66 ■ BRAIN METASTASES

Shauna R. Campbell, Martin C. Tom, and John H. Suh

QUICK HIT ■ Brain metastases are the most common intracranial tumor. Surgery, WBRT, HA-WBRT, and SRS are all treatment options and can be performed in many combinations based on careful patient selection.[1] Key factors for patient selection include performance status, number and size of lesions, histology, and status of extracranial disease. Typically, surgery is reserved for large or symptomatic lesions or when a tissue sample is required. SRS is preferred over WBRT due to less neurocognitive side effects and QOL benefit for patients with limited or intermediate volume intracranial disease.

EPIDEMIOLOGY: Most common intracranial tumor, with ~240,000 cases per year. Brain metastases occur in up to 30% of patients with cancer and are the direct cause of death in 30% to 50% of those. Incidence has increased in the MRI era due to the detection of smaller lesions as well as advances in cancer treatment allowing for longer patient survival.[2] Solitary brain metastasis is defined as a single lesion without evidence of extracranial disease; however, 80% of patients have multiple lesions.

ANATOMY: Most commonly occur at the gray–white matter junction due to decrease in diameter of blood vessels. Typically spherical, well-demarcated lesions with edema: 80% supratentorial, 15% cerebellum, and 5% brainstem.

PATHOLOGY: Most common histologies (overall prevalence) include lung (50%), breast (20%), melanoma (10%), and colon (5%).[2] Histologies with the highest predilection for the development of brain metastases (neurotropism) include SCLC, melanoma, choriocarcinoma, and germ cell. Hemorrhagic lesions are typically melanoma, choriocarcinoma, testicular, thyroid, and renal cell.

CLINICAL PRESENTATION: Variable but most commonly include impaired cognitive function (60%), hemiparesis (60%), headache (50%), aphasia (20%), and seizures (20%).[2]

WORKUP: H&P with detailed neurologic exam.

Imaging: Noncontrast head CT is often first-line test performed to rule out intracranial hemorrhage. MRI with and without contrast is best to detect and characterize small metastases. Biopsy may be necessary if the patient has no evidence of disease elsewhere. For patients presumed to have a single brain metastasis on imaging, up to 10% can be primary brain tumors,[3] although this is likely lower in the MRI era. For multiple lesions, >95% are metastatic rather than primary tumors and biopsy is not required.

PROGNOSTIC FACTORS: Numerous prognostic systems have been developed and updated to reflect contemporary outcomes. The initial RPA was developed by the RTOG, followed by the GPA (Table 66.1), then the diagnosis-specific GPA (Table 66.2), which was recently updated and is available at brainmetgpa.com.[4–6] Brain metastasis velocity (number of new brain metastases per year since initial SRS) ≥4 can help predict survival outcomes.[7]

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Table 66.1: Original Graded Prognostic Assessment					
Graded prognostic assessment					
Characteristic	**0**	**0.5**	**1.0**	**Grade**	**MS (mos)**
Age	>60	50–59	<50	3.5–4	11.0
KPS	<70	70–80	90–100	3	6.9
# CNS metastases	>3	2–3	1	1.5–2.5	3.8
Extracranial metastases	Present	–	Absent	0–1	2.6

Source: From Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys*. 2008;70:510–514. doi:10.1016/j.ijrobp.2007.06.074. With permission from Elsevier.

Table 66.2: Diagnosis-Specific GPA					
Variable	0	0.5	1	1.5	2
	NSCLC				
Age	≥70	<70			
KPS	≤70	80	90–100		
Number of brain mets	≥5	1–4			
Extracranial mets	Present	–	Absent		
EGFR and ALK (adeno only)	Both negative or unknown	–	EGFR or ALK positive		
	Sum = MS (months) by GPA: Adenocarcinoma: 0–1 = 7; 1.5–2.0 = 13; 2.5–3.0 = 25; 3.5–4.0 = 46 Nonadenocarcinoma: 0–1 = 5; 1.5–2.0 = 10; 2.5–3.0 = 13; 3.5–4.0 = NA				
	Breast				
KPS	≤60	70–80	90–100		
Age	≥60	<60			
Number of brain mets	≥2	1			
Extracranial mets	Present	Absent			
Subtype	Triple negative	Luminal A (ER/PR+, HER2–)	–	HER2+ or Luminal B (triple +)	
	Sum = MS (months) by GPA: 0–1 = 6; 1.5–2.0 = 13; 2.5–3.0 = 24; 3.5–4.0 = 36				
	Renal				
KPS	≤70	–	80	–	90–100
Number of brain mets	≥5	1–4			
Extracranial mets	Present	Absent			
Hemoglobin	<11.1	11.1–12.5 or unknown	>12.5		
	Sum = MS (mos) by GPA: 0–1 = 4; 1.5–2.0 = 12; 2.5–3.0 = 17; 3.5–4.0 = 35				
	Melanoma				
Age	≥70	<70			
KPS	≤70	80	90–100		
Number of brain mets	≥5	2–4	1		

(*continued*)

Table 66.2: Diagnosis-Specific GPA (*continued*)					
Extracranial mets	Present	–	Absent		
BRAF	Negative or unknown	Positive			
	Sum = MS (months) by GPA: 0–1 = 5; 1.5–2.0 = 8; 2.5–3.0 = 16; 3.5–4.0 = 34				
	GI				
KPS	<70	–	80	–	90–100
Age	≥60	< 60			
Number brain mets	≥4	2–3	1		
Extracranial mets	Present	Absent			
	Sum = MS (months) by GPA: 0–1 = 3; 1.5–2.0 = 7; 2.5–3.0 = 11; 3.5–4.0 = 17				

Source: From Sperduto PW, Mesko S, Li J, et al. Survival in patients with brain metastases: summary report on the updated diagnosis-specific graded prognostic assessment and definition of the eligibility quotient. *J Clin Oncol*. 2020;38(32):3773–3784. doi:10.1200/JCO.20.01255

TREATMENT PARADIGM

Medical: Glucocorticoids such as dexamethasone are first-line medical therapy to improve symptoms in up to 75% within 1 to 3 days. Acute side effects include insomnia, hypergylcemia, irritability, and weight gain. Effects from long-term use include Cushingoid appearance, gastric ulcers (require GI prophylaxis), osteopenia, and proximal muscle weakness. Radiosensitizers such as motexafin gadolinium[8] and efaproxiral[9] have been studied with no demonstrable benefit.

Neurocognitive Protectant: Memantine is an NMDA receptor antagonist used for dementia and can be given with WBRT to minimize neurocognitive decline as demonstrated on RTOG 0614 (see following).

Surgery: Recommended for larger symptomatic lesions or when tissue diagnosis is necessary. A stereotactic approach with maximal safe resection is standard.

Systemic Therapy: Historically, there has been little role for CHT in the treatment of brain metastases due to the blood–brain barrier with the exception of metastatic germ cell tumors (e.g., testicular); however, with new targeted agents and immunotherapy, there is evidence of improved intracranial efficacy.[10,11] Brain metastases from EGFR and ALK mutant NSCLC, PD-L1 expressing NSCLC, HER2 amplified breast cancer, and melanoma all have approved agents with potential intracranial efficacy; however, these have not yet been proven to replace local therapy.[12]

Radiotherapy: RT is the cornerstone of treatment for brain metastases and is indicated in most patients except for those with exceptionally poor prognosis (see QUARTZ trial following). Options include SRS or WBRT.

Dose: For WBRT, dose options include 30 Gy/10 fx (most common), 37.5 Gy/15 fx (common on older RTOG trials but has not demonstrated improved outcomes),[13] 20 Gy/5 fx, and 10 Gy/1fx. HA-WBRT is delivered with 30 Gy/10 fx. The use of HA-WBRT with a simultaneous integrated boost to metastases is under evaluation.[14–16]

SRS: Traditionally, SRS delivers a single high-dose treatment using multiple converging beams.[17] Metastases are often ideal targets for SRS considering they are small, spherical, well-demarcated, and located at the gray–white matter junction away from critical structures. Dosing is performed per RTOG 9005 (see the following): 24 Gy for lesions ≤2 cm, 18 Gy for lesions 2.1 to 3.0 cm, and 15 Gy for those 3.1 to 4 cm. Lesions ≥2 cm may have worse LC and may be treated with fractionated SRS (common doses include 27 Gy/3 fx or 30 Gy/5 fx)[18–21] or staged SRS delivered 2 to 4 weeks apart.[22,23]

Postoperative SRS to the cavity of a resected brain metastasis decreases the risk of LR. Dose varies by institution but can be defined by the N107C study; 20 Gy if cavity volume <4.2 mL, 18 Gy if 4.2 to 7.9 mL, 17 Gy if 8.0 to 14.3 mL, 15 Gy if 14.4 to 19.9 mL, 14 Gy if 20.0 to 29.9 mL, and 12 Gy if ≥30.0 mL

up to the maximal surgical cavity extent of 5 cm.[24] Preoperative SRS is currently being investigated, as it may address limitations of postoperative SRS including a higher incidence of LF, leptomeningeal disease, and radionecrosis compared with WBRT.[25] Phase III trials comparing pre- and postoperative SRS are currently being conducted (NCT03750227 and NCT03741673).

Of note, SCLC patients have historically been excluded from SRS studies, though recent retrospective data have shown potential for upfront SRS in this population[26] and phase II trials are currently ongoing (NCT03391362, NCT04516070, NCT03297788).

Toxicity: Side effects of SRS include fatigue, headache, nausea, radionecrosis, damage to nearby critical structures (optic nerve, chiasm, brainstem), and neurocognitive decline (less than WBRT). Side effects of WBRT include fatigue, hair loss, skin erythema, headache, nausea, temporary muffled hearing, and neurocognitive decline.

Procedure: See *Handbook of Treatment Planning in Radiation Oncology*, Chapters 3 and 13.[27]

EVIDENCE-BASED Q&A

Is there a benefit to WBRT over best supportive care?

In poor performance patients with NSCLC not eligible for SRS or resection, the benefit of WBRT is questionable based on the QUARTZ study.

Mulvenna, QUARTZ (*Lancet* 2016, PMID 27604504): PRT (noninferiority) of optimal supportive care (OSC) vs. 20 Gy/5 fx WBRT for NSCLC. Primary end point was QALY (calculated using EQ-5D) with a noninferiority margin of 7 QALY days. Enrolled 538 patients, 83% were GPA 0 to 2 and 38% had a KPS <70. Did not demonstrate a difference in OS (HR 1.06, $p = .81$) or QALY days (mean QALYs 46.4 days WBRT vs. 41.7 days OSC, 4.7 QALY-day difference with 90% CI: −12.7–3.3). Dexamethasone use was not significantly different. There were nonsignificant suggestions that WBRT may offer a survival benefit in patients with better prognoses. **Conclusion: Although OSC noninferiority was not met, WBRT may be unnecessary in poor performance patients.** *Comment: Patients selected for this trial were poor performance at baseline; results may not apply to patients with more favorable performance status.*

Is there a benefit to dose escalation or hyperfractionation of WBRT?

There is no benefit to WBRT dose escalation with hyperfractionation.

Regine, RTOG 9104 (*IJROBP* 2001, PMID 9336134): PRT of 445 patients with a KPS ≥70 and NFS 1 to 2 randomized to either 30 Gy/10 fx or WBRT 32 Gy/20 fx with a boost to a total of 54.4 Gy/34 fx at 1.6 Gy BID. There was no difference in survival or grade 3 to 4 toxicity, but one fatal toxicity in the high-dose arm. **Conclusion: No benefit to dose escalation with hyperfractionation.**

What is the role of surgery in patients with a single brain metastasis?

Surgery is beneficial for select patients and is typically reserved for patients with large and relatively few lesions in a resectable location. Three trials have looked at adding surgery to WBRT and two (Patchell I and Noordijk[28]) showed a survival benefit. The third did not show an OS benefit but enrolled poor-performance patients.[29]

Patchell I (*NEJM* 1990, PMID 2405271): PRT of 48 patients with single brain metastasis randomized to biopsy followed by WBRT vs. surgical resection with WBRT (36 Gy/12 fx). Of note, 6 of 54 patients (11%) were found to have a primary brain tumor or benign findings (pre-MRI era) (Results in Table 66.3). **Conclusion: Surgical resection + WBRT for a single brain metastasis improves OS compared to WBRT alone.**

Table 66.3: Patchell I Results						
	LR	**Time to LR**	**DM**	**MS**	**Time to Neurologic Death**	**Functional Independence**
Biopsy + WBRT	52%	21 wk	13%	15 wk	26 wk	8 wk
Surgery + WBRT	20%	59 wk	20%	40 wk	62 wk	38 wk
p value	<.02	<.0001	.52	<.01	<.0009	<.005

Does WBRT improve outcomes after surgery?

Patchell II (***JAMA* 1998, PMID 9809728):** PRT of 95 patients with one brain metastasis and KPS ≥70 randomized to surgery alone vs. surgery with postoperative WBRT (50.4 Gy/28 fx). Nearly all outcomes were improved except survival; however, the trial was not powered for survival (Results in Table 66.4.). **Conclusion: WBRT after surgical resection of a single brain met improves local and distant brain control.**

Table 66.4: Patchell II Results						
	Any Recurrence	**Distant Recurrence**	**LR**	**MS**	**Neurologic Death**	**Functional Independence**
Surgery	70%	37%	46%	43 wk	44%	35 wk
Surgery + RT	18%	14%	10%	48 wk	14%	37 wk
p value	<.001	<.01	<.001	.39	.003	.61

What determines the dose of SRS?

Dosing is based on tumor diameter as established by RTOG 9005. LC for larger metastases is suboptimal with single fx, and various attempts at improving outcomes for these patients are noted in the following.

Shaw, RTOG 9005 (*IJROBP* 2000, PMID 10802351): Phase I/II SRS dose escalation trial for patients with a recurrent primary brain tumor (36%) or metastases (64%) ≤4 cm after receiving previous brain RT ≥3 months prior. Treated to escalating dose levels. MTD was 15 Gy for tumors 3.1 to 4 cm and 18 Gy for tumors 2.1 to 3 cm. Investigators were unwilling to escalate above 24 Gy to tumors ≤2.0 cm even though MTD was not observed. A homogeneity index (ratio of max dose/prescription dose) of ≥2 was associated with increased toxicity. Incidence of radionecrosis was 11% at 2 years.

When added to standard WBRT, does an SRS boost improve survival?

SRS boost improves LC after WBRT, with no clear impact on OS.

Andrews, RTOG 9508 (*Lancet* 2004, PMID 15158627): Patients with one to three new brain metastases each ≤4 cm randomized to WBRT or WBRT + SRS boost. WBRT dose was 37.5 Gy/15 fx and boost was given 1 week after WBRT using RTOG 9005 SRS doses. While there was an improvement in LC, KPS, and steroid use in all patients, the primary endpoint of OS was not met (Table 66.5). Patients with a single metastasis did demonstrate a survival benefit (pre-planned stratification). On an unplanned subset analysis, patients in RPA class I, those with large metastases (>2 cm), squamous or NSCLC, or KPS 90 to 100 experienced a benefit that was not statistically significant after adjustment for unplanned subgroup analyses. **Conclusion: SRS boost improves LC after WBRT.**

Table 66.5: RTOG 9508 Results

RTOG 9508	Mean Survival (mos)						1-Yr LC	Stable/Improved KPS at 6 mos
	Overall	Single Met	*Tumor >2 cm	*RPA Class I	*Squamous/ NSCLC	*KPS 90–100		
WBRT alone	6.5	4.9	5.3	9.6	3.9	7.4	71%	25%
WBRT + SRS	5.7	6.5	6.5	11.6	5.9	10.2	82%	42%
***p* value**	.136	.039	.045	.045	.051	.071	.013	.033

*Subset analysis, *p* value for significance = .0056

If SRS boost does not improve survival compared to WBRT alone, does WBRT improve survival when added to SRS?

Aoyama (*JAMA* 2006, PMID 16757720): Randomized 132 patients with one to four brain metastases all ≤3 cm to WBRT (30 Gy/10 fx) with SRS vs. SRS alone. SRS doses alone were 22 to 25 Gy for tumors ≤2 cm, and 18 to 20 Gy for tumors >2 cm and reduced by 30% if given after WBRT. 49% had a single metastasis, 83% were RPA class II. Primary end point OS. Closed early on interim analysis because of higher than anticipated sample size needed to show a difference in OS. (Complete results in Table 66.6). Rate of LR and any recurrence were decreased significantly by WBRT. **Conclusion: The addition of WBRT does not confer a survival benefit when added to SRS, although not sufficiently powered for this endpoint.**

Table 66.6: Aoyama Trial Results

	MS	Neurologic Death	1-Yr Any Rcurrence	1-Yr LR	1-Yr Distant Recurrence	Neurologic Preservation
SRS alone	8.0 m	19%	76%	27.5%	64%	70%
WBRT + SRS	7.5 m	23%	47%	11%	42%	72%
p value	.42	.64	<.001	.002	.003	.99

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

The addition of WBRT to SRS leads to increased neurocognitive decline without a survival benefit compared to SRS alone in patients with limited brain metastases.

Chang, MD Anderson (*Lancet Oncol* 2009, PMID 19801201): PRT with one to three brain metastases to SRS with or without WBRT (similar arms to Aoyama) with primary endpoint of deterioration of HVLT-R-TR domain by five points at 4 months from treatment. Trial stopped early after 58 patients enrolled due to increased decline in WBRT arm. LC improved from 67% to 100% with WBRT and distant control by 45% to 73%. However, neurocognitive function declined in 23% of SRS patients vs. 49% of WBRT+SRS patients. **Conclusion: SRS + WBRT patients experienced a significant decline in neurocognitive function. SRS alone may be the preferred treatment strategy.** *Comment: MS was 15.2 months (SRS) vs. 5.7 months (WBRT+SRS), suggesting imbalance of patients in two arms.*

Kocher, EORTC 22952 (*JCO* 2011, PMID 21041710): PRT of 359 patients with one to three brain metastases randomized to observation or WBRT (30 Gy/10 fx) after either SRS or surgery. Primary end point was time to WHO PS >2. No difference in OS (10.7 vs. 10.9 months) and WBRT improved local failure (31% SRS, 59% surgery, 19% SRS+WBRT, and 27% surgery + WBRT) and any in-brain failure (42% surgery, 48% SRS, 33% SRS + WBRT, and 23% surgery +WBRT). No difference in the time to PS >2. **Conclusion: WBRT can be omitted in select patients with appropriate imaging follow-up.**

Sahgal, Meta-analysis (*IJROBP* 2015, PMID 25752382): Individual patient level meta-analysis of 359 patients from Aoyama, Chang, and Kocher trials, investigating SRS alone vs. WBRT + SRS in patients with one to four brain metastases. Age was a significant predictor of the effect of WBRT on OS and distant cranial failure. Younger patients treated with SRS alone had a lower hazard of mortality (MS for age ≤50: 13.6 months SRS alone vs. 8.2 months SRS+WBRT). Younger patients (≤50) also did not benefit in terms of distant brain failure, but patients >50 did benefit from the addition of WBRT. The addition of WBRT to SRS showed a local control benefit across all subgroups. **Conclusion: SRS alone may be the treatment of choice for patients ≤50 with one to four brain metastases.**

Brown, NCCTG N0574 (*JAMA* 2016, PMID 27458945): PRT of 213 patients with one to three brain metastases all <3 cm randomized to SRS or WBRT+SRS. Primary end point was declined in any of six cognitive tests (HVLT-R-IR, HVLT-R-DR, COWA, Trailmaking A & B, and Grooved Pegboard) at 3 months >1 standard deviation from baseline. 213 randomized, 111 included in primary endpoint

analysis (63 in SRS arm, 48 in SRS+WBRT arm). Cognitive decline at 3 months was more common after WBRT+SRS than SRS alone (91.7% vs. 63.5%, $p < .001$). This was true across immediate recall, delayed recall, and verbal fluency. QOL was also improved in SRS group with no difference in functional independence. In-brain control was better in WBRT arm (93.7% vs. 75.3% at 3 months, $p < .001$) but survival was not different (10.4 months SRS vs. 7.4 months SRS+WBRT, $p = .92$). **Conclusion: WBRT does not improve survival despite better tumor control and is associated with more cognitive deterioration. SRS alone may be the preferred strategy.**

■ **If WBRT is associated with a decline in neurocognitive function, what are some possible strategies to avoid this?**

Adding memantine and hippocampus sparing are two strategies to decrease the neurocognitive detriment associated with WBRT.

Brown, RTOG 0614 (*Neuro-Oncol* 2013, PMID 23956241): PRT of patients with KPS ≥70 and stable systemic disease randomized to receive 20 mg of memantine vs. placebo during and after WBRT for a total of 24 weeks. Dose was up-titrated by 5 mg weekly starting at 5 mg daily up to 10 mg BID for weeks 4 to 24. Primary endpoint was declined in HVLT-R-DR at 24 weeks compared to baseline, which trended toward improvement ($p = .059$) but statistical power was limited due to patient loss. The memantine arm did have statistically significant longer time to cognitive decline, lower probability of cognitive failure, and superior results for executive function, processing speed, and delayed recognition at 24 weeks. **Conclusion: Memantine is a well-tolerated medication and patients who received memantine compared with placebo had better cognitive function over time, although patient loss to follow-up limited significance of the primary endpoint.**

Brown, NRG CC001 (*JCO* 2020, PMID 32058845): Randomized phase III trial of 518 patients with brain metastases, stratified by RPA and prior SRS/surgery, randomized to WBRT (30 Gy/10 fx) + memantine vs. HA-WBRT + memantine. Primary end point was time to neurocognitive failure, defined as an established decline in one of the neurocognitive tests (HVLT, Trail Making, or COWA). No difference in OS, intracranial PFS, or toxicity between arms. Cognitive failure risk significantly lower in the HA-WBRT arm compared with the WBRT arm (HR 0.76; 95% CI 0.60–0.98; $p = .03$). The lower cognitive failure was secondary to statistically significantly less deterioration in executive functioning at 4 months and learning and memory at 6 months. On MVA age >61 years was also significant for time-to-cognitive failure (HR 0.635, $p= .0016$). HA-WBRT was also associated with less fatigue, difficulty remembering things, speaking, interference of neurologic symptoms with daily activities, and fewer cognitive symptoms (all $p < .05$). **Conclusion: HA-WBRT has comparable efficacy to standard WBRT, but better preserves neurocognitive function with the benefit first appreciated at 4 months pos treatment.**

■ **How many metastases are necessary to warrant WBRT rather than SRS?**

The trend with modern planning systems is to treat with SRS alone to avoid WBRT but the specific number or volume remains unclear.

Yamamato, Japan (*Lancet Oncol* 2014, PMID 24621620): Prospective observational study of patients with 1 to 10 new metastases (maximum <3 cm) treated with SRS alone. Patients with 5 to 10 lesions were compared with patients with one tumor and patients with two to four tumors. Primary end point was OS. Results showed that OS did not differ between the 5 to 10 cohorts when compared to the 2 to 4 cohorts (noninferior). The rate of adverse events was also similar. **Conclusion: SRS may be suitable in patients with up to 10 brain metastases.**

Li, MDACC (ASTRO Abstract 2020): Phase III RCT of 72 patients with 4 to 15 untreated nonmelanoma brain metastases randomized to SRS ($n = 36$) or WBRT ($n = 36$). Prior SRS to one to three brain metastases with at least 3 months interval was permitted. Median number of brain metastases was 8, and 31 patients were evaluable for primary endpoint of HVLT-R-TR at 4 months. WBRT treated patients had greater decline in HVLT-R-TR compared with SRS patients ($p = .041$). MS 10.4 months for SRS and 8.4 months for WBRT ($p = .45$). **Conclusion: Nonmelanoma patients with 4 to 15 brain metastases can be treated with SRS without a detriment in OS based on abstract results.** *Note: Trial was closed early as HA-WBRT became standard.*

What treatment options are there for large metastases who are not surgical candidates?

Larger tumors treated with SRS have suboptimal LC using RTOG 9005 dosing.[30] Strategies to improve LC include fractionated[19–21,31] and staged SRS[22,23,32] with the goal of dose escalation while limiting toxicity such as radionecrosis.[17] Data from prospective studies investigating these SRS techniques to determine the optimal dose, fractionation, and timing for large brain metastases will be important to guide future standards.

Is postoperative SRS to the resection cavity effective at reducing LF after complete resection?

Mahajan, MDACC (*Lancet Oncol* 2017, PMID 28687375): Single-institution PRT of 132 patients randomized after complete resection of one to three metastases to either observation or postoperative SRS. MFU 11.1 months. Primary end point LR. At 12 months, freedom from LR was 43% in the observation group vs. 72% with SRS ($p = .015$). **Conclusion: Following complete resection of brain metastases, postoperative SRS reduces LR compared to observation.**

Can SRS offer similar rates of control in the postoperative setting to WBRT but without the neurocognitive deficits?

In an attempt to maintain control rates while decreasing neurocognitive changes, SRS can be given to the resection cavity, with initial retrospective data favoring a 2-mm margin around the cavity.[33] Note that dosing to the resection cavity is often by volume rather than by diameter, but this varies by institution.

Brown, N107C (*Lancet Oncol* 2017, PMID 28687377): PRT of 194 patients with ≤4 metastases (all <3 cm) with resection of a single lesion (cavity <5 cm), then randomized to WBRT (with SRS to unresected metastases) vs. SRS alone to the cavity and unresected lesions. Co-primary end points were OS and cognitive deterioration free survival (CDFS) at 6 months, defined as death or a drop by 1 standard deviation in one test (HVLT, COWA, Trailmaking A & B). Preferred sequencing was SRS to unresected metastases followed by WBRT within 14 days. Dosing to the surgical bed was 12 to 20 Gy depending on tumor volume (dosing to unresected lesions was 18 to 24 Gy depending on arm and diameter). No difference in OS (MS 12.2 months SRS vs. 11.6 months WBRT, $p = .70$). CDFS was improved in SRS arm: median 3.7 months vs. 3.0 months, $p < .0001$). **Conclusion: Postoperative SRS provides comparable OS with less neurocognitive deterioration as compared to WBRT and is thus preferred. This is an acceptable alternative to WBRT after resection of a brain metastasis with less cognitive deterioration.**

Kayama, JCOG 0504 (*JCO 2018, PMID 29924704*): PRT (noninferiority) of 271 patients with ≤4 lesions surgically resected with only one lesion >3 cm were randomized to SRS or WBRT after surgery. Primary end point was OS. MS 15.6 months on both arms, with HR of 1.05 ($p = .027$) meeting noninferiority criteria. Grades 2 to 4 cognitive dysfunction beyond 90 days was higher in WBRT arm (16.4% vs. 7.7%, $p = .048$) but the proportion of patients whose MMSE did not worsen were similar in both arms. **Conclusion: With respect to OS, postoperative salvage SRS is noninferior to WBRT.**

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