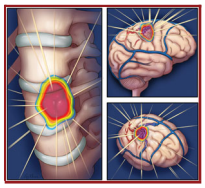

Does Stereotactic Radiosurgery Have a Role in the Management of Patients Presenting With 4 or More Brain Metastases?

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Stereotactic radiosurgery (SRS) and whole brain radiation therapy (WBRT) are effective treatments for management of brain metastases. Prospective trials comparing the 2 modalities in patients with fewer than 4 brain metastases demonstrate that overall survival (OS) is similar. Intracranial failure is more common after SRS, while WBRT is associated with neurocognitive decline. As technology has advanced, fewer technical obstacles remain for treating patients with 4 or more brain metastases with SRS, but level I data supporting its use are lacking.

Observational prospective studies and retrospective series indicate that in patients with 4 or more brain metastases, performance status, total volume of intracranial disease, histology, and rate of development of new brain metastases predict outcomes more accurately than the number of brain metastases. It may be reasonable to initially offer SRS to some patients with 4 or more brain metastases. Initiating therapy with SRS avoids the acute and late sequelae of WBRT. Multiple phase III trials of SRS vs WBRT, both currently open or under development, are directly comparing quality of life and OS for patients with 4 or more brain metastases to help answer the question of SRS appropriateness for these patients.

KEY WORDS: Brain metastases, Stereotactic radiosurgery, Whole brain radiation

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Approximately 170 000 patients are diagnosed with brain metastases each year in the United States.[1] In radiation oncology, a treatment dichotomy has emerged between 2 competing approaches to manage brain metastases: whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS). While WBRT is useful to eliminate microscopic occult disease and simple to deliver, it is associated with cognitive decline, fatigue, alopecia, and worsening performance status.[2-5] SRS has become an increasingly popular treatment modality for targeting brain metastases. It spares most normal brain tissue from clinically relevant radiation doses through steep dose fall-off around the target. However, SRS is more costly than WBRT.[6,7] Multiple phase III trials have compared the 2 modalities in patients with up to 4 brain metastases. They consistently report similar overall survival; however, WBRT is associated with lower rates of distant brain failure (DBF) and higher incidences of neurocognitive decline.[8-14] There is a lack of phase III randomized evidence to support the use of SRS among patients with 4 or more brain metastases.

In this review article, we assess nonrandomized prospective and retrospective data supporting the use of SRS in patients with 4 or more brain metastases. We also review the technological advancements that allow clinicians to treat multiple brain metastases with SRS, the new battery of tests to detect differences in cognitive function after WBRT, and appropriate selection of patients with 4 or more brain metastases for treatment with SRS.

ABBREVIATIONS: BMV, brain metastasis velocity; **DBF,** distant brain failure; **HVLT-R,** Hopkins Verbal Learning Test-Revised; **MRI,** magnetic resonance imaging; **OS,** overall survival; **QOL,** quality of life; **SRS,** stereotactic radiosurgery; **WBRT,** whole brain radiation therapy

TABLE 1. Modern Treatment Modalities Used for Treatment of Multiple Brain Metastases With Immobilization, Treatment Delivery Technique, Image Guidance for Brain Metastases

Device type commercial name	Immobilization	Radiation source	Collimation capabilities	Image guidance	Setup	Disadvantages for treatment of 4 or more brain metastases
Gamma Knife Perfexion Extend Icon	Rigid headframe fixation, Custom bite block, Custom Mask	Cobalt-60 γ rays	Fixed 4, 8, 14, and 18 mm, earlier units Individual sector control for field shaping	Cone beam CT with GK icon	N/A	Treatment time dependent on strength of cobalt sources and number of isocenters
CyberKnife	Frame or frameless thermoplastic face mask	6 MV X rays Robotic arm mounted linac	Fixed, adjustable circular cones or MLC	On board stereoscopic X-ray images	Stereoscopic X-rays	Treatment time dependent on number of isocenters and number of nodes for X-ray beam locations. Dose outside target is 2 to 6 times greater than with GKRS
Rotating Gantry Linear Accelerator[a] TrueBeam Versa Novalis	Frame Mask BrainLab Frameless	6 MV X rays Gantry mounted linac	MLC micro MLC cones	On board stereoscopic X-ray images Cone beam CT Optical	Variable	Low-dose leakage may be greater than Gamma Knife for multiple (>9) small targets due to collimator leakage[58]

MLC, multileaf collimator.

[a]Rotating Gantry Linear Accelerator can be paired with many devices for immobilization, image guidance, and setup. Novalis is specifically designed for SRS, whereas Truebeam and Versa are also proficient in external beam radiotherapy. Gamma Knife and Versa (Elekta, Stockholm, Sweden), CyberKnife (Accuray, Sunnyvale, California), Novalis and TrueBeam (Varian, Palo Alto, California). Brain Lab (BrainLab AG, Munich, Germany).

HISTORIC LIMITATIONS OF TREATING MULTIPLE BRAIN METASTASES: SAFETY AND LOGISTICS

The major historical limitations for treatment of multiple brain metastases have included technical challenges—primarily the length of time needed for treatment of multiple metastatic targets and lack of data corroborating its safety. Technological advancements for linear accelerator and gamma SRS have enabled greatly reduced treatment time and improved dose conformality.

In the early 1990s, linear accelerator arc-based SRS for brain metastases using tertiary, fixed-diameter circular collimators could potentially take several hours due to low dose rates (output factors <1.000 for small fields), use of multiple isocenters (1 or more for each metastases target), manual setting of isocenter coordinates and collimator sizes, and the typical use of multiple arcs per isocenter. Quality assurance procedures performed prior to a linear accelerator SRS delivery were time consuming and often required the linear accelerator to be taken offline during regular clinic hours.[15-17] Linear accelerators capable of delivering SRS more efficiently, including the use of multileaf collimators, became more commonly available in the early 21st century. Such linear accelerator capabilities also enabled extracranial techniques, now known as stereotactic body radiotherapy. Since then, a proliferation of linear accelerator capabilities, including robotic SRS, biplanar image-guided SRS, and other adapted gantry-based systems have evolved for the efficient SRS treatment of brain metastases (Table 1).

Gamma radiosurgery using the Gamma Knife (GK; Elekta AB, Stockholm, Sweden) has also seen dramatic improvements in treatment efficiency. In early GK models (Models U and B) every target coordinate was manually set by the treatment team using mechanical tools, requiring entry to the room by personnel and a minimum changeover time between target "shots" of approximately 5 min. Collimator sizes, selected from 1 of 4 sizes, 4, 8, 14, or 18 mm diameters, each carried in a heavy collimator helmet, were also manually selected by physically positioning the desired collimator helmet on the GK unit. Individual field shaping was performed by physically plugging individual beams in the collimator helmet. Treatment times could be quite long due to the manual operations involved, the number of shots needed for an individual target, and low dose rates due to small collimator size (output factors <1.000 for small fields) and decay of Cobalt-60 sources. Newer GK models (Perfexion, Extend, Icon) have automated coordinate changes and the collimator adjustments and have greatly decreased the treatment time, allowing for a much more streamlined approach to SRS.[18,19] Table 1 outlines modern SRS treatment devices used to treat brain metastases and lists their immobilization, technique, and image guidance available.

TREATMENT SAFETY

No prospective trials have evaluated the dose and volume safety thresholds for SRS as primary outcomes in patients with 4 or more brain metastases. Prospective data evaluating the safety of treating

TABLE 2. Series Reporting Rates of Radiation Necrosis Based on V12

Series	Treated with SRS	Symptomatic vs asymptomatic	V12 RT necrosis threshold	% radiation necrosis
Flickinger[23] n = 85; 45 mo	AVM	Symptomatic	10 cc	30
Ohtakara[59] n = 131; 18 mo	Brain metastases	8.4% symptomatic, 6.9% asymptomatic	8.4 cc	15
Korytko[21] n = 129	Non-AVM brain tumors	Symptomatic	10 cc	25
Blonigen[60] n = 173; 14 mo	Brain metastases	Symptomatic	7.9 cc	10
Minnitti[22] n = 310	Brain metastases	Symptomatic and asymptomatic	8.5 cc	>10

AVM, arteriovenous malformation; RT, Radiation therapy.
[a]N = number of lesions treated, follow up in months.

multiple brain metastases are available in JLGK0901.[20] This trial prospectively followed 1194 patients treated with GK SRS for patients with 1 to 10 brain metastases and limited the cumulative volume of brain metastases to 10 cc. A recent update reported SRS-induced complications in 12% (n = 145) of patients, 30 of whom were treated with steroids for asymptomatic radiographic changes.[20] Although the number of brain metastases treated was not associated with an increased incidence of SRS complications, the maximum diameter of the largest tumor, age, and presence of neurological symptoms were all statistically significant predictors of post-treatment complications. The global maximum dose (<40 Gy vs >40 Gy) and systemic therapy did not predict post-SRS complications in univariate or multivariate modeling. These results indicate that clinicians should consider the treated volume and symptoms from brain metastases, rather than the number of brain metastases, when concerned about adverse side effects from SRS.

The cumulative volume of brain receiving 12 Gy (V12) is consistently used as a predictor of radiation necrosis after SRS (Table 2). The type of lesions treated across multiple series included patients with arteriovenous malformations, brain metastases, benign brain tumors, and patients who had received previous WBRT. Radiation necrosis occurs at a median of 10 to 12 mo after initial SRS.[21-23] Most of the data in these series were generated from patients with a small number of brain metastases, in whom a dominant metastasis represented the largest portion of the V12. Solitary metastases with a V12 of less than 8 to 10 cc have low rates of radiation necrosis (<10%). Beyond this threshold, rates of radiation necrosis increase, approaching 20% to 50%. In the setting of multiple small metastases that sum to a volume of >10 cc, the rate of radiation necrosis may be significantly less, compared to a dominant lesion that occupies the majority of the treated volume. The upcoming CE.7 randomized trial limits any contiguous V12 to less than 8.5 cc, but constrains the cumulative brain V12 to 30 cc.[24]

RADIOSURGERY FOR OLIGOMETASTATIC BRAIN DISEASE

Five prospective randomized trials have compared SRS to SRS + WBRT (Table 3).[9-11,13,14,25] These trials included only patients with 1 to 3 brain metastases, except for a Japanese protocol that allowed up to 4.[11] WBRT after SRS consistently improves local and distant control, but these improvements have not increased overall survival. However, these trials limited enrollment to patients with a life expectancy of >6 mo. In patients with a shorter life expectancy or poor performance status, oral steroids alone or WBRT may be appropriate therapy.[26]

Distant brain failure, defined as a new brain metastasis outside the previous treatment volume, is more likely to occur with SRS alone.[9,27] The increased rate of DBF after SRS has not translated to an increased risk of neurological death, which ranges from 10% to 20%.[9] WBRT can incrementally improve both local failure and distant failure (12-mo brain tumor recurrence 7.5%-45% vs 70%-75%).[11-13] In the context of higher rates of DBF after SRS, follow-up magnetic resonance imaging (MRI) studies 2 to 3 mo after initial SRS are crucial for detecting small, asymptomatic metastases in order to prevent neurological death.[7,28]

For patients with 4 or more brain metastases, one would expect the likelihood of DBF to be greater, compared to <4 brain metastases. What is unclear is whether this increase in intracranial failure translates to a difference in overall survival or neurological death.

QUALITY OF LIFE AND NEUROCOGNITIVE FUNCTION WITH SRS AND WBRT

In 3 of the aforementioned prospective trials, cognitive decline was the primary outcome. Relatively crude means of measuring cognitive function were used in initial trials, which employed a battery of MMSE (JCOG) and performance status (EORTC). Unfortunately, these measures of quality of life (QOL) and cognitive function have poor reproducibility in patients with brain tumors.[29] MMSE can only detect delirium or significant dementia, and is particularly insensitive to detecting neurocognitive problems in this patient population.[30] More recent phase III trials have focused on the late cognitive effects after WBRT or SRS, using more refined neurocognitive tests that assess multiple domains of function (Table 3). The emphasis on neurocognition led to early termination of one trial, because at 4 mo

TABLE 3. Published Randomized Phase III Trials Comparing WBRT vs SRS With Outcomes and Quality of Life (QOL) and Neurocognitive measures

Published Phase III RCT	Year accrual	Number of brain metastases	Comparison	Primary outcome	QOL and neurocognitive measures	Median OS in SRS arm (months)	Approximate OS of top quintile in SRS arm (20%)
RTOG 9508[8]	1996-2001	1-3	WBRT ± SRS	Overall survival	KPS	6.5	18
EORTC 22952-26001[9,10]	1996-2007	1-3	SRS or surgery ± WBRT	Decline in ECOG at 6 mo	EORTC QOL questionnaire	10.9	36
JROSG 99-1[11]	1999-2003	1-4	SRS ± WBRT	Overall survival	Neurologic function grade 0-4 MMSE	8.0	18
MD Anderson[12]	2001-2007	1-3	SRS ± WBRT	Neurocognitive function	HVLT-R, WAIS-III, TMT-A, TMT-B, COWA, LGP	9.2	20
N0574[13]	2002-2013	1-3	SRS ± WBRT	Cognitive deterioration > 1 SD at 3 mo	HVLT-R, TMT-A, TMT-B, COWAT, GPS	10.4	20
NCCTG N107C/CEC-3[14]	2011-2015	1 cavity	SRS vs WBRT	Overall survival and cognitive deterioration free survival	HVLT-R, TMT-A, TMT-B, COWAT, FACT-Br, LASA, Barthel index of ADL	12.2	Not reached after 24 mo of follow-up

KPS, Karnofsky Performance Status; HVLT-R, Hopkins Verbal Learning Test-Recall; TMT, Trail Making Test Part A and Part B; COWAT, Controlled Oral Word Association Test; FACT-Br, Functional Assessment of Cancer Therapy- Brain; LASA, Fatigue/Uniscale Assessment and Linear Analog Self-Assessment; ADL, Barthel Index of Activities of Daily Living.

neurocognitive function was inferior in the WBRT + SRS arm compared to SRS alone.[12] A decline of more than 5 points in the Hopkins Verbal Learning Test-Revised (HVLT-R) total recall was observed in 52% of patients receiving SRS + WBRT and 24% of patients receiving SRS alone.

The N0574 phase III trial has the most comprehensive assessment of cognitive outcomes comparing SRS vs SRS + WBRT.[13] This study enrolled 213 patients to SRS vs SRS + WBRT; they reported that cognitive decline was less frequent after SRS alone than SRS + WBRT (63.5% for SRS alone vs 91.7% for combined; $P < .001$) and QOL at 3 mo favored those treated with SRS alone.[13] Additionally, 16% of patients were "long-term survivors," defined as >12 mo of follow-up. In this small cohort, executive function at 12 mo was significantly higher in those who received SRS, despite a higher rate of intracranial progression compared to the SRS + WBRT arm. The key points from this trial are that (1) higher rates of DBF do not impact neurological function in those treated with SRS, and (2) omitting WBRT is associated with better QOL, despite the development of more brain metastases.

Fine motor functioning also significantly favored the SRS-alone arm at 6 mo, which illustrates that the toxicity of WBRT extends across multiple domains. The severity of cognitive decline is also variable after WBRT; less than 5% of patients experience severe, debilitating dementia, they may also have gait instability and urinary incontinence.[31,32] Some patients treated with WBRT may have an initial decline in cognitive function followed by recovery. This decline may be attributed to a number of factors aside from WBRT, including delivery of systemic therapy. In these situations, time-to-event analysis may not capture recovery after WBRT.[32] Given the detrimental changes in quality of life after WBRT, Urbanic suggested that we are witnessing "the demise of whole brain" treatment, in lieu of treating multiple lesions with SRS for brain metastases and avoiding the irradiation of an entire organ.[33]

Novel approaches to spare cognition in patients receiving WBRT include the addition of memantine, a cognition-enhancing agent, or use of hippocampal-sparing WBRT. The RTOG 0614 study compared patients (regardless of numbers of brain metastases) receiving WBRT vs WBRT + memantine.[34] In the HVLT-delayed recall test assessed at 24 wk, there was less decline in the memantine arm compared to placebo ($P = .059$). This result may have been influenced by the large numbers of patients who were censored due to dropout or death. While patients in the memantine arm also showed improvement on other cognitive tests, the overall magnitude of the benefit was modest (65% vs 54% cognitive decline at 6 mo) compared to studies in which WBRT + SRS was compared to SRS.

In the RTOG 0933 study, a single-arm phase II study of hippocampal-sparing WBRT, results on the HVLT-delayed recall were improved at 4 mo compared to historical controls.[35] However, historic control groups may not be optimal for brain metastasis studies since detection has improved over time with high-resolution MRI. A randomized trial is needed to validate the results of RTOG 0933. In addition, aside from the hippocampus, cognitive function likely has multiple centers within the brain.

TABLE 4. Currently Open and Planned Prospective Phase III Trials Evaluating SRS vs WBRT for 4 or More Brain Metastases

Study	Population and design	Volumetric limitation	Outcomes	Status
Whole brain radiotherapy (WBRT) vs stereotactic radiosurgery (SRS) for 4 up to 10 brain metastases NCT02353000 Netherlands	4-10 brain metastases SRS vs WBRT	Max GTV 30 cc Max diameter of single GTV 2.5 cm	Overall survival, HVLT-R, EORTC, QLQ-C30, EPRTC QLQ-BN20, EORTC QLQ-FA13, Degree of independence, Steroid use	Currently open and accruing Estimated enrollment: 260 Estimated study completion date: April 2019
A prospective phase III randomized trial to compare stereotactic radiosurgery for ≥4 for newly diagnosed nonmelanoma brain metastases brain metastases	4-15 brain metastases on diagnostic MRI, up to 20 on treatment planning MRI SRS vs WBRT	Maximum diameter	Local tumor control, HVLT-R at 4 mo 7 cognitive tests at 1, 4, 6, 9, 12 mo	Currently open and accruing Estimated enrollment: 100 Estimated study completion date: August 2019
Whole brain radiation vs stereotactic radiation (SRS) in patients with 5-20 brain metastases: a phase III, randomized clinical trial NCT03075072 Dana-Farber Cancer Institute, Brigham and Women's	5-20 brain metastases SRS (in 1-5 fractions) vs WBRT (to use hippocampal sparing approach when possible)	Maximum tumor diameter exceeding 5 cm	Quality of Life, MDASI-BT, Overall survival	Currently open and accruing Estimated enrollment: 196 Estimated study completion date 3/30/2022
CMET-48.CE.7 A phase III trial of stereotactic radiosurgery compared with whole brain radiotherapy for 5-15 brain metastases Alliance for Clinical trials in Oncology, Canadian Clinical Trials Group	5-15 brain metastases WBRT vs SRS	Maximum total tumor volume 30 cc	Cognitive deterioration free survival and overall survival	Not yet accruing Estimate enrollment: 206 patients

Thus, sparing only the hippocampus may not avoid the appropriate targets for cognition.[33,36] The currently accruing phase III trial at Dana Farber and Brigham and Women's Hospital is testing hippocampal sparing with WBRT compared to SRS alone for 5 to 20 brain metastases (Table 4). The primary outcome is QOL; results of this trial may shed light on the utility of hippocampal-sparing WBRT. Furthermore, the NRG CC001 phase III trial is investigating memantine with or without hippocampal avoidance, with an endpoint of neurocognitive failure.

For patients with 4 or more brain metastases, the evidence indicates that the decline seen with WBRT is not trivial. Attempts to mitigate these side effects by using pharmacological intervention or novel radiation techniques have been only modestly successful. For patients receiving WBRT, there is no plateau in the incidence or severity of radiation-induced cognitive decline.[3] Once such decline onsets, there are no known successful treatment options.[37] As patients with metastatic disease live longer, the importance of QOL and preservation of neurocognition becomes increasingly relevant.

EXISTING STUDIES OF SRS FOR 4 OR MORE BRAIN METASTASES

Several single-institution reports have demonstrated the feasibility of SRS for multiple brain metastases without excessive toxicity, but these have generally included patients undergoing SRS as a salvage therapy after prior WBRT and/or SRS.[38,39] Control of brain metastases for patients receiving SRS as salvage therapy for local or distant WBRT failure is comparable to that in patients who received SRS followed by delayed WBRT salvage.[40] These results suggest that starting with SRS, and delaying WBRT and its associated neurocognitive toxicity until necessary, may not compromise ultimate local tumor control.

Yamamoto et al[41,42] first published 2 series of case-matched studies of SRS for patients with 1 to 4 vs 5 or more brain metastases and 2 to 9 vs ≥10 brain metastases. These retrospective results showed similar rates of DBF and neurological death. Although survival was similar across groups, a cumulative tumor volume of >10 cc was associated with worse overall survival.

These findings were superseded by a large, multi-institutional phase III observational trial (JLGK0901) from the same researchers.[43] This large prospective study compared outcomes after SRS alone for patients grouped by the number of brain metastases at presentation: 1 (n = 455), 2 to 4 (n = 531), or 5 to 10 (n = 208). The total cumulative tumor volume was limited to <10 cc. Median overall survival was significantly improved for patients with only 1 brain metastasis compared to the other 2 groups (13.9 mo, $P = .0004$). Strikingly, the median survival was 10.8 mo both among patients with 2 to 4 brain metastases and those with 5 to 10 brain metastases ($P = .78$). The fifth quintile of patients in terms of survival with 2 to 4 or 5 to 10 brain metastases survived approximately 30 mo after SRS,

TABLE 5. Series Evaluating Patients With 4 or More Brain Metastases

Study	No. of patients	No. of metastases	1-yr DBF (%)	Median OS (mo)	Predictors early intracranial failure
Serizawa et al[61]	366	5-10	NR	7.4[a]	NR
Chang et al[25]	58	6-10	NR	10	>15 brain metastases
	17	11-15	NR	13	
	33	>15	57.9	8	
Hunter et al[62]	64	5-10	NR	7.5	NR
Rava et al[38]	53	≥10	90	6.5	Male sex
Raldow et al[39]	84	5-9	62	7.6	Age
	19	≥10		8.3	
Ayala-Peacock et al[54]	125	5-10	49	6.2	Progressive systemic disease, Discovery of new metastases at SRS Melanoma, HER2 neg breast
Yamamoto et al[42]	360	2-9	28.5	6.8	NR
	360	≥10	21.7	6.0	
Yamamoto et al[43]	208	5-10	64	10.8	>10 brain metastases
Ali et al[44]	2125	5-10	NR	10.7	NR
		10+			

No., number; DBF, distant brain failure; OS, overall survival; mo, months, Not Reported (NR).
[a]Mean.

suggesting that an upfront SRS strategy would provide significant long-term neurocognitive benefit in this population compared to WBRT. Among patients with more than 2 brain metastases, similar rates were seen for neurological death (5%-7% at 2 yr), rates of repeat SRS (44% at 2 yr), and salvage WBRT (≈10% at 2 yr). Factors that influenced overall survival included sex, control of extracerebral disease, Karnofsky Performance Status, age, and presence of symptoms. Histologic characteristics did not influence median overall survival among these patients. While the trial's QOL metrics and neurocognitive tests were not as rigorous as those in more recent and current trials, the 12-mo Mini-Mental Status Exam scores were similar (93%, 91%, and 92%) across all 3 groups of patients.[20]

The JLGK0901 trial has several important limitations, including possible selection bias (especially among patients with 5 to 10 brain metastases) as well as potential differences in systemic therapy usage in the patients with 5 to 10 brain metastases.[43] In addition, the trial studied a Japanese patient population, with different varieties of cancer (particularly lung cancers with favorable prognosis mutations). Thus, its results may not be directly generalizable to other parts of the world. The volumetric constraint of <10 cc of intracranial disease also limits its generalizability to other populations with a higher volumetric burden of intracranial disease.

The JLGK0901 trial is the only large prospective of patients with more than 4 brain metastases, but multiple retrospective series have supported its conclusions. In a multi-institutional analysis of 5750 patients—including those treated on the JLGK0901 study—the hazard for death increased 4% for every 6 to 7 brain metastases treated. Rates of neurological death were not reported. Intracranial volume and number of brain metastases independently predicted for worse survival.[44] Interestingly, if the volume of brain metastases remained the same, the number of brain metastases still significantly predicted for an increased risk of death. Practically, a patient with 10 cc of disease with 3 brain metastases would have better outcomes than a patient with 10 cc of disease and 10 brain metastases.[44]

Karlsson and colleagues[45] identified 1855 patients treated with SRS alone at 4 European and American institutions; participants had one or multiple brain metastases from various primary sites. Overall survival did not differ between groups with more than 2 metastases (2, 3-4, 5-8, >8 brain metastases). For patients with uncontrolled primary disease, survival did not differ between those with single versus multiple lesions treated. This finding demonstrates the pitfalls of survival analyses comparing intracranial treatment that do not adjust for the competing risk of death from extracranial disease. In another study, patients with more than 15 brain metastases had significantly worse overall survival than patients with 1 to 5, 6 to 10, or 11 to 15 brain metastases.[25] Rava et al[38] retrospectively reviewed patients with >10 brain metastases; patients with breast cancer had worse overall survival than those with metastases from other sites. Among patients treated at the University of Pittsburgh, median overall survival differed between patients with 1 to 4 brain metastases and those with 5 or more brain metastases. However, this difference was not statistically significant on multivariate analyses, after accounting for systemic disease status and extracranial metastases.[46]

Table 5 illustrates outcomes from reports of patients treated with 5 or more brain metastases. In sum, the existing data for treating patients with brain metastases with 4 or more brain metastases are primarily retrospective and subject to selection bias, or both. Treatment with SRS alone is feasible for patients with 4 or more brain metastases and the outcomes are not decidedly

worse than for patients with fewer metastases. However, further prospective randomized data are needed to test these results. Table 4 lists the currently accruing and upcoming phase III trials evaluating SRS vs WBRT in patients with 4 or more brain metastases. It will be imperative to complete these studies given the lack of good data for this patient population.

PREDICTING OUTCOMES FOR PATIENTS TREATED INITIALLY WITH SRS

As both retrospective and prospective studies have repeatedly shown, the absolute number of brain metastases is less prognostic than other factors such as Karnofsky Performance Score, age, histologic features of tumors, and presence of targetable mutations.[47-50] Recently, models have focused on characterizing the rate of intracranial progression and identifying patients at risk of neurological death. Brain metastasis velocity (BMV), the rate that new brain metastases occur after SRS,[51] is highly prognostic for neurological outcome and overall survival. BMV is being considered for use in the CE.7 trial and a prospective validation in an NRG trial.

Factors that independently predict for neurological death by competing risk analysis include melanoma histology, diagnosis-specific Graded Prognostic Assessment, number of brain metastases, and SRS doses. Age, nonmelanoma histology, and advanced systemic disease were more predictive of nonneurological death.[52] While greater numbers of brain metastases predicted a greater risk of neurological death, multiple factors were clearly significant. These results suggest that sole use of the number of metastases as a prognostic factor is somewhat of an oversimplification.

In a series of patients with 1 to 3 lesions initially treated with SRS alone, the presence of multiple metastases was associated with a greater likelihood of intracranial progression.[28] Sawrie et al[53] reported that having more than 3 brain metastases, melanoma histology, or active extracranial disease were each independent predictors of increased incidence of DBF and shorter time to DBF. Finally, in a multi-institutional study, numbers of metastases and melanoma histology were major factors associated with increased incidence of DBF.[54]

In summary, these retrospective series and novel metrics may help guide the decision for appropriate treatment of patients presenting with 4 or more brain metastases. However, validation of these models in prospective trials is necessary.

ECONOMIC IMPLICATIONS OF SRS FOR 4 OR MORE BRAIN METASTASES

The cost of brain metastasis treatment in the United States has become increasingly relevant but difficult to study based on differing reimbursement schemes. Retrospective studies are fraught with selection bias, differing reimbursement schemes, and by the attributes of the model.[55] Cost-effective strategies based on quality-adjusted life years have suggested that for patients with 1 to 3 brain metastases, SRS alone is cost effective compared to SRS + WBRT.[56] In 1 study, SRS was cost-effective among patients with a prognosis of 3 to 6 mo compared to WBRT, but not thereafter.[57] Using a Markov model, Sarkov et al[57] suggested that prognostic models could identify the population more likely to benefit from SRS and would significantly improve the cost-effectiveness of SRS. The planned CE.7 randomized trial will include a much needed prospective, multi-institutional cost assessment, which will contribute to the relative cost-effectiveness of SRS vs WBRT in this population.

CONCLUSION

WBRT has long been a standard treatment option for treatment of brain metastases. Technological improvements have allowed physicians to use SRS to treat 4 or more brain metastases, despite a lack of randomized evidence supporting its use in this population. Initial SRS approaches are utilized due to the increased recognition of WBRT-induced neurocognitive decline. In randomized data for patients with 1 to 3 brain metastases and prospectively collected data for 1 to 10 brain metastases, the increased risk of DBF with SRS alone has not translated into worse overall survival or higher rates of neurological death. The role of SRS in the treatment of brain metastases should be carefully considered on an individual basis. Completion of accrual in multi-institutional trials will be necessary to determine whether SRS is the most appropriate treatment in such patients.

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COMMENTS

The role of stereotactic radiation for the treatment of brain metastasis has been increasing with guidelines for the treatment of patients with 1-4 metastatic lesions recently published.[1] The question of the appropriate treatment for patients with a greater number of metastasis has not been completely resolved. This paper reviews the current literature to discuss reported results of survival, recurrence, complications, including radiation necrosis, as well as neurocognitive consequences. The paper gives an excellent overview and is a reference for the practitioner to consider when treating these patients.

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1. Chao ST, De Salles A, Hayashi M, et al. Stereotactic Radiosurgery in the Management of Limited (1-4) Brain Metastasis: Systematic Review and International Stereotactic Radiosurgery Society Practice Guideline. *Neurosurgery*. Epub, 03 Nov 2017.

Our patients and referring physicians frequently insist upon stereotactic radiosurgery (SRS) because of the expanding systemic therapy options for many cancers and increasing recognition of neurocognitive decline after whole brain radiation therapy. Given the excellent local control rate, favorable side effect profile, and improving efficiency of SRS for patients with brain metastases, we find ourselves frequently pushing the boundaries for number of brain metastases treated and frequency of SRS sessions. This review article provides the current literature evidence for SRS in patients with 4 or more brain metastases. The authors are applauded for their timely work summarizing the evolving technology, selection criteria, cancer control, and toxicity of brain radiotherapy in this patient population.

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