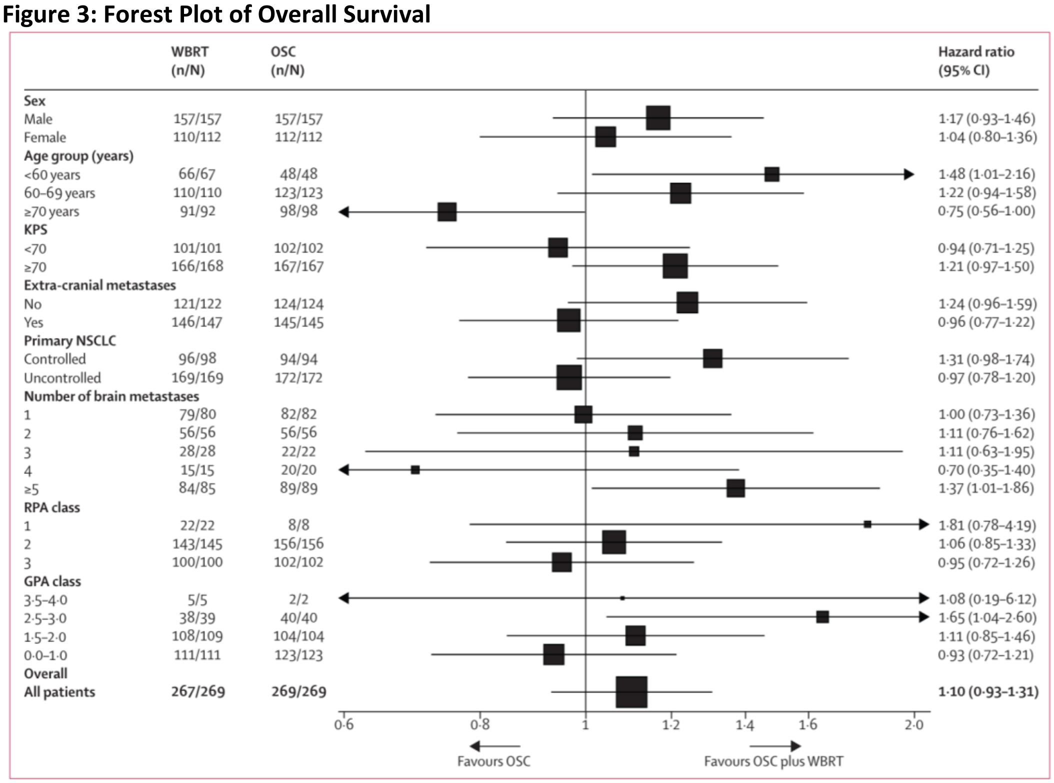
Rommohan, Neuro-Oncology
The whole brain and substructures underwent structural change resembling rapid aging in WBRT vs. healthy controls.
How many times faster "aging:" whole brain 9.32x, cortex 8.05x, subcortical structures 12.57x, hippocampus 10.14x.
In a subset analysis, the hippocampus "aged" 8.88x faster in patients after conventional WBRT versus after HA-WBRT.
Conclusions Our findings suggest that WBRT causes the brain and its substructures to undergo structural changes at a pace up to 13x of the normal aging pace, where hippocampal avoidance offers focal structural protection. Correlating these structural imaging changes with neurocognitive outcomes following WBRT or HA-WBRT would benefit from future analysis.

QUARTZ Study
←R→ 538 patients, NSCLC brain mets unsuitable for surgical resection or stereotactic radiotherapy.
| 1. WBRT + optimal supportive care (OSC) including dexamethasone | 2. or OSC alone |. RT = 20 Gy in 5 fx.
83% GPA 0-2 and 38% KPS < 70.

Mulvenna, Lancet 2016.
OS NS HR 1.06. Median Survival 9.2 weeks vs. 8.5 weeks (NS).
RT = ↑ side effects (drowsiness, hair loss, nausea, and dry or itchy scalp).
RT trended to ↑ mean QALYs 4·7 days (46·4 QALY vs. 41·7 QALY, NS).
Subset < 60 yo: Median OS 10.4 vs. 7.6 weeks (HR 1.48, SS).
Subset good KPS and 1^{O} site controlled = only trending.
Interpretation: Although the primary outcome measure result includes the prespecified non-inferiority margin, the combination of the small difference in QALYs and the absence of a difference in survival and quality of life between the two groups suggests that WBRT provides little additional clinically significant benefit for this patient group.

<u>Criticism: Patients on study were poor KPS. Thus, this study may NOT apply to good KPS patients with brain mets</u>.

Figure 3: Forest Plot of Overall Survival



Historical

Surgery → WBRT

Trial	Tx	RT	N	MS (mo.)	P
Patchell	Biopsy +WBRT	36, 12	23	**4.2**	**< 0.01**
	S +WBRT	36, 12	25	**10**	
Vecht	WBRT	40, 10 BID	31	6.5	Na
	S + WWBRT	40, 10 BID	32	10.8	
Mintz	WBRT	30,10	43	6.3	0.24

Patchell II **Surg vs Surg → WBRT (50.4 in 28 fx).**

Patchell, JAMA 1998. **Surg (GTR on MRI) → 1. Postop WBRT | 2. Obs.**
Dose was 50.4 Gy in 28 fractions over 5.5 weeks.
←R→ 95 pts. **Solitary** brain met. Can have other sites metastases, but KPS >= 70%.
Recall: **Single** brain met = ONLY 1 met in brain. Can have poor body disease.
Solitary brain met = 1 met in brain...but no other sites.
Median f/u 43-48 wks.
Postop RT = ↓ recur anywhere in brain (18% vs 70%), at site of resection (10% vs 46%), as well as other areas in the brain (14% vs 37%). **Decreased neurologic death (6 of 43 pts, 14%; vs 17 of 39, 44%)**.
No difference in overall survival (unlike Patchell #1) or length of time patient remained independent.
To have survival difference, you needed 2000 patients.

Criticism: non-standard whole brain RT dose.
The primary end point was recurrence of tumor in the brain; secondary end points were length of survival, cause of death, and preservation of ability to function independently.

	Any recurrence	Distant recurrence	LR	MS	Neuro Death	Functional Independence
Surg	**70%**	**37%**	**46%**	43 wk	**44%**	35 wk
Surg → RT	**18%**	**14%**	**10%**	48 wk	**14%**	37 wk
P	**SS**	**SS**	**SS**	NS	**SS**	NS

Patchell I **WBRT vs Surg → WBRT (36 Gy in 12 fx)**

←R→. 48 patients. Suspected **single** brain metastasis. Dexamethasone 4mg Q6 hours.
Surgery within 72 hours of randomization.
WBRT within 14 days of surgery; within 48 hours of randomization or biopsy; dose 36 Gy / 12 fx.

Patchell, NEJM 1990
Outcome: **Local recurrence WBRT 52% vs surgery + WBRT 20% (SS)**; time-to-recurrence 5 vs >14 months (SS).
Distant brain recurrence 13% vs. 20% (NS).
QoL (KPS >=70, functionally independent) how long this patient has KPS > 70…. 2 months vs. 9 months (SS).
Survival: Median OS 3 months vs. 9 months (SS), "neurologic death" 6 months vs. 14 months (SS).
No difference in "systemic death".
Toxicity: operative mortality 4%, operative morbidity 8%.
Conclusion: Patients with single brain metastasis treated with surgery + RT live longer, have fewer recurrences, and better quality of life than patients treated with RT alone.

	DM	Time to LR	LR	MS	Time to Time to Neuro Death	Functional Independence
Biopsy → WBRT	13%	**21 wk**	**52%**	**15 wk**	**26 wk**	**8 wk**
Surg → WBRT	20%	**> 59 wk**	**20%**	**40 wk**	**62 wk**	**35 wk**
P	NS	**SS**	**SS**	**SS**	**SS**	**SS**

Vecht, Ann Neuro 1993. **WBRT vs Surg → WBRT (40 Gy in 20 fx)**

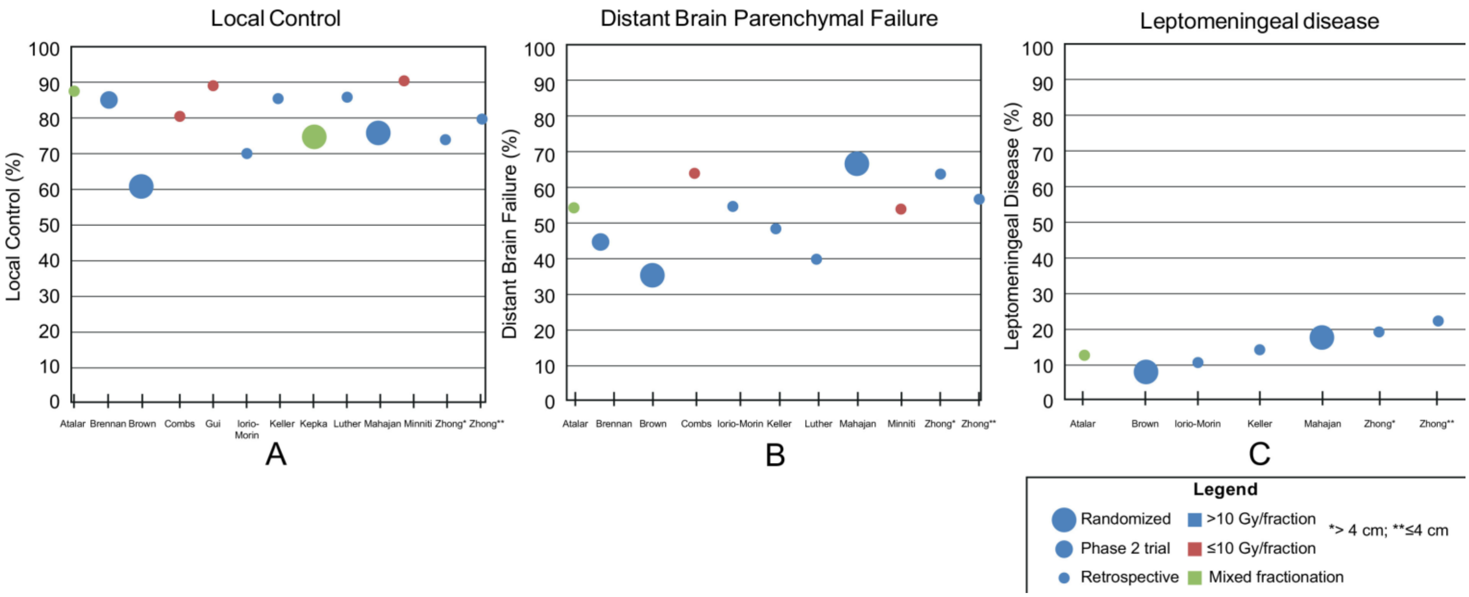
←R→ 63 patients with a single brain met.

Surg → WBRT led to a longer survival (p = 0.04) and a longer FIS (p = 0.06). This was most pronounced in patients with stable extracranial disease (median survival, 12 vs 7 mo; median FIS, 9 vs 4 mo). Patients with progressive extracranial cancer had a median overall survival of 5 months and a FIS of 2.5 months irrespective of given treatment. Improvement in functional status occurred more rapidly and for longer periods of time after neurosurgical excision and radiotherapy than after radiotherapy alone

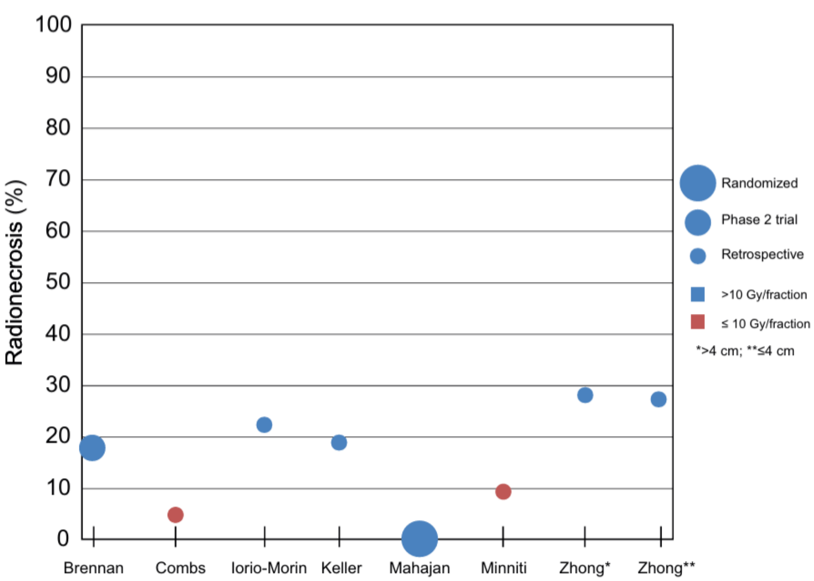
SRS Studies

Surgery → SRS

International Stereotactic Radiosurgery Society ISRS Recommendations: Redmond Review 2021
The purpose of this critical review is to summarize the literature specific to single-fraction stereotactic radiosurgery (SRS) and multiple-fraction stereotactic radiation therapy (SRT) for postoperative brain metastases resection cavities and to present practice recommendations on behalf of the ISRS.



Recommendations	Level of evidence
After surgery for a brain metastasis, postoperative SRS is preferred over observation due to superior local control	I
For patients with 1 resected brain metastasis, ECOG performance status of 0-2, and a resection cavity measuring <5 cm, postoperative SRS to the resection cavity is recommended to minimize cognitive toxicity compared with WBRT.	I
Target volume should include the resection cavity and entire surgical tract with consideration to expand the clinical target volume to include a 5-10 mm expansion beyond the preoperative tumor location along bone flap in those tumors contacting the dura preoperatively, while respecting anatomic barriers, and a 1-5 mm expansion along sinuses for tumors contacting a sinus preoperatively. In addition, a 2-3 mm radial expansion to PTV should be considered.	III
Prescription doses of approximately 30-50 Gy $EQD2_{10}$, 50-70 $EQD2_5$, and 70-90 $EQD2_2$, have been associated with reasonable local control, but formal comparative studies are warranted. **Emerging data suggest single-fraction treatment without dose de-escalation is appropriate in cavities <2 cm in size and that fractionated regimens may provide superior local control compared with single-fraction SRS in patients with large metastases greater than 2.5-3 cm.**	III
The consent process for brain metastases surgery should include a discussion of the risk of surgical dissemination of tumor manifesting as leptomeningeal disease.	III



Conclusions: Although randomized data raise concern for poorer local control after resection cavity SRS than WBRT, these findings may be driven by factors such as conservative prescription doses used in the SRS arm. Retrospective studies suggest high rates of local control after single-fraction SRS and hypofractionated SRT for postoperative brain metastases.

With a superior neurocognitive profile and no survival disadvantage to withholding WBRT, the ISRS recommends SRS as first-line treatment for eligible postoperative patients. Emerging data suggest that fractionated SRT may provide superior local control compared with single-fraction SRS, in particular, for large tumor cavity volumes/diameters and potentially for patients with a preoperative diameter greater than 2.5 cm.

Summary of SRS Effectivenesss: Meta-analysis of 538 studies reporting on 120,756 patients treated with SRS for brain cancer and tumors since 2000, the most treated tumors were metastases (58%), skull base tumors (35%), and gliomas (7%). **Radiographic control was achieved in 82% of metastatic tumor cases, with a 12% median complication rate**.
Asfaw, Cancer Medicine 2025.

ISRS 2023 Guidelines for Small Brain Mets

Table 2 Summary of recommendations

Imaging	• Recent MR imaging (≤7 days from treatment) is a prerequisite for contouring. • Fine-cut MR scans should be acquired (≤1.5-mm slice thickness). • A scan time delay of between 10 and 15 minutes should be applied after contrast injection. • MR sequences should be optimized for SRS to reduce artifacts and geometric distortion. Regular MRI QA is mandatory to monitor geometric distortion as a potential source of error. • CT scans, if used for planning, should be equal to or thinner than MR slice thickness.
Contouring	• All targets and OARs should be contoured to quantitatively assess tumor coverage constraints and OAR tolerance levels. • Margins are associated with an increased dose to normal tissue and need to be carefully considered according to the SRS platform.
Patient treatment	• Sub-millimeter geometric accuracy must be achieved during treatment. To comply with this requirement the choice of immobilization device and in-room imaging should be made based on the achievable accuracy of patient positioning and target localization. Patient immobilization and localization techniques are critical in this regard. • Lower energy beams may reduce dose to normal tissue.
Dosimetry	• Dosimetric accuracy within 5% must be achieved. • Recommendations regarding dosimetrical measurements for small fields have been published by IAEA and AAPM.

Abbreviations: AAPM = The American Association of Physicists in Medicine; CT = computed tomography; IAEA = International Atomic Energy Agency; MR = magnetic resonance; OAR = organ at risk; QA = quality assurance; SRS = stereotactic radiosurgery.

MDACC Single Institution PRT
←R→ 132 patients KPS ≥ 70, with mRI, Complete resection **1-3 brain mets** with a max diameter of resection cavity ≤4 cm.
| 1. SRS of resection cavity within 30 days of surg | 2. Observation |.
All patients in the SRS group were treated within 30 days of surgery and underwent a single session of treatment.
Prescription doses and SRS target volumes were 16 Gy (for ≤10 cc), 14 Gy (for 10·1–15 cc), and 12 Gy (for >15 cc).

Mahajan, Lancet Oncol 2017.
12-month FFLR recurrence 72% vs. 43% (HR 0·46, p=0·015).
There were no adverse events or treatment-related deaths in either group.
Interpretation: SRS of the surgical cavity in patients who have had complete resection of one, two, or three brain metastases significantly lowers local recurrence compared with that noted for observation alone. Thus, the use of SRS after brain metastasis resection could be an alternative to whole-brain radiotherapy.

Fractionated Post-op SRS

Prospective 558 patients resected **ONE brain metastases** → postoperative HypofxSBRT (HSRT)

Exclusion criteria: prior RT and early termination of treatment.

Median total dose of 30 Gy (range, 18-35 Gy) and a dose per fraction of 6 Gy (range, 5-10.7 Gy) were applied.

Time from resection to radiotherapy, median (IQR), d	34 (26-42)
Time from resection to radiotherapy, d[b]	
0-21	78 (13.4)
22-33	196 (33.7)
≥34	307 (52.8)

Eitz, JAMA Network 2020. Fu 1 year.

OS was 65% at 1 year, 46% at 2 years, and 33% at 3 years

LC was 84% at 1 year, 75% at 2 years, and 71% at 3 years.

Radiation necrosis (8.6%) and leptomeningeal disease (13.1%).

MVA for OS: KPS ≥ 80% HR 0.61 (SS), 22-33 days b/t resection → RT (HR, 1.50; SS), and controlled 1^{O} (HR 0.69 SS).

MVA for LC: Single brain metastasis (HR, 0.57; SS) and a controlled 1^{O} tumor (HR, 0.59, P = .02).

Conclusions: To date, this cohort study includes one of the largest series of patients with brain metastases and postoperative HSRT and appears to confirm an excellent risk-benefit profile of local HSRT to the resection cavity. Additional studies will help determine radiation dose-volume parameters and provide a better understanding of synergistic effects with systemic and immunotherapies.

Exposures: A median total dose of 30 Gy (range, 18-35 Gy) and a dose per fraction of 6 Gy (range, 5-10.7 Gy) were applied.

eTable 1. Dose Schemes Used (n=581)

	Total dose [Gy]	EQD2 [Gy]	BED_{10} [Gy]	n
6 Gy x 3	18	24.0	28.8	14
5 Gy x 4	20	25.0	30.0	1
7 Gy x 3	21	29.75	35.7	59
9.5 Gy x 2	19	30.88	37.05	1
5 Gy x 5	25	31.25	37.5	58
5.5 Gy x 5	27.5	35.52	42.63	24
8 Gy x 3	24	36.0	43.2	140
5 Gy x 6	30	37.5	45	17
6 Gy x 5	30	40.0	48	98
9 Gy x 3	27	42.75	51.3	1
5 Gy x 7	35	43.75	52.5	157
9.2 Gy x 3	27.6	44.16	52.99	1
6.5 Gy x 5	32.5	44.69	53.63	4
7 Gy x 5	35	49.58	59.5	5
10.7 Gy x 3	32.1	55.37	66.45	1

BED_{10}: Biologically equivalent doses using a tumor α/β of 10; EQD2: Equivalent dose in 2 Gy

Stanford Experience

RR 442 patients with 501 resected BMs treated over 475 total SRS courses from 2007-2018.

Shi, IJROBP 2020 Median clinical follow-up 10 months

Median OS 13.9 months.

12-month	Local Failure	7%
	Adverse radiation effect	9%
	Distant Intracranial Failure	44%
	Distant Parenchymal Failure	37%
	LMD	13%

The overall incidence of LMD was 15.8% (53% cLMD, 46% nLMD).

OS Classical LMD (cLMD) 2 months vs. nodular LMD (nLMD) 11.2 months (*P* < .01)

Neurologic death similarly 67% vs 41%, (*P* = .02).

A total of 15% of patients ultimately received WBRT.

Conclusions We report the largest clinical experience of postoperative SRS for resected BMs, showing excellent local control and low toxicity. Intracranial failure was predominantly distant, with a rising incidence of LMD.

Pre-op vs. Post-op SRS Study PREOPERATIVE SRS

Prospective 458 patients, 534 BM PREOP n=235 POSTOP n=299

All dose either 27 Gy in 3 fractions or 30 Gy in 5 fractions.

1^{O} composite endpoint defined by (1) LF, (2) nMD, and/or (3) grade 2 or higher (symptomatic) RN.

Notably, 4 (1.7%) pre-op and 14 (4.7%) post-op metastases were diagnosed with nMD (*P* = .088)

Perlow, IJROBP 2025

Composite endpoint 28 (12%) vs. 59 (20%) (*P* = .018).

3-year composite endpoint 15% vs. 20%.

Conclusions In our study, pre-op FSRT compares favorably to post-op FSRT primarily because of a lower incidence of nMD. Differences between treatment groups for symptomatic RN or LF endpoints were comparatively smaller. Prospective validation of pre-op FSRT is needed.

Phase III Pre vs. Post-op SRS PREOPERATIVE SRS

←R→ 103 patients age ≥ 18 yo, ECOG 0-2

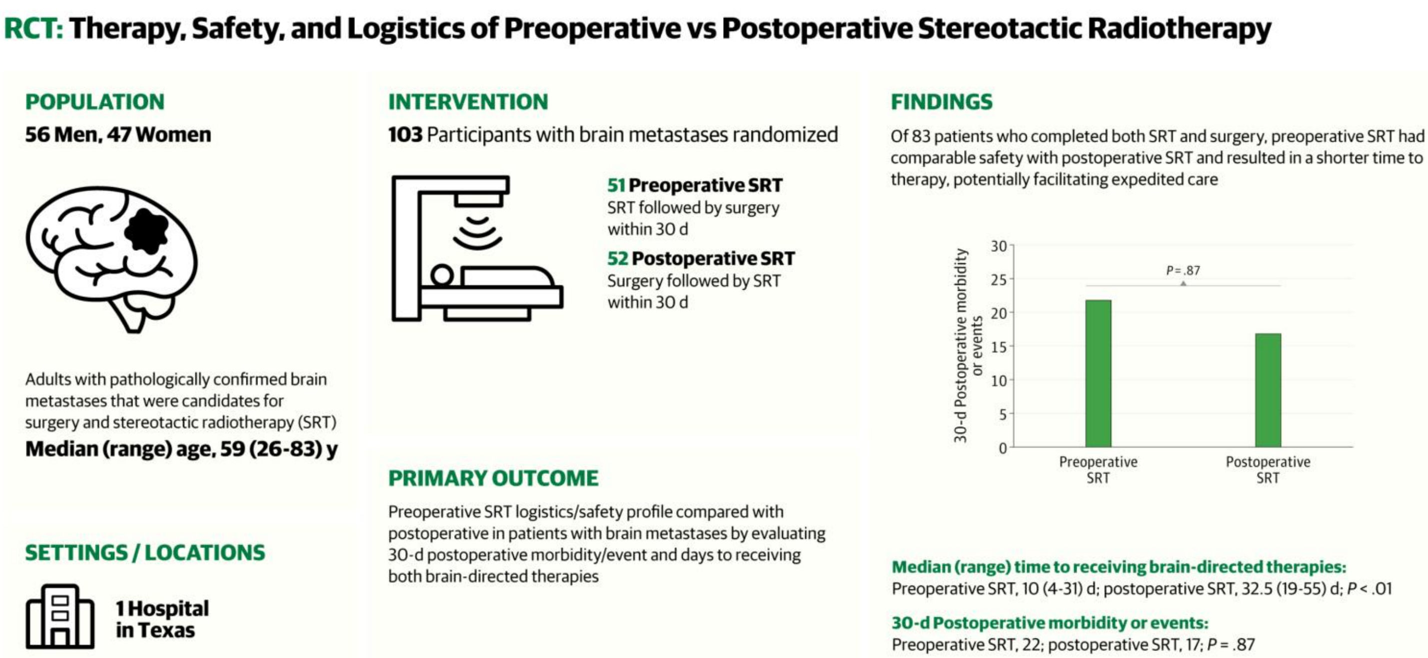
| 1. Preop SRS → Surgery within 1 month | 2. Surgery → Post-op SRS within 1 month |.

Exclusion: radiosensitive histologies (eg, small cell lung cancer and lymphoma), brain metastasis of unknown primary, and/or radiographic evidence of leptomeningeal disease were.

Single (most common 18 Gy x 1) and Multi fraction (most common 9 Gy x 3) SRS allowed.

Histologies: NSCLC (29.1%), RCC (14.6%), melanoma (13.6%), breast cancer (11.7%).

Of the 83 patients (80.6%) who ultimately completed both Surgery and SRS, 70 patients (84%) had 1 to 4 brain metastases at enrollment, 11 (13%) had 5 to 10 lesions, and 2 (2%) had more than 10 lesions.



Yeoba, JAMA Oncology 2025

Completion of both treatments Preop 45 (88%) vs. Postop 38 (73%).

No SS → 30-day postoperative morbidity or postprocedural events.

Yes SS → median (range) time between the 2 Txs 6 (0-24) days vs. 22 (12-42) days (*P* < .001).

→ median (range) time from ←R→ to both Tx 10 (4-31) days vs. 32.5 (19-55) days (*P* < .001).

Conclusions and Relevance In this randomized clinical trial, preoperative SRT had comparable safety to postoperative SRT and resulted in shorter time to treatment completion, potentially facilitating expedited care.

Note: A SS ↑ preop patients were treated on GammaKnife (84% vs. 50%) and had 1 fx SRS (51% vs. 29%)

INTERNO Study PREOPERATIVE SRS

Prospective 179 patients with single- and multi-fraction PREOP- (aka neoadjuvant) SRS for BM.
Eligibility: BM from any primary malignancy and no prior local therapy.
1^{O} composite of LR, any grade radionecrosis (RN), and/or nodular leptomeningeal disease (nLMD).
Primary malignancies included non-small cell lung carcinoma (44 %) and melanoma (17 %).

Median BrM diameter 29 mm.	1 fx SRS 53%	Multi Fx SRS 47%
	1 fx median Dose 18 Gy	Multi Fx 24 Gy in 3 fx (55%) and 27 Gy in 3 fx (25%)

Udovicich, Radiotherapy and Oncology 2025

12-month incidence for the composite endpoint was 8.0 %.
12-month incidence of LR was 4.6 %, any grade RN was 3.6 %, Grade ≥ 2 RN was 1.8 % and nLMD was 1.2 %.
Conclusion Preop SRS results in favourable rates of LR, RN and nLMD. We provide a global experience of this treatment approach with long-term data and the largest cohort of patients undergoing multi-fraction SRS.

UAB Phase I to ↓ LMD PREOPERATIVE SRS

20 patients with tumors 2-6 cm in size with escalating doses 12 and 15 Gy
Retrospective analysis included an expanded preoperative cohort (n = 95) and a **historical postoperative cohort** (n = 107).

Hoyle, Advances in Radiation Oncology 2025

15 Gy was well tolerated → no DLTs in larger tumors (4-6 cm) and 3 DLTs in smaller tumors, not meeting thresholds for dose de-escalation.
In the expanded analysis preoperative SRS significantly reduced rates of nLMD (7.4% vs 27.1%, *P* = .002).
Unchanged: rates of classical LMD (4.2% vs 4.5%)
Local failure (14.6% vs 18.7%)
Median OS 12.8 vs 12.3 months.
MVA confirmed preoperative SRS as protective against nLMD (hazard ratio = 0.18, 95% CI, 0.07-0.43, *P* < .001).
Conclusions Preoperative SRS to 15 Gy is safe for tumors 2 to 6 cm and significantly reduces nLMD without compromising local control or OS. These findings support preoperative SRS as a viable treatment strategy and justify further investigation into optimal dosing and patient selection.

PROPS-BM International **SINGLE vs FRACTIONATED** PREOPERATIVE SRS

Prospective 404 cohort with SRS → 416 resected lesions.
Either → Single Fraction SRS (SF-SRS) n=317 (78.5%)
Multi-fraction SRS (MF-SRS) n=87 (21.5%)

Linac based SRS 89%
Median Dose 15 Gy in 1 fx
Median Dose 24 Gy in 3 fx.

Majority 2/3 no PTV, 1/3 1 mm PTV. SRS → Surgery Median 1 day.
Post-op complication rate was 7%. 2-year risk of LMD was 7.6%.

NOTE: Adverse RT effects (the imaging correlate of radiation necrosis) = 34 of 416 (8.2%), of which 21 (5%) symptomatic.
G1 **=** 13 events (3.2%) G2= 18 (4.3%) G3= 3 (0.7%).
The 3 grade 3 ARE events required surgical resection and were pathologically proven radiation necrosis.

NOTE: 2-year any-grade ARE rate for **PTV margin expansion** of ≤ 1 mm (n = 359) 5.8% vs >1 mm (n = 57) 20.5% (*P* = .004).
LR based on resection → GTR 13.5%, STR 43.8%.
Exclusion: Prior or planned WBRT.

Prabhu, IJROBP 2024

2-year LR SF-SRS 16.3% vs. MF-SRS 2.9% (p=0.004) → confirmed on MVA as well.
Propensity Score Match analysis = 19.8% vs. 3.3% (p=0.003)

Conclusions: Preoperative MF-SRS was associated with significantly reduced risk of cavity LR in both the unmatched and PSM analyses. There was no difference in adverse radiation effect, meningeal disease, or overall survival based on fractionation. MF-SRS may be a preferred option for neoadjuvant radiation therapy of resected BMs. Additional confirmatory studies are needed. A phase 3 randomized trial of single-fraction preoperative versus postoperative SRS (NRG-BN012) is ongoing (NCT05438212).

Table 2. Multivariable Analysis for Cavity Local Recurrence via the Fine and Gray Method

Variable	Hazard ratio	95% CI	P value
Active systemic disease (vs no active systemic disease)	0.33	0.18-0.61	<.001
GTR (vs STR)	0.20	0.08-0.53	.001
Fractionated SRS (vs single fraction)	0.15	0.04-0.62	.01
Type of surgery			
Piecemeal	1 [Reference]	NA	NA
En bloc	0.34	0.13-0.89	.03
Unknown	0.46	0.21-1.05	.07
Primary site			
NSCLC	1 [Reference]	NA	NA
Breast	1.69	0.84-3.43	.14
Melanoma	1.13	0.44-2.92	.80
Kidney cell	3.19	0.04-2.43	.27
Gastrointestinal	2.97	0.95-9.32	.06
Other	1.66	0.64-4.35	.30

Table 3. Multivariable Analysis for Meningeal Disease via the Fine and Gray Method

Variable	Hazard ratio	95% CI	P value
GTR (vs STR)	0.18	0.06-0.55	.003
Primary site			
NSCLC	1 [Reference]	NA	NA
Breast	5.64	1.63-19.6	.01
Melanoma	7.89	2.07-30.1	.003
Kidney cell	4.33	0.64-39.4	.13
Gastrointestinal	2.26	0.24-21	.47
Other	4.60	1.14-18.5	.03
Posterior fossa (vs supratentorial)	2.38	0.98-5.78	.06
Type of surgery			
Piecemeal	1 [Reference]	NA	NA
En bloc	0.43	0.12-1.51	.19
Unknown	0.28	0.06-1.25	.10

PROPS-BM International **SINGLE Standard Dose vs ↓ Dose** PREOPERATIVE SRS

Prospective 307 patients with 307 preoperative SRS treated index lesions at least 1 lesion measuring ≤ 4 cm.

	Std Dose	Reduced Dose
≤ 2 cm lesion	20 Gy	16 Gy
>2 to 3 cm	18 Gy	15 Gy
>3 to 4 cm	15 Gy	

SD was used in 124 patients (40%) and RD was used in 183 patients (60%).

Prabhu, Advances in Radiation Oncology 2025

The cohort consisted of 307 patients with 307 preoperative SRS treated index lesions.
2-year cavity LR 16% vs 15% (*P* = .69), adverse radiation effect 8% vs 6%, (*P* = .77), meningeal disease 2% vs 8% (*P* = .07), composite endpoint of cavity LR, ARE, or nodular meningeal disease (23% vs 22%, *P* = .86), or OS 49% vs 36%, (*P* = .15). Results were similar within each specific lesion diameter subgroup and within the propensity score matched cohorts (n = 168).

Conclusions Both SD and RD single fraction preoperative SRS demonstrate excellent rates of cavity LR and ARE. Cavity LR risk increased with larger lesion size, regardless of SRS dose category. There does not seem to be an advantage in efficacy or toxicity for RD over SD single fraction preoperative SRS. Additional studies are warranted to optimize preoperative SRS dose and fractionation.

Phase I Dose Escalation Trial PREOPERATIVE SRS

Prospective 35 patients with 36 mets ≥ 2 cm received SINGLE fraction SRS prior to resection.

Dose **18 Gy → 21 Gy for 2-3 cm mets**
15 Gy → 21 Gy for 3-4 cm mets
12 Gy → 18 Gy for 4-6 cm mets

Murphy, Neuro-Oncology 2024

The 2-3 cm group had no dose limiting toxicity up to a dose of 21 Gy in 1 fraction.
Two acute grade 3+ events occurred in the 3-4 cm group at a dose of 21 Gy leading to a maximum tolerated dose of 18 Gy in 1 fraction for mets larger than 3 cm. One patient developed late radiation necrosis, and no patients developed leptomeningeal disease.

Conclusions

Preoperative SRS with dose escalation followed by surgical resection for brain metastases greater than 2 cm in size demonstrates acceptable acute toxicity. The phase II portion of the trial will be conducted at the maximum tolerated SRS doses.

SAFESTEREO Phase II

Two arm phase II. Standard arm = 1 or 3 fx SRS. Experimental arm = 5 fractions.
One or more brain mets.
PTV = 0-2 mm expansion. If lesions is in or adjacent to brainstem, PTV margin is 0.
If a margin of 0 mm is used, the max intrafraction motion should be less than 0.5 mm, with a SD of less than 0.25 mm.
Dmax generally 140% Linac and 200% GK.
V100% Dose= 99% PTV coverage.

PTV of brain metastases (cm3)	Dose 1 fraction (Gy)	Dose when metastasis in brainstem (Gy)	Dose 5 fractions (Gy)	Dose when metastasis in brainstem (Gy)
< 1	24	16	35	30
1–10	21	16	35	30
10–20	18	16	35	30
20–65	15 or 3 × 8	No SRS	35	No SRS

Table 2 Organs at risk dose constraints

	1 fraction (Gy)		3 fractions (Gy)		5 fractions (Gy)	
	Optimal	Mandatory	Optimal	Mandatory	Optimal	Mandatory
Brainstem Dmax	10	18	24	27	23	30
Cochlea Dmean	4	9	17	20	22	25
Chiasm Dmax	8	10	15	23	20	25
Lens Dmax	1	3	2	4	3	5
Optic nerves Dmax	8	10	15	23	22	25
Pituary gland Dmean	8	10	15	23	22	25

Dmax Maximum dose, *Dmean* Mean dose

1^{O} local adverse event (LF or radionecrosis).

Crouzen, BMC Cancer 2023

Discussion Currently, limiting the risk of adverse events such as radionecrosis is a major challenge in the treatment of brain metastases. fSRS potentially reduces this risk of radionecrosis and local tumor failure.

PENDING RESULTS

Sunnybrook 5 Fraction SRS

RR 220 patients with 334 brain metastases treated with HSRT.
Median size of treated metastasis 1.9 cm; 60% of metastases were <2 cm in size; 10% were > 3 cm.
70% had multiple mets but only 36% received HSRT to multiple targets and 22% received prior WBRT.
The median total dose was 30 Gy in 5 fractions (46%); 36% of the cohort received <30 Gy (24% received 25 Gy).
Margins 2-3 mm.

Myrehaug, IJROBP 2021.
Median time to LF 8.5 months. 12-month CI of LF 23.8%.
Median time to death 11.8 months 12-month OS 48.2%.
Fifty-two metastases (15.6%) had an adverse radiation effect, of which 32 (9.5%) were symptomatic necrosis.
MVA ↑ LF if dose of <30 Gy vs. ≥ 30 Gy (HR 1.62; *P* = .03) → 6-month LF 13% vs. 5%.
→ 12-month LF 33% vs. 19%
Exploratory analysis demonstrated a dose-response effect observed in all histologic types, including among breast cancer subtypes.
Conclusion Optimal local control is achieved with HSRT of ≥30 Gy in 5 daily fractions, independent of tumor volume and histology, with an acceptable risk of radiation necrosis.

RTOG 91-04

←R→ 445 patients KPS ≥ 70 and NFS 1-2 | 1. 30 Gy in 10 fx | 2. 32 Gy in 20 fx BID (1.6 Gy/fx) → boost 54.4 Gy BID |.

Regine, IJROBP 2001.
No benefit and no difference in G3-4 toxicity. 1 G 5 in arm 2.

Post-op MRI Timing

NOTE: Regarding post-op MRI timing, there is no clear consensus. However, it would be prudent to obtain a post-op MRI within 2-3 weeks and then to start RT within 3-4 weeks.

NOTE: ALLIANCE Inclusion Criteria:
Resection cavity must measure < 5.0 cm in maximal extent and the resection must be complete (gross total resection) on the post-operative MRI obtained =< 30 days prior to pre-registration.

MSK Early Post-op SRS Timing Study
Prospective 438 patients with an objective to **"To evaluate whether adjuvant SRS delivered within a median of 14 days after surgery is associated with ↑LF without a concomitant ↑ in posttreatment adverse radiation effects (PTRE)."**
Patients from 2019 to 2022 and surgery → SRS within a median of 14 days, ensuring all treated within 30 days.
Prospective cohort was compared with a historical cohort (StanRT) of patients with BrM resected between 2013 and 2019 to assess the association of the RapidRT workflow with LF and PTRE.
The 2 cohorts were combined to identify optimal SRS timing, with a median follow-up of 3.3 years for survivors.
Exposure: Timing of adjuvant SRS (14, 21, and 30 days postoperatively).

Bander, JAMA Network Open 2023

1-year PTRE	SRS < 14 days 18.1%		22-30 days 4.1%	**p=0.03**
1-year LF	SRS < 14 days 5.2%	15-21 days 3.21%	22-30 days 6.58%	> 30 days 10.6%

Conclusions: In this cohort study of adjuvant SRS timing following surgical resection of BrM, the optimal timing for adjuvant SRS appears to be within 22 to 30 days following surgery. The findings of this study suggest that this timing allows for a balanced approach that minimizes the risks associated with LF and PTRE.

Cornell Post-op SRS within or after 4 weeks
RR 133 patients 64.5 years median age from 2012-2018. About half had single BM and median BM size 2.9 cm.
GTR 83.5% and > 90% received fractionated SRS.
Median time to SRS was 37 days.

O'Brien, PRO 2021

LR rate was 16.4%.	Time to SRS was predictive of LR.	
Median time surgery → SRS	Without LR vs. with LR	34.0 vs. 61 days (P < 0.1).
Local Recurrence by time of surgery → SRS	**≤ 4 vs. > 4 weeks**	**2.3% vs. 23.6% (*P* < .01).**

Local recurrence-free survival was also improved for patients who underwent SRS at ≤4 weeks (*P* = .02).
Delayed SRS was also predictive of distant recurrence (*P* = .02) but not overall survival.
Conclusions
In this retrospective study, the strongest predictor of LR after postoperative SRS for BM was time to SRS, and a cutoff of 4 weeks was a reliable predictor of recurrence. These findings merit investigation in a prospective, randomized trial.

and Size

Japanese # Brain Met Study
Prospective Observational. SRS w/o WBRT. 1194 patients. 1-10 newly diagnosed brain mets KPS ≥ 70.
SRS < 4 cc given 22 Gy at the lesion periphery. SRS 4-10 cc with 20 Gy. **1^{o} OS between 2-4 mets vs. 5-10 mets**.

Yamamato, Lancet Oncol 2014.
Median OS 1 met 13·9 mo, 2-4 mets 10·8 mo, 5-10 mets 10·8 mo.
SRS adverse events occurred in 101 (8%) patients.
Interpretation Our results suggest that stereotactic radiosurgery without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases. Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side-effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases.

NOTE: 2nd SRS (salvage) 38% OVERALL. 1 met 33% vs. 2-4 or 5-10 mets all 43%.

Japanese Large Met Triple Staged
Single Arm 43 patients. Large brain metastases (> 10 cc in volume). Primary tumors were in the colon in 14 patients, lung in 12, breast in 11, and other in 6. "Peripheral dose" was 10 Gy x 3 fx. The interval between fractions was 2 weeks. The mean tumor volume before treatment was 17.6 ± 6.3 cc.

Higuchi, IJROBP 2009.
CC at 2nd fraction mean tumor volumes were 14.3 cc (18.8% reduction) and 3rd fraction 10.6 cc (39.8% reduction).
Median overall survival period was 8.8 months.
Neurological and qualitative survivals at 12 months were 81.8% and 76.2%, respectively.
Local tumor control rates were 89.8% and 75.9% at 6 and 12 months, respectively.
Tumor recurrence-free and symptomatic edema-free rates at 12 months were 80.7% and 84.4%, respectively.
Conclusions
The 2-week interval allowed significant reduction of the treatment volume. Our results suggest staged stereotactic radiotherapy using our protocol to be a possible alternative for treating large brain metastases.

Japanese Large Met DOUBLE staged.
27 patients with 28 lesions GKSRS with large brain met (vol >15 cm^3 in supratentorial or >10 cm^3 in infratentorial region).
CANNOT HAVE HERNIATION.
DOSE = 20–30 Gy given in 2 fractions 3–4 weeks apart (Many physicians do 13 Gy x 2).

Yomo, J Neurooncol 2012.
Median tumor volumes were 17.8 cm^3 at first GKS and 9.7 cm^3 at second GKS.
LC was 85 % at 6 months and 61 % at 12 months.
OS was 63 % at 6 months and 45 % at 12 months.
The 1-year rate of prevention of neurological death was maintained at 78 %.
Mean KPS ↑ from 61 to 80 at second GKS.
Conclusion: Two-session GKS for large brain mets appears to be an effective tx in terms of both local tumor control and neurological palliation with minimal treatment-related morbidity. These data suggest that two-session GKS could be used as an alternative to surgical resection of large tumors in patients with significant comorbidity and/or at an advanced age. The optimum regimen for dose and fraction schedule remains to be established.

Italian Large Met TRIPLE staged
Single Arm 289 patients with brain met > 2 cm. MULTI FRACTION = 9 Gy x 3.

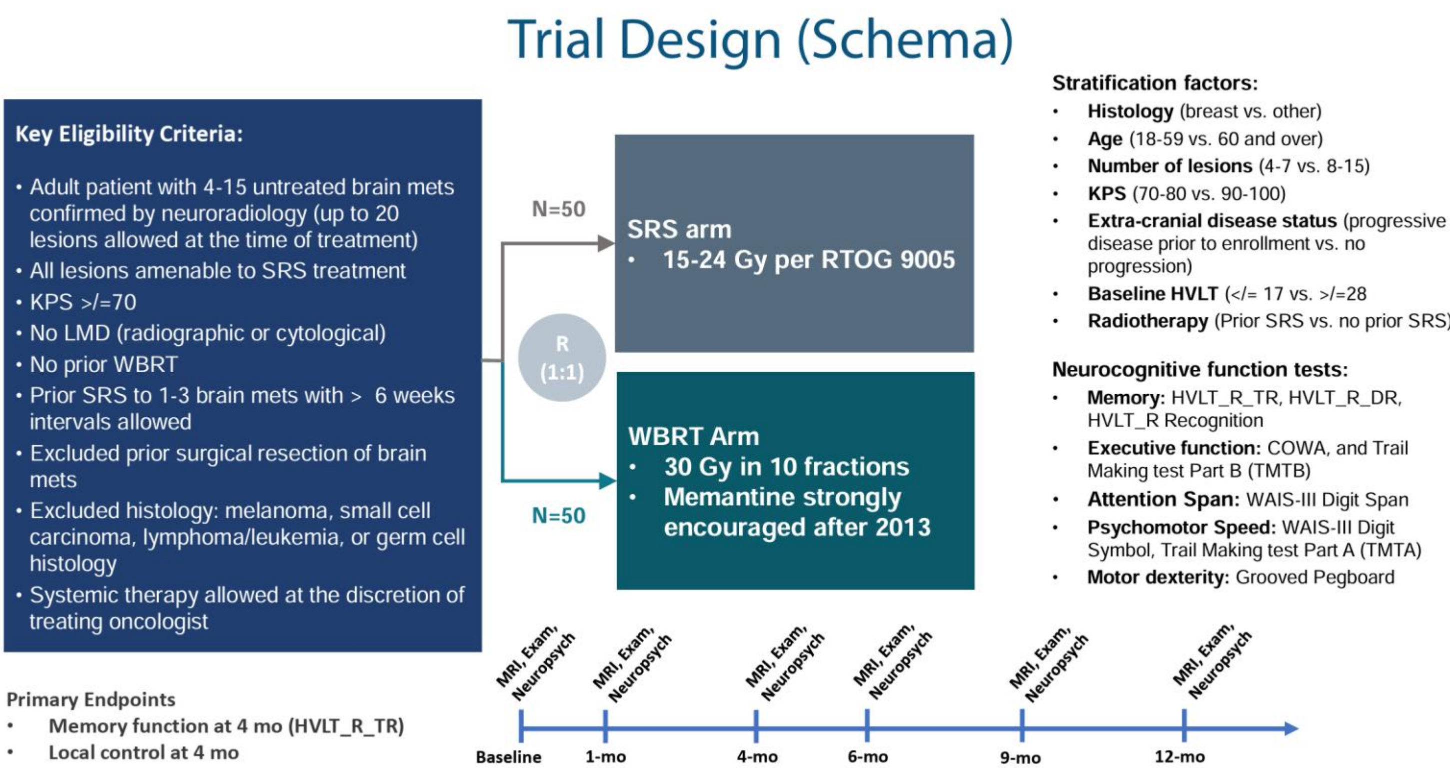
Minniti, IJROBP 2016.
1-year cumulative LC 77% in single-fraction SRS (SF-SRS) group and 91% in the multifx SRS (MF-SRS) group (*P*=.01).
Brain radio necrosis n=31 (20%) vs. n=11 (8%) (*P*=.004).
1-year cumulative incidence rate of radionecrosis was 18% and 9% (*P*=.01)
Conclusions: Multifraction SRS at a dose of 27 Gy in 3 daily fractions seems to be an effective treatment modality for large brain metastases, associated with better local control and a reduced risk of radiation-induced radionecrosis as compared with SF-SRS.

WBRT & SRS Studies

Upfront WBRT vs. SRS

#4-15 MD Anderson Brain Met RTC
←R→ 72 patients from 2012-2019 with 4-15 untreated non-melanoma BMs → | **1. SRS** | 2. WBRT |.
Memantine was encouraged in the WBRT arm after publication of RTOG 0614. In the WBRT arm, 62% of patients received memantine.
Prior SRS to 1-3 BMs with at least 3 months (mos) interval was allowed.
Test of neurocognitive function (NCF) at baseline and longitudinally including tests of learning and memory (HVLT-R), verbal fluency (Controlled Oral Word Association (COWA), and processing speed and executive function (Trail Making Test Parts A/B [TMTA] [TMTB]).

1^{O}s → HVLT-R TR and local control (LC) at 4 mos.
2^{Os} → additional NCF tests, overall survival (OS), distant brain failure, toxicity, and time to systemic therapy.
The trial was terminated early due to slow accrual.
Median # BM = 8.



Li, IJROBP 2020

4-month HVLT-R TR	↑ +0.21 vs. ↓ -0.74 (p = 0.041).
4-month NCF	↑ +0.23 vs. ↓ -0.73 (p = 0.008).
Median OS	10.4 mos vs. 8.4 mos (p = 0.45).
4-month LC	100% SRS vs. 95.5% for WBRT (p = 0.53).

Median time to distant brain failure (DBF 4.3 mos vs.18.1 mos (p = 0.09).

4- month LC 95% SRS vs. 87% WBRT (p = 0.79)
4-month Distant brain control 60% vs 80% (p = 0.37)
Time to systemic therapy 1.7 weeks (SRS) vs 4.1 weeks (WBRT) (p=0.001)
> Grade 3 toxicities 8% (SRS) vs 15% (WBRT)
Radiation necrosis: 17% at patient level and 4% at lesion level

Conclusion
The results from this phase III randomized trial strongly supports the use of SRS in patients with 4-15 brain metastases to 1. better preserve cognitive function and to 2. minimize interruption of systemic therapy, without 3. compromising OS .

Phase III SRS #5-20 BM: SRS vs. HA-WBRT
←R→ 198 patients | 1. SRS | 2. HA-WBRT | median BMs 14 (11-18).
Exclusion: Non-solid primaries, SCLC, LMD.
1^{O} average patient reported symptoms severity over 1^{st} 6 months using **MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT) module** → 22 symptoms and 6 interference measures integral to quality of life, each scored 0-10 (0 = best).
25% of patients underwent prior neurosurgical resection.

Aizer, ASCO 2025
Baseline MDASI- 2.2 (SRS/SRT arm) and 1.9 (HA-WBRT arm), p=0.20.
Respective interference scores were 3.5 and 3.2 (p=0.40).
Averaged **Post-baseline symptom severity scores minus baseline -0.03 vs. 0.59 (Δ -0.62, p<0.001).**
Respective interference estimates -0.62 vs. 0.89 (Δ -1.50, p<0.001).
Median survival was 8.3 and 8.5 months in the SRS/SRT and HA-WBRT arms, respectively (p=0.30).
Conclusions: This phase 3 randomized trial indicates that patients with 5-20 brain metastases experience fewer symptoms and less interference in function after SRS/SRT as opposed to HA-WBRT, without compromise of survival, supporting SRS/SRT as the standard of care in this population. Clinical trial information: NCT03075072.

Surgery → SRS or WBRT

NCCTG N107C/CEC·3 Dose Study North American - USA and Canada Phase III
←R→ 194 patients. **One resected brain met** and a resection cavity < 5 cm in maximal extent.
| 1. SRS 12-20 Gy x 1 | 2. WBRT 30 Gy in 10 or 37.5 in 15 |.
SRS prescribed dose determined by surgical cavity volume:

20 Gy if cavity volume < 4·2 mL
18 Gy if 4·2–7·9 mL
17 Gy if 8·0–14·3 mL
15 Gy if 14·4–19·9 mL
14 Gy if 20·0–29·9 mL
12 Gy if 30·0 mL or maximal surgical cavity of 5 cm.

Note: any unresected metastases → 1 fx SRS
24 Gy if < 1·0 cm
22 Gy if 1·0–2·0 cm
20 Gy if 2·1–2·9 cm max diameter.

7.341 Prescription Specification: The dose should be prescribed to the highest isodose line encompassing the CTV2 (surgical cavity plus 2 mm – see Section 7.331), which can range from 50% to 90% of the maximum dose.

7.344 Dose Conformity: The ratio of the prescription isodose volume to the target volume (CTV2) should be between 1.0 and 2.0. It is understood that this ratio may be difficult to achieve with some very small lesions. For lesions less than 5 mm in size, a ratio up to 3.0 is acceptable. See Radiation Therapy
Quality Control Guidelines (Appendix VII).

Dose Breakdown WBRT n=96 patients 30 Gy in 10 (n=49), 37·5 Gy in 15 (n=43)

SRS Breakdown unable to determine based on study or appendix.

Supplemental Table S3.
Intracranial Brain Control Rates

	Control Estimates (95%CI) SRS	WBRT	Gray's K-sample p-value
Surgical Bed Control			
at 3 months	95·9% (92·0, 99·9)	93·5% (88·7, 98·7)	p = 0·00068
at 6 months	80·4% (72·8, 88·7)	87·1% (80·5, 94·2)	
at 12 months	60·5% (51·3, 71·3)	80·6% (73·0, 89·1)	
Local Control			
at 3 months	84·7% (77·9, 92·1)	96·7% (93·2, 100)	p = 0·00016
at 6 months	69·4% (60·8, 79·1)	92·5% (87·3, 98·0)	
at 12 months	61·8% (52·8, 72·3)	87·1% (80·5, 94·2)	
Distant Brain Control			
at 3 months	88·7% (82·6, 95·2)	96·8% (93·3, 100)	p = 0·00045
at 6 months	72·1% (63·7, 81·6)	94·6% (90·1, 99·3)	
at 12 months	64·7% (55·8, 75·0)	89·2% (83·1, 95·8)	
Leptomeningeal Disease Control			
at 3 months	98·0% (95·2, 100)	97·9% (95·0, 100)	p = 0·62
at 6 months	93·9% (89·2, 98·7)	96·8% (93·3, 100)	
at 12 months	92·8% (87·8, 98·1)	94·6% (90·1, 99·3)	
Total Intracranial Brain Control (based on time to first recurrence of any type)			
at 3 months	79·6% (72·0, 88·0)	90·4% (84·7, 96·6)	p < 0·0001
at 6 months	55·1% (46·1, 65·9)	80·8% (73·1, 89·2)	
at 12 months	36·6% (28·1, 47·8)	72·1% (63·6, 81·8)	

Brown, Lancet 2017.
Cognitive deterioration free survival 3.7 mo vs. 3.0 mo (SS).
6-month cognitive deterioration 52% vs. 85% (SS).
Median OS 12.2 mo vs. 11.6 mo (NS).
Time to intracranial tumor progression 6.4 mo vs. 27.5 mo

6-month surgical bed control 80.4% vs. 87.1% (NS)
Other Side effect: hearing impairment 3% vs. 9%.
NOTE: LMD low (7.2% after SRS and 5.4% after WBRT).

COMMENTARY:
The low SRS LC rates are due to patients receiving < 18 Gy. Per protocol, any spherical lesion with a ~ 3 cm diameter (≈ 14 mL in volume) received maximum 15 Gy in 1 fraction, with patients having ~ 4 cm diameter (≈ 33 mL in volume) receiving 12-14 Gy in 1 fraction, a SRS dose far too low to be effective.

Recall:

20 Gy in 1 fraction	EQD2 50.00 Gy	BED_{10} 60.0 Gy
18 Gy in 1 fraction	EQD2 42.00 Gy	BED_{10} 50.4 Gy
17 Gy in 1 fraction	**EQD2 38.25 Gy**	**BED_{10} 45.9 Gy**
15 Gy in 1 fraction	EQD2 31.25 Gy	BED_{10} 37.5 Gy
14 Gy in 1 fraction	EQD2 28.00 Gy	BED_{10} 33.6 Gy
27 Gy in 3 fraction	EQD2 42.75 Gy	BED_{10} 51.3 Gy
30 Gy in 5 fraction	EQD2 40.00 Gy	BED_{10} 48.0 Gy

Palmer, JAMA Oncology 2022 **Outcomes after 1 year Survival**
54 patients (27 SRS arm, 27 WBRT arm; female to male ratio, 65% vs 35%) were included for analysis with a median follow-up of 23.8 months. Cognitive deterioration SRS (37%-60%) vs. WBRT (75%-91%) at all time points.

More patients ↓ by ≥ 2 SDs in ≥ 1 cognitive tests at 3 mo (22% vs. 70%), 6 mo (19% vs. 46%), 9 mo (20% vs. 50%).

A 2 SD ↓ in ≥ 2 cognitive tests = associated ↓ 12-mo QOL in emotional and functional well-being, general, additional concerns, and total scores.

1-year Total intracranial control 40.7% vs 81.5% (Δ−40.7; 95% CI, −68.1% to −13.4%).
Data were first analyzed in February 2017.

WBRT → ± SRS

RTOG 95-08. ←R→ 333 with **1-3 brain mets**: | WBRT 37.5 in 2.5 fxs | WBRT + SRS within 1 week of finishing WBRT |. Mets must be ≤ 4 cm in size and only 1 mets can be > 3 cm.
Note: RT dose was dependent on the size: 24 Gy to ≤ 2cm, 18 for 2-3cm, 15 for > 3cm. BASE ON RTOG 90-05

Andrews, Lancet 2004. Univariate MS WBRT + SRS better: 4.9 mo → 6.5 mo in **SINGLE brain met.**
Stable or ↑ KPS at 6 months 27% → 43%.
Multivariate → survival ↑ if class 1 or a favourable histological status. SRS also ↓ need for steroids.
Must *consider* SRS + WBRT if **multiple** mets.

	Mean Survival (mo)						1-year LR	Stable / ↑KPS at 6 mo
	Overall	**Single met**	**Met >2 cm***	**RPA class I***	SCC NSCLC	KPS ≥ 90		
WBRT	6.5	**4.9**	**5.3**	**9.6**	3.9	7.4	**29%**	**25%**
WBRT → SRS	5.7	**6.5**	**6.5**	**11.6**	5.9	10.2	**18%**	**42%**
P	0.136	**0.039**	**0.045**	**0.045**	0.051	0.071	**0.013**	**0.033**

*** Subgroup analysis.**

Interpretation: WBRT and stereotactic boost treatment improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable brain metastasis. WBRT and stereotactic radiosurgery should, therefore, be standard treatment for patients with a single unresectable brain metastasis and considered for patients with two or three brain metastases.

± WBRT → SRS

Japanese Radiation Oncology Study Group (JROSG) 99-1 **1999 to 2003**
←R→ 132 patients with **1 to 4 brain metastases**, each < 3 cm in diameter | 1. SRS alone | 2. WBRT → SRS |
WBRT = 30 Gy in 10 fx. The mean SRS dose was 21.9 Gy in SRS alone and 16.6 Gy in WBRT + SRS.
1^{O} OS.

Aoyama, JAMA 2006.

	MS	1-yr Any recurrence	1-year LR	1-year Distant R	Neuro Death	Neuro Preservation
SRS	8 mo	**76%**	**27.5%**	**64%**	19%	70%
WBRT → SRS	7.5 mo	**47%**	**11%**	**42%**	23%	72%
P	NS	**< 0.001**	**0.002**	**0.003**	NS	NS

CONCLUSIONS: Compared with SRS alone, the use of WBRT plus SRS did not improve survival for patients with 1 to 4 brain metastases, but intracranial relapse occurred considerably more frequently in those who did not receive WBRT. Consequently, salvage treatment is frequently required when up-front WBRT is not used.

Aoyama, JAMA 2015 UPDATED
RESULTS: 47 patients favorable prognosis, with DS-GPA scores of 2.5 to 4.0.
41 patients unfavorable prognosis, with DS-GPA scores of 0.5 to 2.0
OS with DS-GPA 2.5-4.0. 10.6 mo vs. 16.7 mo (HR 1.92, P = .04).
OS with DS-GPA 0.5-20 NS
This benefit could be explained by the differing brain tumor recurrence (BTR) rates, in that the prevention against BTR by WBRT had a more significant impact in the DS-GPA 2.5-4.0 group (HR, 8.3; P < .001) vs the DS-GPA 0.5-2.0 group (HR, 3.57; P = .04).
Conclusions and relevance: Despite the current trend of using SRS alone, the important role of WBRT for patients with BMs from NSCLC with a favorable prognosis should be considered. Our findings should be validated through appropriately designed prospective studies.

SRS → ± WBRT

NCCTG N0574
←R→ 213 patients with 1-3 brain mets | 1. SRS | 2. SRS → WBRT |.
WBRT 30 Gy in 12 fx.   SRS 18 - 22 Gy if both   SRS 20 to 24 Gy for SRS alone.
1^{O} cognitive deterioration (decline >1 SD from baseline on at least 1 cognitive test at 3 months).

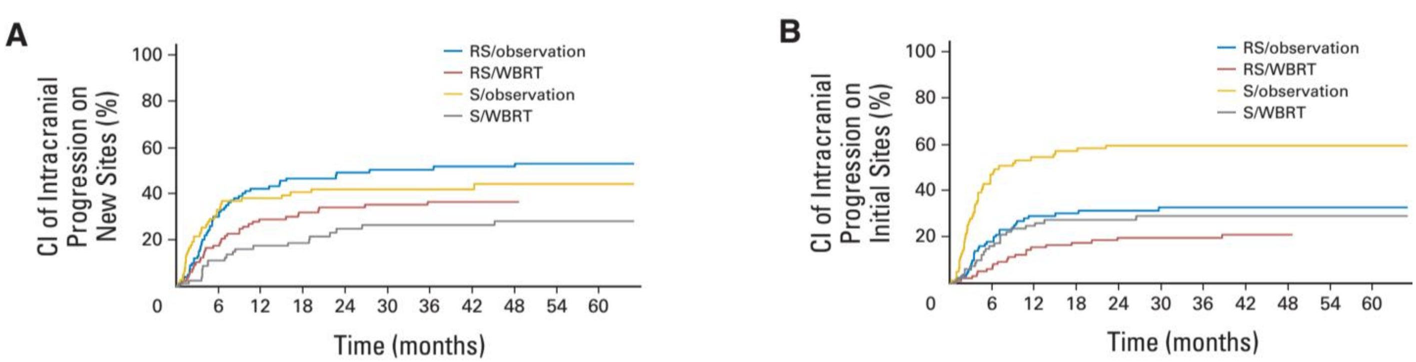
Brown, JAMA 2016.
Cognitive deterioration at 3 months 63.5% vs. 91.7% (SS).
QoL mean Δ from baseline, −1.3 vs −10.9 points (SS).
Time to intracranial failure was significantly shorter for SRS alone compared with SRS plus WBRT (HR 3.6; SS).
No SS in functional independence at 3 months between the treatment groups.
Median OS overall survival was 10.4 months for SRS alone and 7.4 months for SRS plus WBRT (HR 1.02, NS).
For long-term survivors, 3-month incidence of cognitive deterioration 45.5% vs. 94.1% (SS).
Conclusions and Relevance: SRS >> SRS → WBRT for cognitive deterioration. In the absence of a difference in OS, SRS alone may be a preferred strategy for patients with 1 to 3 brain metastases.

Question: If survival is not improved adding SRS to WBRT, do the neurocognitive risks of adding WBRT to SRS outweigh the benefits?

Chang, Lancet Oncology 2009   Trial was stopped early.
←R→ N = 58 | 1. SRS | 2. SRS + WBRT | WBRT = 20 Gy in 12 fractions. Hopkins verbal learning test.
WBRT ↑ rate of cognitive decline   4-month cognitive decline   4/20 (**20%**) vs. 7 /11 (**64%**)
WBRT ↑ LC 67 → 100%.   WBRT ↑ distant control 45% → 73%.
However, MS was 15.2 mo SRS vs. 5.7 mo WBRT + SRS probably due to treatment arm imbalance.

EORTC 22952. ←R→ 359 patients s/p complete resection or SRS, with WHO ≤ 2, 1-3 brain mets. Excluded brain mets of SCLC, lymphoma, leukemia, MM, or germ cell tumors.   199 ←R→ before SRS. 160 ←R→ after surgery.
1^{O} treatment → WBRT | Obs.
SRS criteria ≤ 3 cm and ≤ 2.5 if multiple.

Kocher, JCO 2011.
Results: Median time from baseline to WHO performance status (PS) >2, after OBS 10 mo | after WBRT 9.5 mo.
OS ≈ in WBRT | OBS arms (median, 10.9 | 10.7 months).
WBRT ↓ 2 yr relapse rate at *initial sites* after surg 59% → 27% and SRS 31% → 19%
at new sites after surg 42% → 23%, and SRS 48 → 33%
Salvage therapies used more after OBS than after WBRT.
Intracranial progression related deaths OBS 78 (44%) of 179 | WBRT 50 (28%) of 180 patients.
Conclusion: After radiosurgery or surgery of a limited number of brain metastases, adjuvant WBRT reduces intracranial relapses and neurologic deaths but fails to improve the duration of functional independence and overall survival.
Even though this study wasn't surgery vs SRS, the LC of SRS arm was better than surgery.
Conclusion: Perhaps WBRT can be omitted in select patients.



A

Randomized treatment	O	N	No. of patients at risk									
RS/observation	51	100	43	16	9	6	3	3	2	2	1	1
RS/WBRT	35	99	59	26	16	10	7	5	3	1	0	0
S/observation	34	79	23	15	10	7	4	3	3	1	1	1
S/WBRT	21	81	47	30	23	11	9	8	8	7	6	4

B

Randomized treatment	O	N	No. of patients at risk									
RS/observation	32	100	43	16	9	6	3	3	2	2	1	1
RS/WBRT	20	99	59	26	16	10	7	5	3	1	0	0
S/observation	47	79	23	15	10	7	4	3	3	1	1	1
S/WBRT	23	81	47	30	23	11	9	8	8	7	6	4

Metaanalysis, Sahgal.
←M→ 3 trials ABOVE: **Aoyama, Chang, Kocher.**
Patients 364 of pooled 389 patients met eligibility criteria (51% SRS alone, 49% SRS plus WBRT).
Note: For survival, age was a significant effect modifier (P=.04) favoring SRS alone in patients ≤50 years of age, and NS Δ observed in older patients.

Patients with a single metastasis had **significantly better survival** than those who had 2 to 4 metastases.
For distant brain failure, age was a significant effect modifier (P=.043), with similar rates in the 2 arms for patients ≤50 of age….otherwise, the risk was reduced with WBRT for patients >50 years of age. Patients with a single metastasis also had a significantly lower risk of distant brain failure than patients who had 2 to 4 metastases.

Local control significantly favored additional WBRT in all age groups.

CONCLUSIONS: For patients ≤50 years of age, SRS alone favored survival, in addition, the initial omission of WBRT did not impact distant brain relapse rates. SRS alone may be the preferred treatment for this age group.

TTF Studies

METIS Study
←R→ 298 patients with 1–10 newly diagnosed NSCLC BM for SRS and receiving optimal therapy for extracranial disease.
Exclusion: prior WBRT, presence of known druggable mutations, single operable or recurrent BM were exclusion criteria.
| 1. SRS → by TTFields therapy (150 kHz) | 2. SRS alone |.
1^{O} time to intracranial progression (TTIP, RANO-BM).
2^{O} time to distant progression (TTDP), neurocognitive function, overall survival (OS), quality of life (QoL) and safety.
Median age 63-64, KPS 80 (80%), Median time from NSCLC diagnosis 1.5-2 yrs, AC 75-80%.
Median duration of TTF was 15.7 weeks. Median monthly usage was 67%.

Gondi, ASTRO 2025

Intracranial Progression Rates	2 months	6 months	12 months	24 months
SRS → TTF	13.6%	33.7%	46.9%	53.6%
SRS	22.1%	46.4%	59.4%	65.2%
p	0.034	0.018	0.023	0.031

In 118 pts with immune checkpoint inhibitors (ICI)…
TTIP benefit was ↑↑ (HR 0.63, 95% CI 0.39–1.0; Cox p=0.049; Fine-Gray test p=0.055; post-hoc).
No difference in TTDP was observed overall (HR 0.76, 95% CI 0.51-1.12, p=0.165; post-hoc).
TTF delayed TTDP compared with SRS alone (HR 0.41, 95% CI 0.21–0.81; p=0.009; post-hoc).
Time to neurocognitive failure, OS and radiological response rate **did** not differ significantly.
Device-related AEs were mainly grade =2 skin events.
TTF did not cause QoL deterioration.
TTF ↑ deterioration-free survival and time to deterioration of global health status, physical functioning and fatigue were observed (post-hoc).
Conclusion: By significantly prolonging time to intracranial progression, without deteriorating QoL or cognitive function, TTFields therapy after SRS is a potential new treatment option for pts with NSCLC BM.

Immunotherapy

OCEAN Study Phase II Osimertinib --| Δ T790M
Background: The T790M mutation (Δ T790M) is a major cause of acquired resistance to EGFR TKIs.
Two Cohorts with 66 patients having RT naïve CNS met from Δ EGFR NSCLC.
Cohort 1 Δ EGFR T790M (n=40) Cohort 2 first-line (n=26)
Brain met must be at least 0.5 cm in size. Median brain met 0.84 cm (range 0.5 – 2.7 cm).
All received 80 mg osimertinib daily.
Median age 69 yo and 30% were males. Eight patients (20%) symptomatic. Most had multiple CNS metastases (78%).

Yamaguchi, Thornal Thoracic Oncology 2021
Among 39 patients eligible…
Median brain met-related PFS 25.2 months
Median OS 19.8 months Median PFS 7.1 months
Median Overall Response Rate 40.5%
The BMRR according to the Response Evaluation Criteria in Solid Tumors criteria was 70.0% (n = 20).
Brain metastasis-related PFS with *EGFR* exon 19 deletion 31.8 months vs. exon 21 L858R (8.3 mo; $p = 0.032$).
The treatment-related pneumonitis was observed in four patients (10%).
Conclusions This study evaluated the efficacy of osimertinib against RT-naive CNS metastasis from T790M-positive NSCLC. The primary end point was met, and the results revealed the efficacy of osimertinib in patients with CNS metastasis harboring *EGFR* T790M mutations especially for *EGFR*-sensitizing mutation of exon 19 deletion.

AURA LMD Study
RR 22 patients across AURA Studies/Program with EGFR T790M-positive advanced NSCLC with CNS lesions including LMD after progression after previous EGFR-tyrosine kinase inhibitor therapy received osimertinib (80 mg qd).

Ahn, Journal Thoracic Oncology 2020
LMD objective response rate was 55% and Median LM PFS was 11.1 months and Median LM OS was 18.8 months.
Conclusions
Patients with EGFR T790M-positive NSCLC and radiologically detected LM obtained clinical benefit from osimertinib (80 mg qd).

Concurrent ICI Study
RR 179 patients treated with SRS for brain met 385 brain lesions.
36 patients (with 99 lesions) had ICI within 3 months from SRS.
Concurrent SRT-ICI were more commonly squamous histology (17% vs 8%) melanoma (20% vs 2%) or renal cell carcinoma (8% vs 6%), ($p < 0.001$). Non-small cell lung cancer (NSCLC) compromised 60% of patients receiving ICI ($n = 59$).

Kowalski, Radiation Oncology 2020
1-year LC concurrent SRT-ICI 98% vs. SRT alone 89.5% ($p = 0.0078$).
Subset analysis of NSCLC patients alone, 1-year LC 100% vs. 90.1% ($p = 0.018$).
MVA, only tumor size ≤2 cm was significantly associated with LC (HR 0.38, $p = 0.02$), whereas the HR for concurrent ICI with SRS was 0.26 ($p = 0.08$).
1-year DBF (41% vs. 53%; $p = 0.21$), OS (58% vs. 56%; $p = 0.79$) and RN incidence (7% vs. 4%; $p = 0.25$) were similar for SRT alone versus SRT-ICI, for the population as a whole and those patients with NSCLC.
Note: NS but radionecrosis was 7% vs. 4%.
Conclusion These results suggest SRT-ICI may improve local control of brain metastases and is not associated with an increased risk of symptomatic radiation necrosis in a cohort of predominantly NSCLC patients. Larger, prospective studies are necessary to validate these findings and better elucidate the impact of SRT-ICI on other disease outcomes.

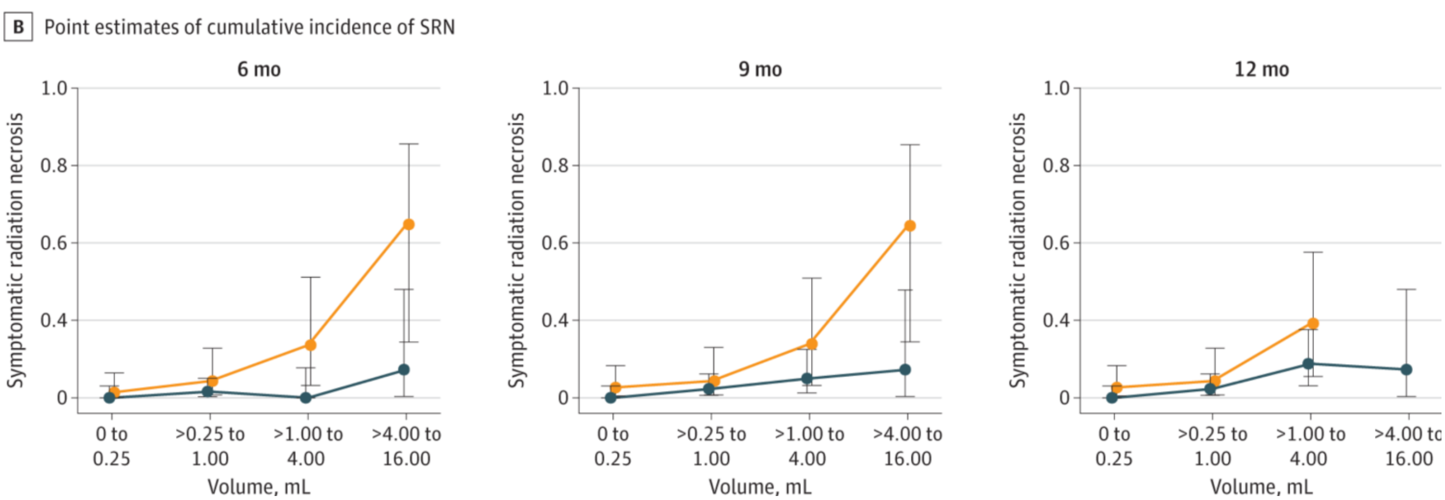
Yale ICI Alone (without SRS) Phase II

Single institution with 42 asymptomatic brain met between 0.5 cm – 2 cm → pembro alone 10 mg/kg IV q2 weeks.
42 patients with at least 18 years of age with Stage IV NSCLC not previously treated or progressing after previous RT.
No neurological symptoms or corticosteroid requirement.
Cohort 1: PD-L1 Expression ≥ 1%   Cohort 2: <1% or unevaluable
1^{O} brain met response (PR or CR).

Goldberg, Lancet 2020   **Median follow-up 8.3 months**
Brain response Cohort 1 (29.7%) vs. Cohort 2 (0%).
Grade 3-4 events: 2 patients with pneumonitis, 1 each with constitutional symptoms, colitis, adrenal insufficiency, hyperglycemia, and hypokalemia.
Treatment-related serious adverse events occurred in six (14%) of 42 patients and were pneumonitis (n=2), acute kidney injury, colitis, hypokalaemia, and adrenal insufficiency (n=1 each). There were no treatment-related deaths.
Interpretation
Pembrolizumab has activity in brain metastases from NSCLC with PD-L1 expression at least 1% and is safe in selected patients with untreated brain metastases. Further investigation of immunotherapy in patients with CNS disease from NSCLC is warranted.

MSK Antibody Drug Conjugate Study

RR 98 patients (82 women, 16 men) with ≥ 1 course of SRT for intact BrM between 2014 – 2022.
All received ≥ 1 dose of trastuzumab emtansine, trastuzumab deruxtecan, or sacituzumab govitecan.
"Concurrent SRS with ADC" = if delivered ≤ 7 days prior or ≤ 21 days (approx 3 half-lives[4]) after ADC.
Radiation necrosis was scored if no viable cancer was identified after resection or if a treated BrM enlarged without hyperperfusion and stabilized with corticosteroids or bevacizumab. Time zero was defined as the first date of SRT. We scored RN at first imaging evidence of necrosis. Cases were censored at subsequent high-dose reirradiation. We The median time from SRT to last imaging was 12.4 (IQR, 0-80.4) months.



Lebow, JAMA Oncology 2023
24-month CI SRN entire cohort was 8.5%.
UVA   Concurrent ADC ↑ SRN (HR 4.01 $P < .001$)
MVA   ↑ SHR (HR 4.31 $P < .001$)
<u>Controlling for **prior RT** (HR 2.99 $P = .01$)</u> and <u>**BrM volume (SHR, 1.14/cm³ $P < .001$)**</u>
24-month risk of sRN (<u>**for previously tx lesions**</u>)   42.0% vs. 9.4%.
Among BrM treated with concurrent ADC, the specific agent was not associated with risk of sRN ($P = .74$).
Grade 4 to 5 sRN after SRT 11 of 156 BrM (7.1%) vs. 3 of 408 (0.7%) treated without concurrent ADC.
Conclusion: To our knowledge, this is the largest study of patients with BrM treated with ADCs and SRT and the only one that includes trastuzumab deruxtecan and sacituzumab govitecan.[6] Antibody-drug conjugates given concurrently with SRT were associated with increased risk of SRN. This risk was modest for small BrM receiving a first course of SRT but was substantial for larger lesions and reirradiated BrM treated with concurrent ADC. Similar effects were observed across all ADCs.

Specific Histology Studies

Metaanalysis of SCLC + SRS
←M→ 7 studies of SCLC patients comparing receiving SRS vs. WBRT ± SRS Boost vs. WBRT alone
1^{O} OS.

Gaebe, Lancet Oncology 2022
SRS alone ↑ OS Vs. WBRT ± SRS boost (HR 0·85; CI 0·75–0·97; n=7 studies; n=18 130 patients)
Vs. WBRT alone (HR 0·77; CI 0·72–0·83; n=7 studies; n=16 961 patients)
Vs. WBRT + SRS boost (HR 1·17, CI 0·78–1·75; n=4 studies; n=1167 patients).
Using single-arm studies, pooled median overall survival from SRS was 8·99 months (95% CI 7·86–10·16; n=14 studies; n=1682 patients). Between-study heterogeneity was considerable when pooled among all comparative studies (I^2=71·9%).
Interpretation These results suggest survival outcomes are equitable following treatment with SRS compared with WBRT in patients with SCLC and IMD. Future prospective studies should focus on tumour burden and differences in local and distant intracranial progression between WBRT-treated and SRS-treated patients with SCLC.

SCLC 1-10 Brain Met SRS Study
Prospective 100 patients with SCLC or an extrathoracic small cell primary and 1-10 brain metastases (median number 2).
Exclusion: Previous brain RT including prophylactic cranial irradiation.

Aizer, JCO 2025
Median OS 10.2 months Only 22% of patients required salvage WBRT.
In total, 20 neurologic deaths were observed, relative to 64 non-neurologic deaths.
1-year neurologic death was 11.0%
Note: historical rate in patients managed with WBRT was 17.5%.
Conclusion Our prospective, multi-institutional study demonstrated low rates of neurologic death when SRS/SRT as opposed to WBRT is used in patients with SCLC and 1-10 brain metastases who are surveilled closely post-treatment, supporting the utility of stereotactic approaches in this population.

PERMEATE Trial
Phase II 40 patients median age 50.5, ERBB2-Positive Advanced Breast Cancer and Brain Metastases
Treatment | 1. Fractionated SRS | 2. WBRT |.
All received pyrotinib (400 mg, once daily) and capecitabine (1000 mg/m^2, twice daily, on days 1-14 of each 21-day cycle) from first day of radiotherapy to the seventh day after the completion of radiotherapy and continued until disease progression or unacceptable toxic effects.

Yang, JAMA Oncology 17.3 months
1-year CNS PFS 74.9% Median CNS PFS 18.0 months
1-year PFS 66.9% Median PFS 17.6 months.
CNS objective response 85% (34 of 40). Median OS not reached.
The most common grade 3 or 4 treatment-related adverse event was diarrhea (7.5%).
Asymptomatic radiation necrosis was identified in 4 of 67 lesions (6.0%) treated with fractionated stereotactic radiotherapy.
Conclusions and Relevance The results of this trial suggest that radiotherapy combined with pyrotinib and capecitabine is associated with long intracranial survival benefit in patients with *ERBB2*-positive advanced breast cancer and brain metastases with an acceptable safety profile. This combination deserves further validation.

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TURBO-NSCLC **EGFR or ALK TKI ± SRS**

RR 317 patients TKI-naïve with EGFR- and ALK-driven NSCLC with BM treated with CNS-penetrant TKIs ± SRS up-front.
200 TKI-only and 117 TKI + SRS.
250 (79%) and 61 (19%) patients received osimertinib and alectinib, respectively.
Patients TKI + SRS more likely to have BM ≥1 cm (*P* < .001) and neurologic symptoms (*P* < .001) at presentation.

Pike, JCO 2024

Median OS TKI vs. TKI + SRS groups (median 41 *v* 40 months, respectively; *P* = .5).
12-month CNS progression TKI + SRS 17% vs. 29%.
MVA TKI + SRS ↑ time-to-CNS progression HR 0.63 (*P* = .033).
↑ Local CNS control HR 0.30 (*P* < .001)
NS distant CNS control
Subgroup analyses ↑ TKI + SRS if BM ≥1 cm diameter for time-to-CNS progression and CNS PFS.

Characteristic	TKI (n = 200), No. (%)	TKI + SRS (n = 117), No. (%)	*P*[a]
Site of first progression			.069
CNS progression as a component of first progression	67 (34)	25 (21)	
Extra-CNS only	70 (35)	50 (43)	
No known disease progression	63 (32)	42 (36)	
First CNS progression type			.008
Distant only	31 (16)	29 (25)	
Local progression as a component of first progression	**50 (25)**	**14 (12)**	
No CNS progression	119 (60)	74 (63)	
Salvage brain radiation			.5
No	148 (74)	92 (79)	
Yes	50 (25)	25 (21)	
Other	2 (1.0)	0 (0)	

Conclusion

The addition of up-front SRS to CNS-penetrant TKI improved time-to-CNS progression and local CNS control, but not OS, in patients with BM from EGFR- and ALK-driven NSCLC. Patients with larger BM (≥1 cm) may benefit the most from up-front SRS.

MSK Breast Cancer BM with SRS

RR 274 ERBB2+ with any BM (including LMD) with treatment 2010-2022.
Median age 53.7 years.
At CNS metastasis diagnosis, 73 (26.6%) presented with CNS-only disease.

Ferraro, JAMA Network Open 2025 `Median FU 3.7 years

OS LMD 1.24 years vs. extracranial mets 2.16 years vs. parenchymal or dural CNS disease only 3.57 years (SS).
Of 192 patients (70.1%) who died, 106 (55.2%) died of a CNS-related cause.
CNS-only disease group → 3-year CNS-related death rate 33.98%.
3-year death rate from other causes 6.07%
MVA for CNS-related death, LMD (hazard ratio, 1.87; 95% CI, 1.19-2.93; *P* = .007) and treatment with whole-brain radiotherapy (hazard ratio, 1.71; 95% CI, 1.13-2.58; *P* = .01) were associated with CNS-related death.
Conclusions and Relevance In this cohort study, 55.2% of deaths among patients with *ERBB2*$^+$ breast cancer and brain metastasis were due to CNS-related causes, with the greatest risk among patients with LMD. CNS-only presentation was associated with improved survival but a higher rate of CNS-related death, supporting an approach of aggressive local therapy for select patients.

WBRT vs. HA

NOTE: As physicians grow increasingly reliant on SRS, and as emerging data continue to support its efficacy (particularly in treating multiple metastatic lesions simultaneously) the clinical need for Hippocampal Avoidance has become progressively less relevant. What was once viewed as an intermediary approach between SRS and WBRT is now losing its necessity with the expanding role and precision of SRS leading to comparable LC with less neuro-toxicity. See section on Upfront WBRT vs. SRS.

Hippocampal Sparing RTOG 09-33
Phase II Single arm. Brain mets 30 Gy in 10 fraction.
1^{O} Hopkins Verbal learning Test with Revised Delayed Recall (HVLT-R-DR)
The historical control demonstrated a 30% mean relative decline in HVLT-R DR from baseline to 4 months.
To detect mean relative decline ≤ 15% in HVLT-R DR after HA-WBRT, 51 pt required to ensure 80% power with α = 0.05.
Hippocampus sparing max 16 Gy and D100% ≤ 9 Gy

Gondi, JCO 2014
Mean relative decline in HVLT-R DR from baseline to **4 months was ↓ 7.0%** (95% CI, −4.7% to 18.7%), significantly lower in comparison with the **historical control of ↓ 30%** **(SS)**. No decline in QOL scores was observed. Two grade 3 toxicities and no grade 4 to 5 toxicities were reported. Median survival was 6.8 months.
Conclusion Conformal avoidance of the hippocampus during WBRT is associated with preservation of memory and QOL as compared with historical series.

NRG CC001
←R→ 518 patients brain metastases → | 1. HA-WBRT + memantine | 2. WBRT + memantine |.
1^{o} time to cognitive function failure, defined as decline using the reliable change index on at least one of the cognitive tests.
2^{o} OS, intracranial pfs, toxicity, and patient-reported symptom burden.

Gondi, IJROBP 2023 Median follow-up 12 months
Conclusions
With median follow-up exceeding 1 year, HA during WBRT + memantine for brain metastases leads to sustained preservation of cognitive function and continued prevention of patient-reported neurologic symptoms, symptom interference, and cognitive symptoms with no difference in survival or toxicity.

Brown, JCO 2020 Median follow-up 7.9 months
Risk of cognitive failure ↓ with HA-WBRT aHR 0.74; 95% CI, 0.58 to 0.95; P = .02.
4-month ↓ executive function 23.3% vs. 40.4% (P = .01)
6-month ↓ learning 11.5% vs. 24.7% (P = .049)
6-month ↓ memory 16.4% vs. 33.3% (P = .02).
Treatment arms did not differ significantly in OS, intracranial PFS, or toxicity.
At 6 months, using all data, patients who received HA-WBRT plus memantine reported less fatigue (P = .04), less difficulty with remembering things (P = .01), and less difficulty with speaking (P = .049) and using imputed data, less interference of neurologic symptoms in daily activities (P = .008) and fewer cognitive symptoms (P = .01).
Conclusion
HA-WBRT plus memantine better preserves cognitive function and patient-reported symptoms, with no difference in intracranial PFS and OS, and should be considered a standard of care for patients with good performance status who plan to receive WBRT for brain metastases with no metastases in the HA region.

Download: PDF Original Protocol

“Memory Avoidance” RT Phase 2
10 patients with > 15 brain mets received memory avoidance whole brain radiation (MA-WBRT).
Contours Hippocampi, amygdalae, corpus callosum, and fornix were contoured.
Patients were not eligible for MA-WBRT if they had metastases in these substructures.
A memory-avoidance region was created using a 5-mm volumetric expansion around these substructures.
Hotspots were avoided in the hypothalamus and pituitary gland.
Coverage of brain metastases was prioritized over memory avoidance dose constraints.
Dose constraints for these avoidance structures included a D100% ≤ 9 Gy and D0.03 cm^3 ≤ 16 Gy (variation to 20 Gy).
LINAC-based volumetric modulated arc therapy plans were generated for a prescription dose of 30 Gy in 10 fractions.
On average, the memory avoidance structure volume was 37.1 cm^3 (range, 25.2-44.6 cm^3), occupying 2.5% of the entire whole brain target volume.

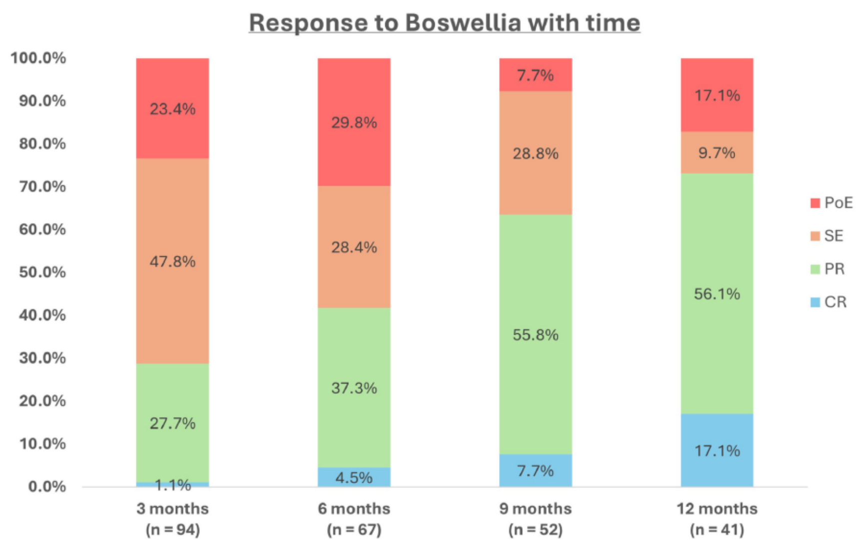
Perlow, Advances in Radiation Oncology 2023
All treatment plans met the D100% dose constraint, and 8 of 10 plans met the D0.03 cm^3 constraint, with priority given to tumor coverage for the remaining 2 cases. Target coverage (D98% > 25 Gy) and homogeneity (D2% ≤ 37.5 Gy) were achieved for all plans.
Conclusions Modern volumetric modulated arc therapy techniques allow for sparing of the hippocampus, amygdala, corpus callosum, and fornix with good target coverage and homogeneity. After enrollment is completed, quality of life and cognitive data will be evaluated to assess the efficacy of MA-WBRT to mitigate declines in quality of life and cognition after whole brain radiation.

Spanish PREMER: A GICOR-GOECP-SEOR Study for **SCLC**
←R→ 150 patients with SCLC (71.3% with limited disease) to | 1. PCI; 25 Gy in 10 fractions | 2. HA-PCI |.
1^{O} delayed free recall (DFR) on the Free and Cued Selective Reminding Test (FCSRT) at 3 months

Rodríguez de Dios, JCO 2021 Median Follow-up 40 months
3-month ↓ DFR from baseline 5.8% vs. 23.5% (OR 5, *P* = .003).
Analysis of all FCSRT scores showed a decline on the total recall (TR; 8.7% *v* 20.6%) at 3 months; DFR (11.1% *v* 33.3%), TR (20.3% *v* 38.9%), and total free recall (14.8% *v* 31.5%) at 6 months, and TR (14.2% *v* 47.6%) at 24 months.
The incidence of brain metastases, OS, and QoL were not significantly different.
Conclusion
Sparing the hippocampus during PCI better preserves cognitive function in patients with SCLC. No differences were observed with regard to brain failure, OS, and QoL compared with standard PCI.

Side Effect Studies

Boswellia Serrata Study
<u>Purpose:</u> Radiation necrosis (RN) is a dose-limiting toxicity of stereotactic radiosurgery (SRS) for brain metastases. Oral corticosteroids are not optimal for long-term management, given multiple side effects. Boswellia serrata (BS) is an over-the-counter supplement traditionally known for its anti-inflammatory properties and has recently been shown to reduce cerebral edema. We evaluated the response rates of BS in a series of patients with RN after SRS for brain metastases.
RR 100 patients with ANY grade RN after SRS received BS (for ≥ 2 months at target dose 4050-4500 mg/day), of which 94 patients had adequate follow-up.
Median SRS dose was 24 Gy in 3 fractions RN G1 44%, G2 47%, and G3 9%.respectively.
1^{O} Response base don ≥30% decrease in edema volume on T2-fluid-attenuated inversion recovery MRI vs. baseline.



Upadhyay, IJROBP 2025
CR 12% PR 48%
Stable edema 28% Progression of edema 12%.
Overall ORR was 59.6%.
ORR based on Grade G1 62%, G2 63%, and G3 33%.
The median duration of response in patients with CR or PR was 13.9 months.
Among 69 patients (73%) never had steroids, had prior steroids only, or had a stable or ↓ steroid ≤4 mg per day of dex for at least >1 week prior to starting Boswellia, the ORR was 63.8%.
Toxicity GI G1 14%, GI G2 2%.
A total of 67% of patients remained on BS at the last follow-up.
Conclusions Our study suggests that BS is a safe and feasible treatment option for grade 1 to 3 RN after SRS. Further prospective studies comparing BS with a placebo are warranted.

Memantine RTOG 06-14
←R→ 508 patients with brain metastases received WBRT → | 1. placebo | 2. Memantine |.
Memantine must be within 3 days of initiating RT for 24 weeks.
KPS ≥ 70 and stable systemic disease. Memantine is a NMDA antagonist used for dementia.
Dosing = 5 mg daily, 5am 5pm (BID), 10am 5pm (BID), 10am 10 pm (BID).

Brown, Neuro-Oncol 2013.
Grade 3 or 4 toxicities and study compliance were similar in the 2 arms.
Delayed recall at 24 weeks (P = .059) trending in favor of memantine.
<u>(Statistical power limited due to patient loss, that's why it was trending)</u>
SS Time to cognitive decline (HR 0.78, SS), **executive function**, and **processing speed** all favoring memantine.
CONCLUSIONS: Memantine was well tolerated and had a toxicity profile very similar to placebo. Although there was less decline in the primary endpoint of delayed recall at 24 weeks, this lacked statistical significance possibly due to significant patient loss. Overall, patients treated with memantine had better cognitive function over time; specifically, memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed in patients receiving WBRT.

ATHENA Phase II
←R→ 110 patients with brain metastases | 1. Brain RT + neuropsychology eval + intervention | 2. brain RT alone | .
Cognition measured by Hopkins Verbal Learning-Revised, Controlled Oral Word Association Test, and Trail Making Test A/B.
Cognitive decline = a decline on at least one assessment using the reliable change index.

Perlow, ASTRO 2025 Planned Secondary Analysis

UVA	Cognitive Preservation	KPS >70 vs. = 70 ($p = 0.044$)
	Cognitive Decline	↑ brain tumor volume ($p=0.044$) Intracranial progression ($p=0.034$) Systemic progression ($p = 0.005$)
MVA	Cognitive Preservation	KPS > 70 ($p=0.011$)
	Cognitive Decline	Systemic progression ($p=0.026$).

Radiation and Systemic Therapy did not impact the above.

Conclusion
For brain metastases patients treated with radiotherapy, baseline performance status and systemic progression may be more predictive of cognitive decline than traditional implicating factors such as type of radiation, age, number of brain metastases, or systemic therapy administration. Cognitive intervention strategies for any patient with poor performance status or progressing systemic disease may be warranted. These findings will be further investigated with multi-institutional ATHENA Consortium data.

Retrospective Radionecrosis and OS Study
RR 697 patients with 4536 brain mets, 11 international NSCLC (57.3%), melanoma (36.3%), and RCC (6.4%) → SRS and ICIs.
Treatment-related imaging changes (TRICs) → MRI, PET/CT, or MR spectroscopy, and consensus required.
Median Age 66 years
All received single fraction SRS median dose 20 Gy.

Lehrer, Journal of Neurosurgery 2022 13.6 months
TRICs were observed in 9.8% of patients. The median OS for all patients was 24.5 months.

UVA ↑ OS	KPS (HR 0.98, $p < 0.001$), TRICs (HR 0.67, $p = 0.03$), Female sex (HR 0.67, $p < 0.001$), prior resection (HR 0.60, $p = 0.03$).
MVA ↑ OS	KPS (HR 0.98, $p < 0.001$), TRICs (HR 0.66, $p = 0.03$)
TRICs ↑by	$V12Gy \geq 10\ cm^3$ (OR 2.78, $p < 0.001$), prior WBRT (OR 3.46, $p = 0.006$), RCC histology (OR 3.10, $p = 0.01$)
Median OS	**with TRICs 29 months** vs. without TRICs 23.1 months ($p = 0.03$).

Conclusions TRICs following ICI and SRS were associated with a median OS benefit of approximately 6 months in this retrospective multicenter study. Further prospective study and additional stratification are needed to validate these findings and further elucidate the role and etiology of this common clinical scenario.

MSK Proton CSI (pCSI) for LMD and Circulating Tumor Cell Detection
Single Institution case series 58 patients treated with pCSI for LM.
PrepCSI CTCs, the change in CTC post-pCSI (Δ CTC), and MRIs were examined.

Wijetunga, Neuro-Oncology Advances 2021
Median CNS-PFS 6 months Median OS 8 months.
Pre-pCSI CTCCSF < 53/3mL was associated with improved CNS-PFS (12.0 vs 6.0 months, P < .01).
Parenchymal brain metastases (n = 34, 59%) on pre-pCSI MRI showed worse OS (7.0 vs 13 months, P = .01).
Through joint modeling, CTCCSF was significantly prognostic of CNS-PFS (P < .01) and OS (P < .01).
Δ CTC-CSF ≥37 cells/3mL, the median Δ CTC-CSF at nadir, showed improved CNS-PFS (8.0 vs 5.0 months, P = .02) and further stratified patients into favorable and unfavorable subgroups (CNS-PFS 8.0 vs 4.0 months, P < .01).
No associations with CTCblood were found.
Conclusion. We found the best survival observed in patients with low pre-pCSI CTCCSF and intermediate outcomes for patients with high pre-pCSI CTCCSF but large Δ CTC-CSF . These results favor additional studies incorporating pCSI and CTCCSF measurement earlier in the LM treatment paradigm.

Note: Generally, CSF cytology is not fully reliable to detect LMD. Research is underway to develop other techniques that are more accurate. For instance, a RR of 43 CSF samples from 22 patients of known LMD, cell-free tumor DNA was positive in 40 (93%), but cytology was only positive in 31 (72%) – White, JAMA Network Open 2021.

Phase I CSI Proton Therapy for LMD
20 patients with LMD receiving 30 Gy in 10 fraction with proton CSI.
1^{O} Treatment related toxicity. Dose limiting toxicity DLT defined as ≥ G3 non-hematologic toxicity or ≥ G4 hematologic tox.

Yang, Neuro-Oncology
Two patients in the dose expansion cohort experienced DLTs consisted of grade 4 lymphopenia, grade 4 thrombocytopenia, and/or grade 3 fatigue. All DLTs resolved without medical intervention. The median CNS PFS was 7 months (95% CI: 5–13) and the median OS was 8 months (95% CI: 6 to not reached). Four patients (19%) were progression-free in the CNS for more than 12 months.
Conclusion
Hypofractionated proton CSI using proton therapy is a safe treatment for patients with LM from solid tumors. We saw durable disease control in some patients.

Other Studies

SRS Brainstem Met Study
←M→ Metaanalysis of 32 RRs showing 1446 patients with 1590 BSM.
SRS (most common technique) GK 16 Gy in 1 fraction (to 50% IDL).

Chen, JAMA Oncology 2021
1-year LC 86% in 1410 patients across 31 studies
OR 59% in 642 patients across 17 studies
Symptom improvement 55% in 323 patients across 13 studies.
Deaths from BSM progression after SRS were rare (19 of 703 [2.7%] deaths across 19 studies)
Neurologic death rate in patients with BSM (24%) was equivalent to the neurologic death rate in patients with BM who were treated on prospective trials.
The rate of treatment-related grade 3 to 5 toxic effects was 2.4% in 1421 patients across 31 studies.
Conclusions: These results compared favorably to trials of targeted or immunotherapy for BM, which had a wide objective response rate range from 17% to 56%.

Chemotherapy Timing Study
RR 262 patients with brain mets reporting the SRS alone vs. SRS + systemic treatment on LC.
Chemotherapy and targeted therapy were temporarily discontinued around irradiation but otherwise concurrent.
211 (81 %) patients received systemic treatment.

1 Fx SRS Dose:	25 Gy	< 1 cm^3
	22 Gy	1–10 cm^3
	20 Gy	10–15 cm^3
	18 Gy	15 cm^3.

Multi Fx if… Size > 2.5 cm diameter or volume > 8 cm^3, or near optic chiasm or brainstem.
15 Gy x 2
10 Gy x 3
Patients who received SRS after surgical resection of BM were classified as 'post-operative'.
No margins were applied.

Van Schie, Radiotherapy & Oncology 2024
Median time to local failure of irradiated brain metastases = 18 months.
Median OS 20 months. **Symptomatic radiation necrosis (RN) occurred in 36 (14 %) patients.**
LC ↓ with breast cancer histology (HR 2.3, p = 0.038) and without any systemic treatment (HR 2.1, p = 0.034).
A diameter > 2.5 cm was associated with a higher risk of radiation necrosis.
No association was found between systemic treatment in combination with local RT and symptomatic RN.
Conclusion Patients who received any form of systemic treatment had better local control after stereotactic radiosurgery for brain metastases. We did not find an association between systemic treatment and the incidence of radiation necrosis.

Meta-analysis of Perilesion Edema (PLE)
←M→ 9 studies 829 patients 1742 BM treated with SRS. Primary analysis → 8 studies 1455 BM.

Akhavan-Sigari, IJROBP 2025
PLE associated ↑ risk LF (HR = 1.82).
Subgroup analyses: Studies defining PLE using numeric cutoffs = ↑ LF HR = 1.71.
Studies dichotomizing ± PLE observed ↑↑ risk LF HR = 2.78
Sensitivity analysis incorporating all 9 studies confirmed a significant association between PLE and local failure but introduced notable heterogeneity (HR = 1.68; 95% CI, 1.17-2.43; I2 = 81.3%).
Conclusion Pretreatment PLE in BM is associated with an ↑ risk of LF following SRS, with LF rates more than doubling in lesions exhibiting edema at the time of treatment. Future research should explore the potential of edema-reducing therapies administered at the time of SRS to improve treatment outcomes.