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Stereotactic Radiosurgery in the Management of Limited (1-4) Brain Metastases: Systematic Review and International Stereotactic Radiosurgery Society Practice Guideline

BACKGROUND: Guidelines regarding stereotactic radiosurgery (SRS) for brain metastases are missing recently published evidence.

OBJECTIVE: To conduct a systematic review and provide an objective summary of publications regarding SRS in managing patients with 1 to 4 brain metastases.

METHODS: Using Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, a systematic review was conducted using PubMed and Medline up to November 2016. A separate search was conducted for SRS for larger brain metastases.

RESULTS: Twenty-seven prospective studies, critical reviews, meta-analyses, and published consensus guidelines were reviewed. Four key points came from these studies. First, there is no detriment to survival by withholding whole brain radiation (WBRT) in the upfront management of brain metastases with SRS. Second, while SRS on its own provides a high rate of local control (LC), WBRT may provide further increase in LC. Next, WBRT does provide distant brain control with less need for salvage therapy. Finally, the addition of WBRT does affect neurocognitive function and quality of life more than SRS alone.

For larger brain metastases, surgical resection should be considered, especially when factoring lower LC with single-session radiosurgery. There is emerging data showing good LC and/or decreased toxicity with multisession radiosurgery.

CONCLUSION: A number of well-conducted prospective and meta-analyses studies demonstrate good LC, without compromising survival, using SRS alone for patients with a limited number of brain metastases. Some also demonstrated less impact on neurocognitive function with SRS alone. Practice guidelines were developed using these data with International Stereotactic Radiosurgery Society consensus.

KEY WORDS: Stereotactic radiosurgery, Brain metastases, Guideline, Review

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Brain metastases affect up to 30% of all cancer patients and are the most common neurological complication of cancer.¹ Lung cancer, breast cancer, kidney cancer, and melanoma are the most common primary tumors that metastasize to the brain.²

The incidence of brain metastases in these populations is increasing due to more routine use of surveillance MRI, improved survival such that patients are living long enough to develop brain metastases, and more effective systemic therapies able to control extracranial disease

ABBREVIATIONS: CNS, central nervous system; DC, distant control; EORTC, European organisation for research and treatment of cancer; GPA, Graded Prognostic Assessment; HRQOL, health-related quality of life; ISRS, International Stereotactic Radiosurgery Society; JROSG, Japanese Radiation Oncology Study Group; LC, local control; MMSE, Mini-Mental Status Examination; NCCTG, north coast cancer treatment group; NSCLC, non-small cell lung cancer; OS, overall survival; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RPA, recursive partition analysis; RTOG, radiation therapy oncology group; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole brain radiation

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such that the sanctuary site of the central nervous system (CNS) is becoming a more frequent site of progression.

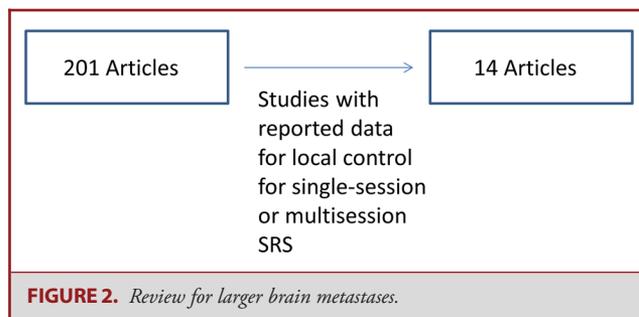
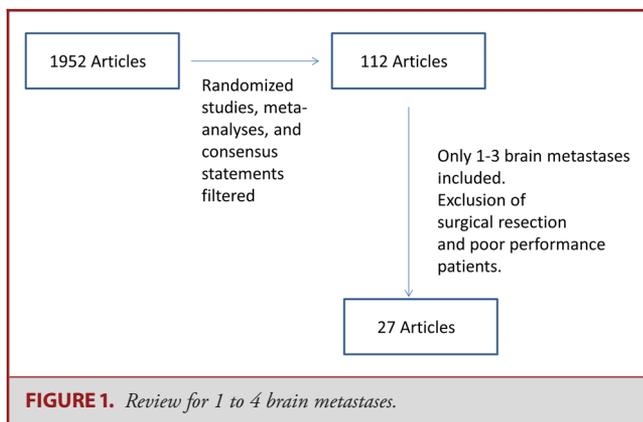
Prognosis with this diagnosis is still considered to be poor; however, subsets of patients can be identified based on prognostic factors who can live well beyond expectations and several years beyond diagnosis with limited brain metastases.³ Along with increasing therapeutic options for patients with metastatic cancer, organ-sparing radiation treatment approaches have been developed to minimize morbidity. In particular, stereotactic radiosurgery (SRS) has become an increasingly recognized standard of care, with or without whole brain radiation (WBRT), and more recently the role of SRS alone has been supported by the literature and professional societies for a patient presenting with 1 to 4 brain metastases. This guideline is presented as a summary of the evidence, and provides treatment guidelines specific to this patient population.

METHODS

A systematic review was performed using Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).⁴

Search Strategy

The authors conducted a systematic review using PubMed and Medline from 1946 up to November 20, 2016. Using the search terms of “stereotactic radiosurgery” and “brain metastases,” 1952 articles were found. As this guideline is focused on clinical trials and high-level evidence (randomized trials, meta-analyses, and published consensus guidelines), a filter was applied yielding 112 articles. These 112 articles were further filtered manually for those that applied to “1 to 4 brain metastases.” Surgical resection and poor performance status patients (defined as Karnofsky Performance Status <70) were beyond the scope of this consensus guideline, so these articles were mostly excluded. Published consensus guidelines were also included for comparison. A total of 27 prospective studies, critical reviews, meta-analyses, and published consensus guidelines were reviewed (see Figure 1).



The authors also conducted a systemic review using PubMed/Medline specifically for “radiosurgery” and “large brain metastases” from 1946 up to November 20, 2016. This yielded a total of 201 studies. These were manually reviewed and 14 studies were selected. Given relative lack of prospective studies, retrospective studies were included (see Figure 2).

Review

Each article was reviewed, specifically focusing on overall survival (OS), local control (LC), distant control (DC), and neurocognitive endpoints. These endpoints are a focus for this guideline.

Development of Practice Guideline

After compilation of the articles, these were subgrouped into various topics according to the questions they supported and answered. Bias was assessed in each study. Due to rigorous screening upfront, none of the studies used were felt to be too biased and needed to be excluded. From this, recommendations were generated which were reviewed and approved by the International Stereotactic Radiosurgery Society (ISRS) treatment guidelines committee.

RESULTS

Whole Brain in Combination with SRS

With the development of cranial SRS, the first question to answer in randomized trials was its role as an adjunct to the current standard of care at that time, WBRT. The number of metastases allowed for SRS at that time was up to 3 or 4, and the individual tumor dimension no greater than approximately 3 cm in widest diameter, largely because of technical limitations of the apparatus at the time.

Kondziolka et al⁵ provided initial insight by randomizing 27 patients with 2 to 4 brain metastases to WBRT alone vs WBRT and SRS boost. Brain metastases had to be 2.5 cm or less. WBRT was given in 12 fractions for a total dose of 30 Gy and the SRS dose was 16 Gy in a single fraction. Local failure in patients receiving WBRT alone was 100%, but only 8% in those receiving SRS boost, suggesting poor LC with WBRT alone. Median time to local failure was 6 mo with WBRT alone compared to 36 mo with WBRT and SRS ($P = .0005$). DC was not specifically reported upon, but any brain failure was less in those receiving SRS boost ($P = .002$). Neurocognitive function was not assessed.

Survival was 11 mo in those receiving an SRS boost, and 7.5 mo in those receiving WBRT alone. Although this difference in survival was not statistically significant ($P = .22$), or expected given the small sample size and the primary endpoint not powered to address survival, and given the poor LC rates with WBRT, it was suggested that SRS boost be considered for patients with a reasonable survival expectation following diagnosis of their brain metastases.

A much larger randomized study was conducted by the Radiation Therapy Oncology Group (RTOG).⁶ Three hundred thirty-three patients with 1 to 3 brain metastases were randomized to WBRT vs WBRT and SRS (RTOG 1995-2008).⁶ In general, there was no difference in survival between the groups. For patients with a single brain metastasis, survival increased from 4.9 to 6.5 mo with the addition of SRS ($P = .039$). It was also observed that in those patients who were recursive partition analysis (RPA) class I, survival improved from 9.6 to 11.6 mo with the addition of SRS ($P = .045$). Overall, 1-yr LC improved from 71% to 82% with SRS ($P = .01$); however, only less than half of the patients in the study had adequate imaging at 3 mo for central review. DC was not specifically analyzed, but overall rates of intracranial control were no different between the 2 arms ($P = .13$). Neurocognitive testing was not performed for this study. A secondary analysis of RTOG 95-08 was recently reported that segregated patients according to the Graded Prognostic Assessment (GPA) score, which represents a modern prognostic scoring system as compared to the RPA.⁷ What was observed was a survival advantage regardless if the patient had 1, 2, or 3 brain metastases in patients with a high GPA (3.5-4). This result strengthens the observations that SRS, when given with WBRT, improves LC and OS in those patients with optimal prognostic factors.

SRS Without WBRT

One potentially concerning long-term side effect of WBRT is its effect on neurocognition. DeAngelis et al⁸ reported in 1989 on patients who developed dementia following WBRT. This sparked a debate that continues today: Does WBRT need to be given upfront for patients with a limited number of brain metastases?

Proponents for WBRT would argue that the neurocognitive effects of WBRT are less consequential than the potential neurocognitive effects of progression within the brain and the costs of repeated radiosurgery to treat distant brain recurrence. Those against WBRT would argue that the neurocognitive effects of WBRT are worse than the effect from progression of brain metastases and that recurrences are effectively treated with minimal neurocognitive impact with more SRS or delayed WBRT. From the 4 randomized trials reported evaluating SRS alone to SRS plus WBRT, the data are more consistent with the latter than the former.

The first reported prospective study was published by Aoyama et al.⁹ The Japanese Radiation Oncology Study Group (JROSG) conducted a phase III study (JROSG 99-1) and randomized 132

patients to SRS and WBRT vs SRS alone. The number of brain metastases had to be 4 or less and the lesions needed to be 3 cm or less in diameter. The original primary study endpoint was OS with the secondary points being brain recurrence, need for salvage brain treatment, preservation of function, radiation toxicity, and cause of death. The primary endpoint was changed from OS to brain tumor recurrence when interim analysis determined 805 patients were necessary to detect an OS difference. As such, there was no difference in survival. At 12 mo, brain tumor recurrence decreased from 76% without WBRT to 47% with WBRT ($P < .001$). The 1-yr freedom from new brain metastasis was also improved for the group receiving WBRT (64%) compared with the SRS alone group (41.5%; $P = .003$). Thus, more salvage treatment was given in the SRS alone group. There did not appear to be any significant difference in toxicity from radiation, death from neurological causes, or differences in systemic or neurological functional preservation. Optionally, neurocognitive function was assessed using the Mini-Mental Status Examination (MMSE). In 28 patients where MMSE was available at least once at follow-up, there was no difference after treatment between the 2 arms. The authors felt that WBRT could be safely omitted. An alternative conclusion that is adopted by proponents of WBRT is that WBRT improves brain metastasis control and should be delivered.

A subgroup secondary analysis of JROSG 99-1 was recently reported 9 yr later. The authors observed that in non-small cell lung cancer (NSCLC) patients with a diagnosis-specific GPA score of 2.5 to 4 (favorable prognosis), there appears to be an improvement in OS with the addition of WBRT to SRS.¹⁰ Patients treated with SRS alone had a median survival of 10.6 mo, but those treated with SRS and WBRT had a median survival 16.7 mo ($P = .04$). This could be explained by a lower rate of brain metastases recurrence in patients who receive WBRT ($P < .01$). Patients with a poor prognosis did not show a survival benefit, however. Although suggestive, this substudy was small with only 47 patients in the favorable prognosis group and 41 patients in the poor prognosis group. The patient numbers are even smaller at 12 mo with 24 remaining in the favorable prognosis group and only 8 in the poor prognosis group. It is hypothesis generating with respect to a subgroup of patients who may live an extended period that may benefit from maximal intracranial control. However, other studies refute this hypothesis when considering more modern data.

In order to determine the neurocognitive impact of these treatments, Chang et al¹¹ performed a phase III study at the MD Anderson for patients with 1 to 3 brain metastases comparing SRS plus WBRT vs SRS alone. Neurocognitive function as measured by the Hopkins Verbal Learning Test-Revised was the primary endpoint. After accrual of 58 patients, interim analysis demonstrated a 96% probability that the SRS + WBRT arm would show a statistically significant decline in learning and memory function (total recall) at 4 mo, and so the trial was stopped early. Similar to the JRSOG study, there was a higher rate of CNS recurrences in the group receiving SRS alone; 73% of patients

in the SRS + WBRT group did not develop CNS recurrence at 1 yr, compared to 27% of patients who received SRS alone ($P = .0003$). The 1-yr DC was 45% for the SRS group and 73% for the SRS plus WBRT group ($P = .02$). Unlike the Aoyama study,⁹ the median OS was 15.2 mo for the SRS alone group vs 5.7 mo for the SRS plus WBRT group ($P = .02$). This difference in survival was speculated to be from more local surgical salvage in SRS alone patients, earlier start to systemic therapy in the SRS alone group, or higher systemic burden in those randomly assigned to SRS plus WBRT. Given the improved neurocognitive outcomes and potential for OS improvement, the authors conclude that SRS alone with close and careful follow-up is preferred over WBRT + SRS. This approach would decrease neurocognitive loss from WBRT, which outweighs potential neurocognitive loss from recurrent brain metastases.

Kocher et al¹² published the results of an European Organisation for Research and Treatment of Cancer (EORTC) phase III trial for patients with a limited number of brain metastases with stable solid tumors, comparing adjuvant WBRT with observation after either surgery or SRS. OS was no different whether or not they received WBRT upfront.¹² WBRT did decrease the risk of relapse. However, the duration of functional improvement (defined as the median time to World Health Organization performance status of 2) was 10 mo in the observation group and similarly, 9.5 mo in the group with WBRT ($P = .71$). Hence, while it did reduce the risk of brain recurrence, it did not improve the duration of functional independence or OS. Soffietti et al¹³ looked specifically at health-related quality of life (HRQOL) in this group of patients.¹³ There were better HRQOL scores for global health in the observation only arm vs those who received WBRT at 9 mo ($P = .0148$). Physical function at 8 wk, cognitive functioning at 12 mo, and fatigue at 8 wk were better for those who did not receive WBRT.

Given the general consensus that SRS alone does not appear to lead to a decrement in survival and improved neurocognitive function, Sahgal et al¹⁴ performed a rigorous, individual patient data meta-analysis of the JROSG, MD Anderson, and the EORTC studies. This involved a total of 364 patients of 389 pooled patients. Meta-analysis demonstrated improved survival in patients 50 yr old and younger with SRS alone compared to SRS + WBRT (10 mo vs 8.2 mo, $P = .04$). There was no difference in the rate of distant brain metastases in those who received WBRT or not for patients 50 yr old or less. As a result, the authors hypothesized that exposure to the harmful effect of WBRT without the benefit specific to distant brain control may explain the survival advantage for SRS alone.

Brown et al¹⁵ recently reported the results of North Coast Cancer Treatment Group (NCCTG) N0574 study which was a phase III study of SRS alone vs SRS + WBRT in patients with 1 to 3 brain metastases. Like the Chang et al¹¹ study, their primary endpoint was neurocognitive function, but it was much larger trial with 208 patients randomized. They defined cognitive progression as a decline of greater than 1 standard deviation from

baseline in any of 7 cognitive tests at 3 mo. Cognitive progression was higher after WBRT and SRS at 91.7% vs SRS alone at 63.5% ($P < .001$). Immediate recall, delayed recall, and verbal fluency were all significantly worse with the addition of WBRT. In long-term survivors, defined as those living 12 mo or more, cognitive deterioration was more frequent in patients receiving SRS + WBRT. This reached statistical significance for executive functioning at 12 mo with Trail Making Test Part B difference of 42.9% between the 2 arms ($P = .05$). The 12-mo intracranial control was 50.5% with SRS alone and 84.6% with SRS and WBRT. Median OS was 10.4 mo for SRS alone vs 7.4 mo with addition of WBRT ($P = .92$), but the study was not powered for survival. The results of this study confirmed the results of Chang et al¹¹ as a larger study, and the authors concluded that for patients with 1 to 3 brain metastases amenable to SRS, SRS alone may be the preferred.

Table 1 summarizes these results. In general, for patients with 4 or less brain metastases, these trials demonstrate 4 key points.¹⁶ First, there is no decrement in survival with withholding WBRT in patients with a limited number of brain metastases. Next, SRS alone achieves high rates of LC, but this can increase with the addition of WBRT. That said, keep in mind that LC is a harder endpoint to study as it can be complicated by radiation necrosis and pseudoprogression. Third, there are more new distant brain metastases when WBRT is not given upfront. This results in more frequent salvage treatment and a quarter of these patients will ultimately require WBRT. Finally, the risk of neurocognitive decline is less when with SRS alone, but not eliminated.

With respect to timing of the intervention, a recent randomized study conducted in Korea evaluated the timing of treating brain metastases with SRS relative to starting chemotherapy. In patients with a limited number of brain metastases, there does not appear to be any benefit or detriment to doing SRS prior to starting systemic therapy for patients with asymptomatic brain metastases from NSCLC vs starting systemic therapy without treating the brain.¹⁷ Median OS was equivalent between the SRS group and the upfront chemotherapy group (14.6 mo vs 15.3 mo, respectively; $P = .418$). However, there was a trend to longer CNS progression-free survival, lower symptomatic brain progression rate, and lower rate of CNS salvage therapy in the SRS group. Delaying chemotherapy and treating brain metastases first, which is the typical approach, may be favored, although delaying brain metastases treatment if urgent chemotherapy is needed appears to be safe.

Alternatively, there are newer data suggesting that systemic therapy can be given concurrently with SRS for brain metastases. Shen et al¹⁸ looked at 193 patients treated with SRS, of which 37% received myelosuppressive chemotherapy or targeted/immune therapy agents. Myelosuppression was minimal in this group of patients and did not appear to be influenced by what or when systemic therapy was given. Four percent developed grade 3 to 4 neurotoxicity. Although the grade of neurotoxicity was higher with the concurrent use of immune therapy and

TABLE 1. Summary of SRS Alone vs SRS + WBRT

Study	Arm	1-yr LC (%)	1-yr DC (%)	OS (mo)	Neurocognitive/QOL
Aoyama et al ⁹	SRS	72.5 ($P = .002$)	36.3 ($P = .003$)	8.0 ($P = .42$)	MMSE same in both arms
	SRS + WBRT	88.7	58.5	7.5	
Chang et al ¹¹	SRS	67 ($P = .012$)	45 ($P = .02$)	15.2 ($P = .02$)	Statistically significant decline in learning and memory function in WBRT arm
	SRS + WBRT	100	73	5.7	
Kocher et al ¹²	SRS	69 (2-yr, $P = .04$)	52 (2-yr, $P = .023$)	10.9 ($P = .89$)	Decreased HRQOL at 9 mo with WBRT arm ¹³
	SRS + WBRT	81 (2 yr)	67 (2 yr)	10.7 (includes surgical resection)	
Sahgal et al ¹⁴	SRS (≤ 50 years old)	68 (crude rate, $P = NS$ with respect to age)	35 (crude rate, $P = .04$ with respect to age)	13.6 ($P = .04$ with respect to age)	N/A
	SRS + WBRT (≤ 50 years old)	89	49	8.2	
	SRS (> 50 years old)	74	50	10.1	
	SRS + WBRT (> 50 years old)	88	72	8.6	
Brown et al ¹⁵	SRS	72.8	69.9	10.4 ($P = .92$)	More deterioration in immediate recall, delayed recall, and verbal fluency in WBRT arm
	SRS + WBRT	90.1	92.3	7.4	

dexamethasone use was lower with targeted therapy, there was no difference in the rate of radiation necrosis between the therapies. There was no difference in grade of neurotoxicity, dexamethasone use, or radiation necrosis with respect to timing of the systemic therapy relative to SRS. Of interest, those with a new diagnosis of primary cancer with brain metastasis, those treated with concurrent systemic therapy and SRS had improved survival compared to SRS alone (41.6 mo vs 21.5 mo, $P < .05$). Kim et al¹⁹ further support these results. This study looked at 1650 patients, 27% of which received concurrent systemic therapy. Concurrent systemic therapy, when given to patients receiving SRS and WBRT as opposed to SRS alone, appears to increase the risk of radiation necrosis. In particular, radiation necrosis only increased in those receiving vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKIs; 14.3 vs 6.6%, $P = .04$) and epidermal growth factor receptor TKIs (15.6% vs 6.0%, $P = .04$). Other systemic therapy such as cytotoxic chemotherapy, hormonal therapy, and other targeted therapies such as BRAF inhibitors and immune therapy did not appear to increase the risk of radiation necrosis when given concurrently with SRS. This falls in line with the results of RTOG 0320 which showed more toxicity and worse survival in patients receiving erlotinib or temozolomide in addition to WBRT and SRS for 1 to 3 brain metastases compared to WBRT and SRS alone.²⁰

Due to the results of many of these studies, ASTRO released a consensus statement as part of their "Choosing Wisely Campaign," recommending against the routine use of WBRT in addition to SRS for a limited number of brain metastases.²¹ This message was also put forth by Sahgal, Larson, and Knisely²² as an editorial to further clarify the optimal approach such that

SRS alone is favored with WBRT reserved as one of many salvage options. The National Comprehensive Cancer Network and Deutsche Gesellschaft für Radioonkologie are amongst other groups that have recommended SRS as a favorable treatment option in this patient cohort. The ISRS guideline committee supports this approach.

Larger Brain Metastases

Larger brain metastases pose a unique challenge in that these are often symptomatic, cause mass effect, and neurological signs and symptoms. Surgical resection has been considered a more reliable therapy with respect to reversing neurological deficits as compared to WBRT and/or SRS. In fact, for patients with single brain metastases, surgery has been shown in a phase III study to improve survival compared to whole brain radiation alone. Patchell et al²³ reported OS following resection with WBRT to be 40 wk compared to 15 wk with biopsy with WBRT ($P < .01$).²³ Following surgical resection, there is concern for recurrence in the resection cavity which typically occurs in 50% of patients if radiation withheld. As a result, WBRT has been used to minimize recurrence by sterilizing the resection cavity. In another randomized trial by Patchell et al,²⁴ WBRT decreased intracranial failure from 70% to 18% ($P < .001$). It also decreased local recurrence from 46% to 10% ($P < .001$).²⁴ Kocher et al¹² also assessed this and found that WBRT reduced local recurrence from 59% to 27% ($P < .001$). For solitary brain metastases greater than 2 or 3 cm in size, surgery may be favored.

The single fraction SRS dosing is typically lowered for larger brain metastases to reduce the rate of late complications,

TABLE 2. Summary of SRS for Large Brain Metastases

Study	N	Single session 1-yr LC (%)	1-yr OS (%)	Median dose	Multisession 1-yr LC (%)	1-yr OS (%)	Median Dose	P for LC (single vs multi)	Comments
Kim et al ²⁸	98	71	36	20 Gy in 1 fx	69	31	36 Gy in 5 fx	.31	More toxicity with single session
Minitti et al ²⁷	298	77	53	15-18 Gy in 1 fx	91	56	27 Gy in 3 fx	.01	Less radiation necrosis with multisession
Wegner et al ²⁹	36				63	13	12-27 Gy in 2-5 fx		
Oermann et al ³⁰	214	LC not reached for radioresistant vs 30.9 mo for radioresistant (P = .46)		20 Gy in 1 fx	LC 14.4 mo for radioresistant vs 41.5 mo for radioresistant (P = .001)		20 Gy in 2-5 fx		
Navarria et al ³¹	102				96	69	27-32 Gy in 3-4 fx		Gamma Knife (Elekta, Stockholm, Sweden; frame kept on for 3-4 d)
Kim et al ³²	36				90	66.7	24 Gy in 3 fx		Significantly higher rate of radiation necrosis w/single session
Eaton et al ³³	75	72.8	66.7	15 Gy in 1 fx	74.4	71.6	21-30 Gy in 3-5 fx	.8	No difference in OS between the two groups. Authors recommended considering higher biological equivalent dose (BED) w/fractionated SRS
Wiggenraad et al ³⁴	92	54		15 Gy in 1 fx	61		24 Gy in 3 fx	.93	
Feuvret et al ³⁵	36	58	164 d	14 Gy in 1 fx	100	504 d	23.1 Gy in 3 fx	.06	
Nishizaki et al ³⁶	71				83	47			
Zimmerman et al ²⁶	62	68	22	15 Gy in 1 fx	76	56	30-35 Gy in 5 fx		
Ernst-Stecken et al ³⁷	51				61	45	27 Gy in 2 fx		Each session given 3-4 wk apart
Yomo et al ³⁸	27								
Han et al ³⁹	80	85	39	14 Gy in 1 fx					

TABLE 3. Summary of ISRS Consensus Statement

Criteria	Consensus statement
Single brain metastasis	SRS alone if surgery is not required; WBRT reserved for salvage
2-4 brain metastases	SRS alone if surgery is not required; WBRT reserved for salvage
Larger (>3 cm) brain metastases	Surgical resection should be considered. If surgery is not offered, may consider SRS. There is emerging data for multisession/staged SRS as a more favorable treatment option as compared to single-session SRS.

specifically radiation necrosis. Unfortunately, this appears to decrease the rate of tumor control, as demonstrated by Vogelbaum et al.²⁵ A dose of 24 Gy resulted in 1-yr LC of 85%, whereas 15 or 18 Gy resulted in a 1-yr LC less than 50%. Studies to date seem to demonstrate improved control with dose escalation and hypofractionation²⁶ as compared to single fraction/session SRS. Minitti et al²⁷ compared single session vs multisession SRS in 298 patients. One-year LC with multisession SRS was 91% vs 77% with single session ($P = .01$). Radiation necrosis was also less, with multisession SRS at 8% vs 20% with single session ($P = .004$). Our review looking at single session vs multisession (hypofractionated) SRS is summarized in Table 2. The data suggest that 27 Gy in 3 fractions or 30 Gy in 5 fractions yields greater rates of LC with the least risk for radiation necrosis.

Similar concerns exist regarding the use of adjuvant WBRT given the results observed for the use of WBRT in addition to SRS, although WBRT in addition to SRS may improve LC for larger metastases.²⁶ That said, the possible improved LC from hypofractionated SRS may be sufficient and adjuvant WBRT can be avoided.

Limitations

Only high-quality studies were chosen for this guideline, thus limiting bias. Studies are ongoing regarding larger brain metastases and this guideline will likely need to be updated once those studies mature.

ISRS CONSENSUS RECOMMENDATION (SEE TABLE 3)

Single Brain Metastasis

SRS alone should be offered for patients not requiring surgery, and WBRT reserved as one of many salvage therapies.

WBRT on its own represents suboptimal treatment.

Two to Four Brain Metastases

SRS alone is the recommend upfront treatment and WBRT reserved as one of many salvage treatment options.

Surgery is reserved for those metastases that require urgent resection based on the patients clinical signs and symptoms.

WBRT on its own represents suboptimal treatment.

Larger Brain Metastases (Defined as 3 cm or Greater in Diameter)

Surgical resection should be considered. If surgery is not offered, consider SRS. The role of hypofractionated/multisession radiosurgery is emerging. Single session dose is 15 Gy, but a few studies suggest either improved LC or decreased toxicity with multisession SRS. Recommend dose for multisession SRS is 27 Gy in 3 sessions or 30 Gy in 5 sessions.

CONCLUSION

Historically, WBRT was felt to improve intracranial control when added to SRS. It was debatable whether intracranial recurrence affected neurocognitive function, more or less, as compared to the effects of WBRT. Recent studies from Aoyama et al,⁹ Chang et al,¹¹ Kocher et al,¹² and Brown et al²⁵ have proven that the neurocognitive side effects and reduction in quality of life parameters are indeed associated with WBRT as opposed to the delayed onset of new brain metastases. This is with the caveat of routine surveillance post-treatment with MRI and the use of salvage treatments upon recurrence as clinically indicated. This systematic review also probed the treatment of large brain metastases for which there is only emerging literature. There is a potential benefit from hypofractionated (multisession) SRS as compared to single fraction SRS, and from surgical resection followed by adjuvant radiation if they are symptomatic. As such, it is the recommendation by ISRS that patients with 1 to 4 brain metastases with reasonable performance status and prognosis be treated with SRS alone, with WBRT reserved as one of many salvage therapeutic options.

Disclaimer

These guidelines should not be considered inclusive of all methods of care or exclusive of other methods or care reasonably directed to obtain similar results. The physician must make the ultimate judgment depending on characteristics and circumstances of individual patients. Adherence to this guideline will not ensure successful treatment in every situation. The authors of this guideline and the ISRS assume no liability for the information, conclusions, and recommendations contained in this report.

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COMMENT

This International Stereotactic Radiosurgery Society (ISRS) Practice Guideline represents the most up-to-date guidelines for stereotactic radiosurgery (SRS) in the management of limited (1 to 4) brain metastases. The meta-analysis by Sahgal et al¹ has confirmed the lack of detriment to overall survival by omitting whole brain radiotherapy. The results of the most recently published phase III randomized trial by Brown et al² have corroborated those from the phase III trial by Chang et al³ with regard to neurocognitive function. The results of the Korean phase III trial comparing upfront SRS and observation of limited asymptomatic brain metastases have provided practice guidance in this commonly encountered situation. Based on retrospective studies, hypofractionated stereotactic radiotherapy (HSRT), also called multisession SRS, for limited larger metastases appears to achieve better therapeutic ratio compared to single

session SRS. All these updates provide better guidance for clinical practice.

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