Impact of 2-staged stereotactic radiosurgery for treatment of brain metastases ≥ 2 cm

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OBJECTIVE Stereotactic radiosurgery (SRS) is the primary modality for treating brain metastases. However, effective radiosurgical control of brain metastases ≥ 2 cm in maximum diameter remains challenging and is associated with suboptimal local control (LC) rates of 37%–62% and an increased risk of treatment-related toxicity. To enhance LC while limiting adverse effects (AEs) of radiation in these patients, a dose-dense treatment regimen using 2-staged SRS (2-SSRS) was used. The objective of this study was to evaluate the efficacy and toxicity of this treatment strategy.

METHODS Fifty-four patients (with 63 brain metastases ≥ 2 cm) treated with 2-SSRS were evaluated as part of an institutional review board–approved retrospective review. Volumetric measurements at first-stage stereotactic radiosurgery (first SSRS) and second-stage SRS (second SSRS) treatments and on follow-up imaging studies were determined. In addition to patient demographic data and tumor characteristics, the study evaluated 3 primary outcomes: 1) response at first follow-up MRI, 2) time to local progression (TTP), and 3) overall survival (OS) with 2-SSRS. Response was analyzed using methods for binary data, TTP was analyzed using competing-risks methods to account for patients who died without disease progression, and OS was analyzed using conventional time-to-event methods. When needed, analyses accounted for multiple lesions in the same patient.

RESULTS Among 54 patients, 46 (85%) had 1 brain metastasis treated with 2-SSRS, 7 patients (13%) had 2 brain metastases concurrently treated with 2-SSRS, and 1 patient underwent 2-SSRS for 3 concurrent brain metastases ≥ 2 cm. The median age was 63 years (range 23–83 years), 23 patients (43%) had non–small cell lung cancer, and 14 patients (26%) had radioresistant tumors (renal or melanoma). The median doses at first and second SSRS were 15 Gy (range 12–18 Gy) and 15 Gy (range 12–15 Gy), respectively. The median duration between stages was 34 days, and median tumor volumes at the first and second SSRS were 10.5 cm³ (range 2.4–31.3 cm³) and 7.0 cm³ (range 1.0–29.7 cm³). Three-month follow-up imaging results were available for 43 lesions; the median volume was 4.0 cm³ (range 0.1–23.1 cm³). The median change in volume compared with baseline was a decrease of 54.9% (range –98.2% to 66.1%; $p < 0.001$). Overall, 9 lesions (14.3%) demonstrated local progression, with a median of 5.2 months (range 1.3–7.4 months), and 7 (11.1%) demonstrated AEs (6.4% Grade 1 and 2 toxicity; 4.8% Grade 3). The estimated cumulative incidence of local progression at 6 months was 12% $\pm$ 4%, corresponding to an LC rate of 88%. Shorter TTP was associated with greater tumor volume at baseline ($p = 0.01$) and smaller absolute ($p = 0.006$) and relative ($p = 0.05$) decreases in tumor volume from baseline to second SSRS. Estimated OS rates at 6 and 12 months were 65% $\pm$ 7% and 49% $\pm$ 8%, respectively.

CONCLUSIONS 2-SSRS is an effective treatment modality that resulted in significant reduction of brain metastases ≥ 2 cm, with excellent 3-month (95%) and 6-month (88%) LC rates and an overall AE rate of 11%. Prospective studies with larger cohorts and longer follow-up are necessary to assess the durability and toxicities of 2-SSRS.

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KEY WORDS large brain metastasis; 2-staged radiosurgery; 2-SSRS; hypofractionated radiosurgery; Gamma Knife; radiosurgery; local control; radiation necrosis; oncology; stereotactic radiosurgery

ABBREVIATIONS 2-SSRS = 2-staged stereotactic radiosurgery; AE = adverse effect; BED = biologically effective dose; CTCAE = Common Terminology Criteria for Adverse Events; FSRS = fractionated stereotactic radiosurgery; GPA = graded prognostic assessment; hypo-FSRS = hypofractionated stereotactic radiosurgery; KPS = Karnofsky Performance Scale; LBM = large brain metastases; LC = local control; MLD = maximum linear dimension; OS = overall survival; RN = radiation necrosis; RPA = recursive partitioning analysis; SRS = stereotactic radiosurgery; SSRS = staged stereotactic radiosurgery; TTP = time to local progression; WBRT = whole-brain radiation therapy.

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BRAIN metastases arise in 20%–40% of patients diagnosed with systemic cancer, a number that is expected to increase with individualized oncological therapies and overall improved patient survival.^{33,35,67} Furthermore, brain metastasis management can profoundly affect both patient quantity and quality of life; therefore, available treatment strategies must be carefully evaluated and optimized to improve patient outcomes.^{49,65} Stereotactic radiosurgery (SRS) is an essential modality in treating brain metastases and has demonstrated efficacy in several randomized trials and multicenter studies, whether performed alone or in combination with whole-brain radiation therapy (WBRT).^{1,31,54,61,63} Recently, SRS as a stand-alone therapy has progressively gained favor because it results in minimal impact on the delivery of systemic treatment options and may be synergistic with novel immunotherapy agents.^{36,50,53} Most compelling regarding SRS as a monotherapy, however, is that the addition of WBRT has been shown to be associated with greater adverse neurocognitive effects,^{9,11,14,31} especially when compared with SRS alone, and SRS combined with careful surveillance may allow WBRT and its associated toxicities to be deferred or avoided entirely.

Large brain metastases (LBM) are typically described as measuring either ≥ 2 –4 cm in maximum diameter or ≥ 4 –15 cm³ in volume and, traditionally, these tumors have been treated with surgery and WBRT.^{4,22,32,42,44,52} Recently, SRS, fractionated stereotactic radiotherapy, or a combination of these modalities with more conventional treatment options has been studied in the management of LBM.^{15,18,27,34,42,76} However, optimal treatment paradigms with radiosurgery remain unclear and controversial and are associated with a relatively inferior control rate compared with smaller lesions.^{6,16,18,22,32,40,41,44,57,70,76} Furthermore, potential significant treatment-associated toxicities, most notably adverse effects (AEs) of radiation,^{1,56,60} and their management remain concerning in patients with LBM.

This article presents the results of a novel approach using staged-SRS (SSRS) treatments over 2 sessions separated by several weeks or a few months. To date, to our knowledge, only 3 other studies (from 2 centers in Japan) have been published describing the use of SSRS in the management of brain metastases.^{24,74,75} In this article, we present the largest series in the literature (63 LBM) evaluating the impact of 2-staged SRS (2-SSRS) for brain metastases ≥ 2 cm. The purpose of this study was to perform a volumetric assessment of the response of LBM to this treatment strategy in terms of local control (LC) rates and treatment-related toxicity, as well as to determine the impact of 2-SSRS on overall survival (OS) in this patient cohort.

Methods

An institutional review board–approved retrospective analysis was conducted in patients with systemic cancer and brain metastases ≥ 2 cm in maximum linear diameter treated with planned 2-SSRS between June 2012 and January 2016. Patient demographic data, primary tumor characteristics, brain metastases volumes, follow-up dura-

tion, progression-free survival, and OS were evaluated in the cohort. Patients with SRS to postoperative resection cavities were excluded to avoid confounding bias. Patients were selected for planned 2-SSRS if they were not surgical candidates or on the basis of surgeon-patient preference in the absence of evidence of clinically raised intracranial pressure. Typically, the second SSRS was scheduled to occur approximately 1 month after the first SSRS, with some variation depending on patient and other systemic treatment factors.

SRS Technique and Target Volume Determination

All cases were treated using Gamma Knife Perfexion (Elekta), according to our standard institutional protocol. Patients were immobilized with head-frame fixation for each planning and treatment delivery session. Target delineation was performed using high-resolution 3D Gd-contrast-enhanced volumetric T1-weighted MRI (if not contraindicated) on the Leksell Gamma Plan software (Elekta), and no margins were applied to the targets. All patients also underwent CT scanning so that we could diminish the risk of targeting errors when using MRI sequences alone, which are susceptible to geometrical distortion. If other metastases were identified on the imaging studies, they were treated concurrently. Dexamethasone 10 mg intravenously was given at each SRS session, per institutional protocol for SRS, and individualized doses postprocedurally as clinically indicated.

Similar to the treatment protocol described by Yomo and Hayashi⁷⁴ and Yomo et al.,⁷⁵ staged treatment was performed in 2 sessions, covering 100% of the target and treating to a total of 24–33 Gy (median 30 Gy) across both sessions (according to the radiation oncologist's dose preference in consultation with the treating neurosurgeon). This resulted in a total biological equivalent prescription dose of approximately 44–73 Gy (median 62.5 Gy) if this was administered as a single session (calculated using the linear quadratic formula; assuming α/β 10 for brain metastases⁵⁹).

Determination of Response to Treatment

Response to treatment was determined using direct volumetric measurement of the enhancing mass on volumetric MRI scans (1 mm–thick slices) or thin-cut CT scans (when MRI was contraindicated) at the first and on all subsequent available imaging follow-ups. Volumes for the first and second SSRS were obtained from the Leksell Gamma Plan database, derived from the volumetric planning done on the treatment days using software (Elekta), whereas tumor volumes at subsequent imaging intervals were determined using Digital Imaging and Communications in Medicine images uploaded into iPlan software (Brainlab). Tumor contours and posttreatment volumes were then compared with volumes on the 2-SSRS treatment days.

In the event of increasing lesion size at the first follow-up after 2-SSRS, radiological and/or pathological information was used to discriminate between treatment failure and radiation injury/radiation necrosis (RN). Specifically, stabilization or shrinkage of a previously enlarged lesion

and/or decreased cerebral blood volume on perfusion MRI was considered to be related to RN, whereas continued increase in the size of the mass and/or increased cerebral blood volume was considered to be indicative of tumor progression/treatment failure. If equivocal, the case was reviewed by a multispecialty brain tumor board for adjudication.

Statistical Analysis of Patient Parameters and Treatment Outcomes

Patient characteristics related to sex, age at diagnosis, primary pathology, interval from diagnosis to 2-SSRS, Karnofsky Performance Scale (KPS) score, recursive partitioning analysis (RPA) class, graded prognostic assessment (GPA) group, extracranial disease status, total intracranial disease burden, prior intracranial treatments, and prescribed dose at first and second SSRS are summarized, using median values for continuous factors and percentages for categorical factors.

The following outcomes were specifically examined. 1) OS was determined using the Kaplan-Meier method and measured from the first SSRS to death or last follow-up. 2) Response to treatment was evaluated in a uniform cohort, in which all patients had 3-month imaging studies after the second SSRS to fully evaluate the impact of both stages of the radiosurgery at the first follow-up MRI. Similar to response criteria used in the RECIST (response evaluation criteria in solid tumors) guidelines for solid tumors (version 1.1),¹⁷ response was defined as tumor volume $\geq$ 30% decreased, progression if tumor volume was $\geq$ 20% increased, and stable otherwise. 3) Time to local progression (TTP) was measured from first SSRS to date of definitive progression. As is the convention in brain radiosurgery studies, LC is traditionally reported as metastases that are stable or smaller following SRS.

Response was analyzed using methods for binary data. That is, patient-specific factors such as prior treatment, age, and the number of smaller lesions present were analyzed using Fisher's exact test, the Cochran-Armitage trend test, and the Wilcoxon rank-sum test, whereas generalized linear mixed models were used for the analysis of lesion-specific factors (e.g., tumor volume-related variables) to account for the patients who had > 1 lesion treated with 2-SSRS. The Fine and Gray model, log-rank test, and conventional Cox proportional hazards model were used for the analysis of TTP, OS, and patient-specific factors. Extensions to these models that use a marginal approach to account for the possible clustering of lesions within patients were used for the analysis of lesion-specific factors. Measured factors such as tumor volume were analyzed as continuous variables, but for convenience, a recursive partitioning algorithm was also used to categorize these data. All data analysis was performed using SAS version 9.4.

Results

Patient Characteristics

Between June 2012 and January 2016, 54 patients with 63 brain metastases ≥ 2 cm were treated with planned 2-SSRS; patient characteristics and outcomes are summarized in Table 1. Forty-six patients (85%) had 1 large brain

metastasis treated, 7 patients (13%) had 2 LBM treated, and 1 patient (2%) had 3 LBM concurrently treated with 2-SSRS. Of these patients, 29 (54%) were women, with a median age at radiosurgical treatment of 63 years (range 23–83 years). The most common primary cancers were non-small cell lung (43%), renal (15%), breast (13%), and melanoma (11%), with a median interval from primary tumor diagnosis to 2-SSRS of 21.9 months (range 0–192.2 months).

The KPS score was obtained in all cases immediately prior to initial 2-SSRS; most patients (70%) had a good performance status, with a KPS score ≥ 80 . Based on RPA classification, which considers age, KPS score, controlled primary tumor, and extracranial metastases,²⁰ 7 patients (13%) were RPA Class I, 39 patients (72%) were RPA Class II, and 8 patients (15%) were RPA Class III. In terms of GPA score, which reflects age, KPS score, presence of extracranial metastases, and number of cranial metastases,^{63,64} 17% of patients had a GPA score of 0–1, 74% had a GPA score of 1.5–2.5, 6% had a GPA score of 3.0, and 4% had a GPA score of 3.5. Hence most patients (91%, $n = 49$) belonged to the 2 poorest GPA prognostic groups. A majority of patients (57%, $n = 25$) had extracranial metastases at the time of 2-SSRS, and many patients had prior systemic therapy (65%, $n = 35$). Of note, relatively few patients had prior WBRT (17%, $n = 9$) or prior intracranial surgery for other lesions (9%, $n = 5$).

The locations of the 63 brain metastases ≥ 2 cm were variably distributed throughout the brain, with 79% of the tumors ($n = 50$) in the supratentorial compartment, and 21% ($n = 13$) in the cerebellum and/or brainstem. No location seemed to have an impact on response to treatment, including those in the posterior fossa ($p =$ not significant), where management of mass effect from large lesions is particularly critical.

Treatment Characteristics

The median prescription dose used at the first SSRS was 15 Gy (range 12–18 Gy) at the 54% isodose line (range 50%–64%). At the second SSRS, the median prescription dose was also 15 Gy (range 12–15 Gy) at the 53% isodose line (range 50%–70%). The median interval between first and second SSRS was 34 days, and the median interval between first SSRS and first follow-up MRI was 85 days. There was no effect of dose at either stage of the 2-SSRS treatments in terms of 3-month response to treatment, TTP, or OS (Tables 1 and 2). With the 2-SSRS treatment, no patient experienced significant or unanticipated pin-site issues that required intervention or treatment delay at either treatment session.

At the time of the 2-SSRS treatment, patients presented with either 1 (the index tumor) or up to a total of 9 brain metastases. All tumors other than those treated with planned 2-SSRS were treated during the same treatment session (i.e., with single-session SRS), according to standard practice at our institution, which is also typically consistent with the RTOG 90–05 dosing schedule.⁵⁶ Patients with ≤ 2 brain metastases (excluding the 2-SSRS–treated tumor[s]) experienced significantly longer OS compared with those who had ≥ 3 brain metastases (median 18.0 vs 4.4 months, respectively; $p = 0.005$).

TABLE 1. Patient characteristics and outcomes following 2-SSRS treatment of LBM

Factor	No. (%) or Med (range)	Response at 3-Mo MRI, No. (%) or Med (range)		p Value	Med OS (mos) or Hazard Ratio*	p Value	Time to Progression, Hazard Ratio Subdistribution	p Value
		No	Yes					
Sex								
Female	29 (54)	5 (23)	17 (77)		10		Reference	
Male	25 (46)	4 (24)	13 (76)	1	13.3	0.95	2.77	0.21
Age at diagnosis (yrs)	61 (23–78)	65 (37–78)	61 (23–77)	0.29	1*	0.82	1.03	0.26
Age at 1st SSRS (yrs)	63 (23–83)	72 (37–82)	61 (23–83)	0.34	1.01*	0.46	1.04	0.24
Primary cancer								
Non–small cell lung	23 (43)							
Renal	8 (15)							
Breast	7 (13)							
Melanoma	6 (11)							
Esophageal	4 (7)							
Colon	2 (4)							
Other (bladder, endo- metrial, small cell carcinoma, thyroid)	4 (7)							
Radioresistant tumor								
No	40 (74)	7 (25)	21 (75)		10.8		Reference	
Yes (renal or melanoma)	14 (26)	2 (18)	9 (82)	1	13.3	0.91	1.91	0.39
Time from primary diagnosis to 2-SSRS (mos)	21.9 (0–192.2)	14.2 (0.5–120.3)	17.3 (0–166.4)	0.83	1.01*	0.05	1	0.51
Pre–2-SSRS KPS score								
90–100	20 (37)	2 (13)	13 (87)		19.3			
80	18 (33)	3 (20)	12 (80)		10			
70	8 (15)	1 (20)	4 (80)		4.1			
50–60	8 (15)	3 (75)	1 (25)	0.03	3.2	0.03	1.53	0.18
≥ 80	38 (70)	5 (17)	25 (83)		19.3		Reference	
< 80	16 (30)	4 (44)	5 (56)	0.17	4	0.04	1.23	0.8
RPA class								
I	7 (13)	2 (33)	4 (67)		4.9			
II	39 (72)	4 (14)	25 (86)		13.3			
III	8 (15)	3 (75)	1 (25)	0.28	3.2	0.1	3.17	0.1
GPA group								
0–1	9 (17)	1 (20)	4 (80)		6.5			
1.5–2.5	40 (74)	7 (23)	23 (77)		10.8			
3	3 (6)	0	2 (100)		NA			
3.5	2 (4)	1 (50)	1 (50)	0.64	NA	0.19	0.81	0.11
Intracranial hemorrhage								
No	40 (74)	5 (19)	22 (81)		13.3	Refer- ence	Reference	
Yes, pre 2-SSRS	8 (15)	2 (25)	6 (75)		NA	0.63	0.65	0.48
Yes, post 2-SSRS	6 (11)	2 (50)	2 (50)	0.37	7.4	0.48	1.19	0.78
No. of lesions at initial 2-SSRS but not treated w/ 2-stage procedure (i.e., not LBM)								
0	22 (41)	6 (35)	11 (65)		13.2			
1	16 (30)	2 (17)	10 (83)		19.3			
2	6 (11)	1 (20)	4 (80)		26			

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TABLE 1. Patient characteristics and outcomes following 2-SSRS treatment of LBM

Factor	No. (%) or Med (range)	Response at 3-Mo MRI, No. (%) or Med (range)		p Value	Med OS (mos) or Hazard Ratio*	p Value	Time to Progression, Hazard Ratio Subdistribution	p Value
		No	Yes					
No. of lesions at initial 2-SSRS but not treated w/ 2-stage procedure (i.e., not LBM) (continued)								
3	4 (7)	0	1 (100)		3.2			
4	4 (7)	0	3 (100)		4.8			
5 or 8	2 (4)	0	1 (100)	0.14	3.7	0.1	0.44	0.02
0, 1, 2	44 (81)	9 (26)	25 (74)		18		Reference	
> 2	10 (19)	0	5 (100)	0.32	4.4	0.005	NA	
Extracranial metastases								
No	19 (43)	5 (31)	11 (69)		18		Reference	
Yes	25 (57)	4 (22)	14 (78)	0.7	10.8	0.43	0.75	0.71
Prior WBRT								
No	45 (83)	9 (27)	24 (73)		10.8		Reference	
Yes	9 (17)	0	6 (100)	0.3	NA	0.85	0.9	0.91
Prior surgery								
No	49 (91)	8 (24)	26 (76)		10		Reference	
Yes	5 (9)	1 (20)	4 (80)	1	NA	0.99	NA	
Prior systemic therapy								
No	19 (35)	2 (14)	12 (86)		13.3		Reference	
Yes	35 (65)	7 (28)	18 (72)	0.44	6.5	0.38	0.52	0.39
Prescription dose for 1st SSRS (Gy)								
12	2 (3)	1 (50)	1 (50)		NA			
15	46 (73)	7 (25)	21 (75)		10		Reference	
18	15 (24)	1 (8)	12 (92)	0.31†	NA	0.16†	1.39	0.60†
Associated isodose line (%)	53 (50–67)	54 (50–59)	53 (50–67)	0.56	0.97*	0.45	1.01	0.86
Prescription dose for 2nd SSRS (Gy)								
12	18 (29)	1 (8)	12 (92)		26		Reference	
15‡	45 (71)	8 (27)	22 (73)	0.28	6.5	0.12	1.32	0.69
Associated isodose line (%)	53 (50–70)	51 (50–58)	54 (50–70)	0.41	0.98*	0.55	1.07	0.21
Brainstem/cerebellum								
No	50 (79)	7 (22)	25 (78)		10.8		Reference	
Yes	13 (21)	2 (18)	9 (82)	0.82	10	0.87	1.91	0.38
Tumor vol at 1st SSRS (cm³)	10.5 (2.4–31.3)	13.9 (5.8–22.0)	9.3 (2.4–31.3)	0.74	1.03*	0.36	0.83	0.01
< 9	24 (38)	3 (17)	15 (83)		NA		Reference	
≥ 9	39 (62)	6 (24)	19 (76)	0.61	10	0.33	0.28	0.05
Tumor vol at 2nd SSRS (cm³)	7.0 (1.0–29.7)	13.7 (5.1–19.0)	5.4 (1.0–29.7)	0.11	1.02*	0.49	0.94	0.17
≤ 3.5	14 (22)	0	11 (100)		26		Reference	
> 3.5	49 (78)	9 (28)	23 (72)	0.10	6.5	0.04	0.95	0.94

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Response of Tumor to Treatment and LC

The median tumor volume at first SSRS was 10.5 cm³ (range 2.4–31.3 cm³), with a decrease to 7.0 cm³ (range 1.0–29.7 cm³) at the time of the second SSRS ($p < 0.001$).

The median maximum linear dimensions (MLDs) of treated tumors at the time of first and second SSRS were 3.3 cm (range 2.1–5.1 cm) and 2.9 cm (range 1.3–5.08 cm), respectively (Table 2). No hemorrhage was observed in

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TABLE 1. Patient characteristics and outcomes following 2-SSRS treatment of LBM

Factor	No. (%) or Med (range)	Response at 3-Mo MRI, No. (%) or Med (range)		p Value	Med OS (mos) or Hazard Ratio*	p Value	Time to Progression, Hazard Ratio Subdistribution	p Value
		No	Yes					
Absolute change from 1st SSRS to 2nd SSRS (cm ³)§	-2.0 (-19.6 to 6.7)	-0.76 (-3.0 to 6.7)	-3.8 (-17.7 to 3.5)	0.12	0.98*	0.6	1.212	0.006
≤ -5.0	21 (33)	0	14 (100)		10		Reference	
> -5.0	42 (67)	9 (31)	20 (69)	0.04	10.8	0.9	NA	
Relative change from 1st to 2nd SSRS (%)§	-17.3 (-87.6 to 88.1)	-12.2 (-13.7 to 88.1)	-40.0 (-87.6 to 35.3)	0.1	1.2*	0.74	1.02	0.05
≤ -20	31 (49)	0	23 (100)		18		Reference	
> -20	32 (51)	9 (45)	11 (55)	0.0006	6.5	0.27	7.89	0.05
Tumor vol at 3 mos (cm ³)§	4.0 (0.1–23.1)				1.03*	0.42	1.04	0.57
< 1.5	11 (26)				22		Reference	
≥ 1.5	32 (74)				11.2	0.12	1.49	0.72
Absolute change from 1st SSRS to 3-mo MRI (%)§	-5.2 (-24.6 to 9.2)				0.99*	0.77	1.47	0.04
Relative change from 1st SSRS to 3-mo MRI (%)	-54.9 (-98.2 to 66.1)				1.34*	0.63	1.03	0.1

Med = median; NA = not available (the median could not be calculated).

* Hazard ratio.

† 15 versus 18 Gy.

‡ One patient received 14 Gy.

§ Negative values indicate a decrease; positive values indicate an increase.

74% of patients (n = 40); 15% of patients (n = 8) had intralesional blood prior to 2-SSRS, and 11% of patients (n = 6) developed de novo hemorrhages after 2-SSRS. However, there was no effect of hemorrhage on the MRI response at 3-month MRI follow-up, nor on TTP or OS (p = not significant).

Overall, 57 of the 63 lesions (90%) demonstrated early LC following the first SSRS, with 42 lesions (67%) demonstrating a decrease in volume of $\geq 30\%$ and 15 lesions (24%) remaining stable. The median decrease in these lesions was 2.0 cm³ (range 19.6 cm³ decrease to 6.7 cm³ increase), which corresponds to a median decrease of 17.3% (range 87.6% decrease to 88.1% increase). Of note, among the 6 lesions that were considered to have progressed ($\geq 20\%$ tumor volume increase), which were specifically

noted at the time of the second SSRS, 2 demonstrated sustained regression on later MR images, 2 lesions (both in the same patient) showed transient improvement after the second SSRS and then progressed on further follow-up, and 2 lesions progressed in 1 patient who died shortly after the second SSRS (the death was related to systemic disease progression).

Follow-up measurements were available for 43 lesions at the 3-month MRI, with a median volume of 4.0 cm³ (range 0.1–23.1 cm³). A median change in volume was observed between the first SSRS and first follow-up MRI of -54.9% (-98.2% to 66.1%; p < 0.001). Overall, 41 of the lesions (95%) demonstrated LC 3 months after 2-SSRS, with 34 (79%) demonstrating a decrease in volume of $\geq 30\%$ and 7 (16%) remaining stable in size (Table 1; Figs. 1 and 2). In univariable analysis, the absolute and relative change between the first and second SSRS (p = 0.04 for ≤ -5.0 vs > -5 cm³ and p = 0.0006 for $\leq -20\%$ vs $> -20\%$) were both prognostic for response, as was better performance status (p = 0.03). In multivariable analysis, only the relative change in tumor volume was shown to be independently prognostic. Figure 3 presents an illustrative case of the response to 2-SSRS in a patient with renal cell carcinoma.

Overall, 7 patients (13%) showed progression in 9 lesions (2 patients had 2 LBM that progressed). The median time to progression (from the first SSRS) was 5.2 months (range 1.3–7.4 months); the estimated cumulative incidence for TTP at 6 months was 12% (equivalent to an LC rate of 88% at 6 months; Fig. 1B). For TTP, greater volume of disease at baseline (p = 0.01 overall and p = 0.05 for

TABLE 2. Radiosurgical treatment parameters for 2-SSRS

Parameter	1st SSRS: Med Value (range)	2nd SSRS: Med Value (range)
Tumor vol (cm ³)	10.5 (2.4–31.3)	7.0 (1.0–29.7)
MLD (cm)	3.3 (2.1–5.1)	2.9 (1.3–5.08)
Prescribed dose (Gy)	15 (12–18)	15 (12–15)
Max dose (Gy)	28.8 (23.4–38)	27.5 (19.1–31)
Prescription isodose (%)	54 (50–64)	53 (50–70)
Conformality index	1.44 (1.20–2.66)	1.45 (1.22–2.22)
Gradient index	2.97 (1.77–3.88)	2.8 (1.9–3.7)

FIG. 1. Kaplan-Meier plots. **A:** OS from time of first SSRS (median estimated survival 10.8 months). **B:** TTP from first SSRS, demonstrating an estimated cumulative incidence of $12\% \pm 4\%$ at 6 months (equivalent to an LC rate of 88%) and a median TTP of 5.2 months (range 1.3–7.4 months). **C:** Effect of the absolute decrease in volume on TTP ($p = 0.006$). For illustrative purposes, the decrease has been dichotomized at the median (2 cm^3). **D:** OS-based prognostic group demonstrating an estimated median OS for the favorable group of 26.0 months versus 3.0 months for the unfavorable group ($p < 0.0001$).

< 9 vs $\geq 9 \text{ cm}^3$), smaller absolute and relative decreases in tumor volume from baseline after the first SSRS ($p = 0.006$ and $p = 0.05$, respectively), and a greater number of additional concurrent small brain metastases ($p = 0.02$) were all associated with a higher risk of progression. Multivariable analysis of TTP found the absolute decrease in tumor volume after the first SSRS to be the only independent predictor of TTP ($p = 0.006$) (Fig. 1C).

AEs of Radiation

AEs of radiation were identified as clinical and/or radiological findings related to lesion enlargement not associated with tumor progression. Specific patient characteristics are shown in Table 3. A total of 7 lesions (11%) demonstrated AEs at a median of 6.7 months after the first SSRS (range 2.2–14.0 months). The median volume of these 7 lesions was 15.69 cm^3 (range $5.5\text{--}31.27 \text{ cm}^3$) at first SSRS, a volume that did not seem to be significantly different from the rest of the cohort ($p = 0.11$). Of these, 5 lesions were identified as AEs based on imaging findings

as described in the *Methods*, and 2 lesions were pathologically confirmed to be RN. Clinically, 3 lesions (4.7%) were nonsymptomatic and 4 lesions (6.3%) were symptomatic. According to the National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE version 4.03) related to brain necrosis, 2 of these 4 lesions (3.17%) were associated with Grade 2 toxicity and were controlled with steroid administration alone, and the 2 other lesions demonstrated Grade 3 toxicities and were managed with surgery (1 patient underwent craniotomy and resection of the lesion, and 1 patient had laser ablation treatment for RN). Overall, 5 patients remain alive, and 2 of the 7 patients have died. One patient succumbed to systemic progression and another to leptomeningeal disease (LMD). Of the 2 patients who experienced Grade 3 toxicity, 1 remains alive 8 months after 2-SSRS and the second patient died as a result of causes related to LMD progression.

Survival

At the time of the study, 48% (26 of 54) of the patients

FIG. 2. Overall percentage change in tumor volume at the first post 2-SSRS MRI. Lesions are separated into 4 groups: those that showed decreases after each procedure (the vast majority [28 of 43]); those that showed an increase after the first SSRS but a decrease after the second SSRS, with the net result being a decrease (in all except for 1 case); those that showed a decrease after the first SSRS but an increase after the second SSRS; and a single patient whose disease progressed through both 2-SSRS treatments.

had died, and the median OS was estimated to be 10.8 months (95% CI 4.9–26.0). Most deaths were related to the patient's systemic disease ($n = 17$, 65%) or the cause of death is unknown ($n = 4$, 15%); only 3 deaths (12%) are attributed to the patient's neurological disease (Fig. 1A). The 6- and 12-month actuarial survival rates after 2-SSRS were $65\% \pm 7\%$ and $49\% \pm 8\%$, respectively. Prognostic factors negatively affecting OS in univariable analysis were interval from diagnosis of the primary to 2-SSRS ($p = 0.05$), performance status KPS score < 70 ($p \leq 0.04$), larger number of smaller (< 2 cm maximum diameter) lesions present ($p = 0.10$ overall and 0.005 for ≤ 2 versus > 2 cm), and greater volume of tumor present at second SSRS ($p = 0.04$ for ≤ 3.5 cm³ versus > 3.5 cm³).

On multivariable analysis, as shown in Table 4, performance status ($p = 0.01$), the number of concurrent smaller brain metastases ($p = 0.009$), and tumor volume remain-

ing at the time of second SSRS ($p = 0.04$) were all independently prognostic of OS. Table 5 shows that by simply counting the number of poor survival factors present, 2 prognostic groups can be identified: a favorable group that consists of patients with 0 or 1 poor risk feature and comprises 65% ($n = 35$) of the study population and an unfavorable group (2–3 poor risk features) that comprises 35% ($n = 19$) of the patients. The median OS for the favorable group was estimated to be 26.0 months versus 3.0 months for the unfavorable group ($p < 0.0001$) (Fig. 1D).

Discussion

The treatment of LBM is challenging and influenced by many direct tumor-related issues as well as overall patient considerations. Specifically, CNS factors such as mass effect and associated neurological impact, tumor location,

FIG. 3. Axial T1-weighted Gd-enhanced MR images of the brain demonstrating response to 2-SSRS at different time points. **A:** Before the initial 2-SSRS (volume 14.49 cm³). **B:** At the time of the second SSRS (volume 2.64 cm³). **C:** Three months after 2-SSRS (volume 1.09 cm³). **D:** Six months after 2-SSRS (volume 0.66 cm³). **E:** Twelve months after 2-SSRS (volume 0.06 cm³). **F:** At the final follow-up 21.4 months after 2-SSRS (volume 0.02 cm³).

overall intracranial disease burden, and prior therapy for CNS disease must be taken into account. Furthermore, these issues all need to be addressed within the framework of the underlying pathology, patients' performance status and comorbidities, extent of extracranial disease, systemic treatment options, timing required for therapeutic regimen

delivery, as well as individual patient quality-of-life values. LBM are typically treated with resection followed by adjuvant radiation.^{16,26,29,34,48,51,62,69} However, when surgical options are not appropriate or not desired, radiation becomes the primary modality in the management of these patients.

TABLE 3. Specific patient and lesion characteristics in cases in which RN was identified

Lesion No.	Primary Pathology	Vol 1st SSRS Dose (cm ³ /Gy)	Vol 2nd SSRS Dose (cm ³ /Gy)	Total Dose (Gy) α/β 10	Vol Max (cm ³)	Time to RN (mos)	RN Diagnosis	Vol at Last FU (cm ³)	Status	Cause of Death	Change Vol Max to Current (%)	Change Vol Initial to Current (%)
1	Lung	8.20/18	8.70/15	66	10.06	12	Imaging	3.41	Alive	NA	-66.1	-58.41
2	Lung	15.69/12	13.71/15	54	32.45	7	Pathology	NA (resection)	Deceased	Neurologic (LMD)	NA	NA
3	Lung	26.43/15	13.39/12	54	42.84	13.5	Imaging	NA	Deceased	Systemic	NA	NA
4	Renal	5.1/18	3.10/12	60	9.59	5.8	Imaging	8.93	Alive	NA	-6.9	75.1
5	Esophagus	13.91/15	15.63/15	60	27.41	2.0	Imaging	15.33	Alive	NA	-44.03	10.21
6	Esophagus	25.10/15	15.70/15	60	17.53	5.7	Imaging	16.62	Alive	NA	-5.2	-33.78
7	Melanoma	31.27/15	29.70/15	60	30.31	5.5	Pathology	NA (resection)	Alive	NA	NA	NA

FU = follow-up; LMD = leptomeningeal disease; NA = not available.

TABLE 4. Multivariable analysis of prognostic factors affecting survival

Factor	Hazard Ratio (95% CI)	p Value
No. of smaller lesions		
0–2	Reference	
> 2	3.42 (1.35–8.64)	0.009
KPS score		
≥ 80	Reference	
< 80	2.82 (1.28–6.21)	0.01
Vol remaining at 2nd SSRS (cm ³)		
≤ 3.5	Reference	
> 3.5	4.50 (1.04–19.41)	0.04

Historically, WBRT was considered the standard of care for managing patients with LBM who were not surgical candidates;^{33,45} however, both modest LC and concerns regarding toxicities related to the use of WBRT^{3,9,11,13,14,58,66} have generated substantial interest in potentially treating brain metastases with focal radiation options. Several studies have demonstrated the value of single-fraction SRS in patients with brain metastases where it provides excellent LC.^{2,11,30} In terms of radiosurgical dosing, many centers treat brain metastases according to Radiation Therapy and Oncology Group guidelines (RTOG 90–05).^{1,56}

Particularly related to larger brain metastases, this dose-escalation study demonstrated a maximum tolerated dose in tumors with MLD ≥ 2 cm, where AEs of radiation were observed at 18 and 15 Gy for tumors with MLD of 2–3 and > 3 cm MLD, respectively. Unfortunately, in contrast to excellent tumor control rates and the modest toxicities observed in tumors < 1 –2 cm^{10,40} treated with single-fraction SRS, results for LBM are relatively suboptimal due to the decreased response rate and the increased risk of neurotoxicity.^{18,23,55,60,68,70,72,73} Specifically, using the RTOG-recommended 15-Gy dose, the 1-year LC rates for tumors > 3 cm were reported to be 37%–62%.^{12,41,56}

Moreover, in a study from our own center stratifying outcomes relative to dose delivered to the tumor margin, Vogelbaum et al.⁷⁰ evaluated LC in 202 patients with brain metastases and found the 1-year LC rate to be only 49% in those receiving 18 Gy and 45% in those receiving 15 Gy, in sharp contrast to the 85% control rate achieved with 24 Gy SRS ($p = 0.005$). However, treating LBM with high single-fraction doses such as 24 Gy would be prohibitive and has been associated with 58% Grades 3–5 CNS toxicity, even for brain metastases measuring 2.1–3.0 cm.⁵⁶

More recently, in an attempt to overcome the modest LC observed in the management of LBM and also to decrease the radiation toxicity associated with SRS treatment, several novel strategies have been explored. Retrospective and prospective studies evaluating both hypofractionated SRS (hypo-FSRS), typically delivered in 3–6 fractions,^{18,19,25,27,28,38,39,42–44,46,71,72} and staged SRS^{24,74,75} have been investigated in the management of LBM. The rationale was to increase the prescribed dose and hence the LC while decreasing the morbidity of radiation injury, by distributing the dose over time and perhaps to smaller targets at the time of second treatment. The management of LBM with

TABLE 5. Two distinct prognostic groups based on identified independent predictors

Prognostic Group	No. of Poor Prognostic Factors*	No. (%)	12-Mo Survival Rate	Med Survival, Mos
Favorable	0 or 1	35 (65)	68% $\pm$ 11%	26.0 (10.8–NA)†
Unfavorable	2 or 3	19 (35)	14% $\pm$ 9%	3.0 (1.3–3.7)

NA = not available (upper bound of the CI could not be calculated).

* Poor prognostic factors are > 2 additional small lesions, KPS score < 80, or volume remaining at second SSRS > 3.5 cm³.† $p < 0.0001$.

each of these strategies is presented in Table 6, where specific study characteristics, response to treatment, and toxicities are compared. A useful comparison between various treatment paradigms is also presented in the table by normalizing the various fractionation schemes using the linear quadratic model to estimate the biologically effective dose (BED) relative to a standard 2-Gy fractionation scheme (using α/β 10 for tumor tissue) in each study.^{21,47}

With the evolution of frameless radiosurgery, alternative treatment strategies using hypo-FSRS options to dose-escalate treatment of LBM could be explored. In a study of 36 patients, Feuvret et al.¹⁸ presented one of the earliest series to directly compare the response of LBM (> 3 cm) to FSRS or SRS. The 1-year LC rates were significantly different at 100% and 58%, respectively ($p = 0.06$); however, the 2 treatment groups experienced similar toxicities post-treatment (FSRS, 25% Grade 2 vs SRS, 29.2% Grades 1–2).

In a recent, much larger study in 289 patients with LBM (> 2 cm), Minniti et al.³⁹ also directly compared tumor control rates and radiation-related toxicity using either an FSRS regimen (9 Gy $\times$ 3) or SRS. The authors reported that superior cumulative LC rates were achieved at 12 months follow-up when patients were treated with FSRS compared with single-fraction SRS (90% vs 77%; $p = 0.01$). Furthermore, this improved LC rate was also associated with a lower risk of RN (9% vs 18%, respectively; $p = 0.01$). In contrast, Wiggenraad et al.⁷² similarly compared LC and treatment-related toxicity in patients with LBM (> 13 cm³) treated with FSRS (8 Gy $\times$ 3) versus 15 Gy SRS; however, they found no difference in the LC rates (61% vs 54%, respectively; $p = 0.93$). They postulated that similar BEDs between the groups may have contributed to the comparable outcomes.

Similarly, in 260 patients treated with either SRS (not all of whom had LBM) or FSRS using 2 different hypo-FSRS regimens (5 Gy $\times$ 7 and 4 Gy $\times$ 10), Fokas et al.¹⁹ demonstrated no difference between treatment arms in terms of 12-month LC rates (73%, 75%, and 71%, respectively; $p = 0.191$). However, Grades 1–3 toxicity was significantly higher in the SRS group (14%) compared with either of the FSRS regimens (6% and 2%, respectively; $p = 0.01$). Hence, although some apparent advantages exist to FSRS in contrast to single-session SRS in the management of LBM, the optimal fractionation scheme remains to be clarified.

Staged radiosurgery is also a novel concept in the man-

agement of LBM. This approach attempts to provide an increased overall dose to the tumor in 2 or 3 discrete and divided sessions aimed at improving LC compared with SRS. Distinct from the daily hypo-FSRS, SSRS further aims to mitigate radiation toxicity with a longer interlude between treatments, capitalizing on the interval tumor volume shrinkage that is often observed between sessions so that a smaller volume of brain is irradiated in the subsequent staged treatment. In addition, a smaller tumor is associated with a steeper dose fall off and thereby a lower BED to the surrounding normal tissue.

Several studies have demonstrated that the volume of brain receiving radiation seems to be the most significant predictor of RN. In RTOG 90–05, Shaw et al.⁵⁶ found that maximum tumor diameter was significantly associated with toxicity ($p = 0.054$). In this study, tumors 31–40 mm and 21–30 mm had a 16.0 $\times$ and 7.3 $\times$ respective risk of developing CNS toxicity compared with tumors $\leq$ 20 mm, a toxicity presumed to be related to the volume of normal brain irradiated in each of the treatment arms. In a series of 63 patients (with 173 brain metastases), Blonigen et al.⁸ demonstrated a risk of 68.8% RN in patients in whom tumors > 14.5 cm³ or > 10.8 cm³ received 10 or 12 Gy, respectively, to the peri-tumoral normal brain. The volumes of brain receiving a specific dose V_{10Gy} and V_{12Gy} were also significant predictors ($p = 0.0001$) of RN in the Minniti et al.³⁷ series of 206 patients with 310 brain metastases < 3.5 cm in maximum diameter treated with SRS. Specifically, there was a 10% symptomatic and a 24% overall rate of RN in this series. Tumor volume represented a significant risk factor for RN ($p = 0.02$) on multivariate analysis, and a $V_{10Gy} > 12.6$ cm³ and $V_{12Gy} > 10.9$ cm³ were associated with a 47% risk of RN. In 2014, the same group³⁸ published a series of 135 patients with 171 metastases treated with hypo-FSRS (27 Gy/3 fractions or 36 Gy/3 fractions), where they demonstrated a 9% 1-year actuarial risk of RN. On multivariate analysis, only the normal brain volumes receiving 18 Gy (V_{18Gy}) and 24 Gy (V_{24Gy}) represented significant independent risk factors for RN ($p = 0.03$).

Higuchi et al.²⁴ published the first SSRS series, in which 43 patients with LBM (> 10 cm³) were treated with 30 Gy in 3 staged fractions (3-SSRS) delivered in 2-week interfraction intervals. Tumor volumes decreased by 18.8% (second SSRS) and 39.8% (third SSRS) ($p < 0.0001$). Overall tumor shrinkage was observed in 90.7% of the tumors, achieving the aim of this strategy, which was to irradiate a smaller volume of brain with each subsequent treatment. This resulted in 6- and 12-month LC rates of 89.8% and 75.9%, respectively, with only 1 patient developing CTCAE Grade 3 toxicity that required surgery.

In 2012, Yomo et al.⁷⁵ published a prospective SSRS study evaluating 27 patients with LBM treated with 20–30 Gy using a 2-stage fractionation scheme with an interfraction interval of 3–4 weeks. They observed an 85% and 61% LC rate at 6 and 12 months, respectively, after the delivery of 20–30 Gy in 2 fractions. Local recurrence was treated with resection in 2 patients (related to tumor progression in 1 patient and predominantly RN admixed with tumor in the other patient), and 3 patients were treated with further salvage SRS and are reported as having successful tumor control posttreatment. In this series, a total of 3

TABLE 6. Studies of patients with data specifically addressing only LBM treated with single-fraction SRS, hypo-FSRS, or SSRS (3-SSRS and 2-SSRS)

Authors & Year	No. of Pts (no. of LBM)	Med LBM Size, cm (max)	Med LBM Vol, cm ³ (max)	Med SRS Dose, Gy (range) [protocol]	Estimated 2-Gy BED (α/β 10)	Med Survival (mos)	% Survival at 6/12 Mos	% LC at 6/12 Mos	Definition of Local Recurrence	Radiation AEs [CTCAE v. 4.03 grade]*
Single-fraction SRS										
Feuvret et al., 2014	24	3.78 (4.70)	15.69 (33.06)	14.2 (13–15.8)/1 fx	24.92–33.97	5.4	45/27	68/58	25% vol	29.2% [Gr 2 (HA, aphasia, Szs, &lor hemiparesis)]
Han et al., 2012 ²²	80	3.98 (5.66)	22.4† (49.6)	13.8† (10–16)/1 fx	16.67–34.67	7.9	63.8/39.2	92/85	25% vol	38% [Gr 3–5 18.8%]
Lee et al., 2014	109	> 3.0†	16.8 (74.8)	18 (16–26)/1 fx	34.67–78.0	8.3	NA	NA	10% vol	<1% [Gr 2–3]
Minniti et al., 2016	151	≥ 2.0†	8.8 (24.1)	NA [2–3 cm 18 Gy; ≥ 3 cm 15–16 Gy]	31.25–42.0	13.4	NA/53	94/77	Any increase of tumor on 2 MRIs	20.5% [Gr 3 8.6% (Sx)]
Vogelbaum et al., 2006	85	2.4 (3)	NA	[18/1 fx]	42	NA	NA	87/49	Clinical & radio-graphic	NA
	41	3.3 (4.5)	NA	[15/1 fx]	31.25	NA	NA	71/45	Clinical & radio-graphic	NA
Wiggenraad et al., 2012	41	NA	NA§	[15/1 fx]	31.25	5.3	41/23	89/54	25% diameter	15% [Gr 3 2.4% (Sx)]
Yang et al., 2011	70	> 3.0†	13.7 (31.7)	16 (12–19)/1 fx	22–45.92	8.2	41.1/NA	67/NA	10% vol	48% [17.2% symptomatic, Gr NA]
Zimmerman et al., 2016	62	3.5 (5.8)	NA	15 (10–18)/1 fx	16.67–42.0	6.6	58/22	78/68	20% diameter	5.9% [Gr NA]
Hypo-FSRS										
Feuvret et al., 2014	12	4.47 (5.95)	29.4 (52.52)	23.4 (12–25.74)/ 3 hfx [23.1/3 hfx]	14–39.85	16.6	84/58	100/100	25% vol	25% [Gr 2 (HA/Sz/hemiparesis)]
Fokas et al., 2012	61	NA¶	2.04 (27.5)	NA [35/7 hfx]	43.75	7	36/19	NA/75	NA	6% [Gr 3 2% (HA, neurocognitive, or motor deficits)] plus 2% (Sx)
	61	NA¶	5.93 (26.8)	NA [40/10 hfx]	46.67	10	38/21	NA/71	NA	2% [Gr 3 1% (HA, neurocognitive or motor deficits)]
Inoue et al., 2014	88	NA	16.2 (NA)	NA [27–30/3 hfx for 10–19.9 cm ³ LBM; 31–35/5 hfx for 20–29.9 cm ³ LBM; 35–42/8–10 hfx for > 30 cm ³ LBM]	39.4–53.4	9	NA	NA	15% vol	11.4% [Gr 2 8.0 % (steroids)]
Jeong et al., 2015	37	> 3.0†	17.6 (49.6)	35 (30–41/3–5 hfx)	NA**	16	81.1/65.5	NA/87	25% diameter	15.8% [Gr 2 13.2%; Gr 3 2.6% (Sx)]
Jiang et al., 2012	40	4.1 (5.5)	17.5 (64.7)	40 (20–53) [median 10 hfx (range 4–15 hfx) & 23 pts also received a boost of 10–35 Gy in 2–10 hfx 1–3 mos after 1st Tx]	NA**	15	NA/55.3	NA/94.2	25%††	12.5% [Gr ? 10% ("serious late toxicities"); Gr 5 2.5%]
Minniti et al., 2016	138	≥ 2.0†	12.5 (47.9)	NA [27/3 hfx]	42.75	13.4	NA/56	97/90	Any increase of tumor on 2 MRIs	8% [Gr 3 2.9% (Sx)]

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TABLE 6. Studies of patients with data specifically addressing only LBM treated with single-fraction SRS, hypo-FSRS, or SSRS (3-SSRS and 2-SSRS)

Authors & Year	No. of Pts (no. of LBM)	Med LBM Size, cm (max)	Med LBM Vol, cm ³ (max)	Med SRS Dose, Gy (range) [protocol]	Estimated 2-Gy BED (α/β 10)	Med Survival (mos)	% Survival at 6/12 Mos	% LC at 6/12 Mos	Definition of Local Recurrence	Radiation AEs [CTCAE v. 4.03 grade]*
Hypo-FSRS (continued)										
Murai et al., 2014	54	≥ 2.5†	≥ 8†	NA [18–30/3 hfx to 21–35/5 hfx]	24–50	6	52/31	77/69	25% diameter	7.4% [Gr 1 5.5; Gr 2 1.9]
Narayana et al., 2007	20	3.5 (5)	NA	[30/5 hfx]	40	8.5	NA/42	NA/70	NA	15% [Gr 2 (steroids)]
Navarra et al., 2016	102	2.9 (5.0)	16.3 (64.5)	NA [27/3 hfx or 32/4 hfx]	42.75–48.0	14	NA/69	NA/96	Radiographic increase on serial MRIs	11.8% [Gr 2 5.9% (steroids); Gr 3 5.9% (Sx)]
Wegner et al., 2015	36	NA	15.6 (82.7)	24 (12–27)/2–5 hfx	35.5–52.8	3	22/13	73/63	20% diameter	0%–22% [Gr 1–2]
Wiggenraad et al., 2012	51	NA	NA§	[24/3 hfx]	36	5.3	41/23	81/61	25% diameter	25% [Gr NA]
3-SSRS										
Higuchi et al., 2009	43	NA	17.6† (35.5)	NA [30/3-SSRS]	50	8.8	NA	89.8/75.9	Significant increase	11.6% [Gr 3 2.3% (Sx)]
2-SSRS										
Yomo et al., 2012	27	NA	17.8 (53.3)	13.3 (10–16) [20–30/2-SSRS]	33.3–62.50	11.9	63/45	85/61	20% vol	11.1% [Gr 3 (7.4% emesis; 3.7% hemiparesis) plus 3.7% (Sx RN w/ some viable tumor cells)]
Yomo & Hayashi, 2014	58	NA	16.4 (56.1)	14 (10–16) [20–30/2-SSRS]	33.3–62.50	11.8	NA/47	85/64	20% vol	8.6% [Gr 3]
Present study	54 (63)††	3.3 (5.1)	10.54 (31.27)	15 (12–18) [24–33/2-SSRS]	44–72.88	10.8	65/49	88/**	20% vol	12.9% [Gr 1 5.5%; Gr 2 1.9%; Gr 3 5.5% (Sx)] expressed per lesion as concurrent LBM treated 11.1% [Gr 1 4.8%; Gr 2 1.6%; Gr 3 4.8% (Sx)]

1 fx = single-fraction delivery; fx = fraction; Gr = grade; HA = headache; hfx = hypo-fractionated delivery; NA = not available; pts = patients; Sz = seizure; Tx = treatment.

Studies listed twice have data extracted based on stratification by lesion size and by response to treatment.

* Denoted adverse according to individual study (nonuniform criteria); represents both acute and delayed toxicity reported.

† Mean.

‡ Minimum size (no median or range given).

§ Large with planning treatment volume > 13 cm³ or brain stem lesions; 76% > 3 cm.

¶ > 3 cm (76%) and/or "eloquent location."

** Unable to calculate.

†† Unknown if volume or diameter measured.

‡‡ Denotes only LBM treated with 2-SSRS (not the entire intracranial burden).

patients developed CTCAE Grade 3 toxicity (2 acute and 1 delayed) and required steroids. Although outcomes were similar to other reports, this study demonstrated that LBM could be successfully treated with 2-SSRS with minimal treatment-related morbidity.

As a follow-up study, in 2014, Yomo and Hayashi⁷⁴ published another prospective study evaluating longer-term outcomes in 58 patients following 2-SSRS. Similar to their first experience, 2-SSRS demonstrated effective LC rates (85% at 6 months) with acceptable toxicity and durable tumor control, with a 1- and 2-year neurological death-free survival rate of 91% and 84%, respectively. Furthermore, 18 of 22 patients (82%) with a pretreatment KPS score < 70 regained their independence with a KPS score > 70 , an important factor that would probably have an impact on their opportunities for systemic therapy and potentially affect their OS.

To our knowledge, this study is only the fourth published series evaluating the impact of SSRS. Overall, we present data on 54 patients. However, it is important to highlight that in the current series, 7 patients (13%) had 2 concurrent LBMs that were both treated with simultaneous 2-SSRS, and 1 patient had 3 concurrent LBM treated with 2-SSRS during the same session. Yomo and Hayashi⁷⁴ mentioned 58 patients with 61 LBM, suggesting that 3 patients may have had 2 LBM treated concurrently, although this is not further described in the paper. To our knowledge, this is the only series where 15% of patients had ≥ 2 synchronous LBM treated with a given radiosurgical strategy. This group of patients had substantial intracranial burden of disease, 26% of patients had radioresistant tumors, 91% belonged to the 2 poorest GPA prognostic groups, and 30% had a poor KPS score; despite these factors, based on available data, there are some indications that 2-SSRS may be more favorable than other approaches.

Based on comparisons with data from the LBM studies described in Table 6 (some series included resection cavity treatments in the LBM cohort), the median survival in our study exceeded that of 6 of 7 SRS cohorts. In our study, the median survival of 10.8 months represented a median 37% increase compared with the other studies (range -19% to 103%). Furthermore, the median survival in our study exceeded that of 7 of 12 FSRS studies, with our data representing a median 14% increase compared with the other studies (range -35% to 260%). Of note, the median survival in our study was 23% higher than the 3-SSRS study by Higuchi et al.²⁴ and fairly similar to that in the 2-SSRS studies by Yomo and Hayashi⁷⁴ and Yomo et al.⁷⁵

Indeed, although our median survival was marginally lower in both cases (by 8%–9%), this too argues that there is a meaningful impact on survival related to 2-SSRS relative to other treatment options, as shown by 2 independent centers. Upon evaluating the impact of treatment at 1 year, the 12-month survival rate in our study exceeded that of 4 of 5 single-fraction studies with data showing that the median difference in 12-month survival was 81% higher in our study (range -8% to 123%). The 12-month survival rate in our study also exceeded that of 6 of 11 FSRS studies with data demonstrating that the median difference in 12-month survival was 17% higher in our study (range -29% to 277%). The 12-month survival rate in our study

was comparable to those in the other 2-SSRS studies, where it was just 4% and 9% higher. No data regarding the 12-month survival rate were reported in the 3-SSRS study.

Upon specifically evaluating 6-month LC, the rate in our study exceeded that of 5 of 8 single-fraction studies; the median difference was marginally higher (7%) in our study (range -6% to 31%). The LC rate in our study also exceeded that of 3 of 5 FSRS studies; the median difference was again marginally higher (9%) in our study (range -12% to 20%). Six-month LC rates were similar across the various SSRS studies; the LC rate was 2% lower in our study compared with the 3-SSRS study and 4% higher than in both of the other 2-SSRS studies.

Comparisons such as these cannot be used to reach definitive conclusions about the efficacy of 2-SSRS, in part because not all studies have completely comparable populations and do not consistently define or report identical metrics. However, they do have merit in that taken collectively, they provide some broad, qualitative indications that 2-SSRS appears to be comparable or even superior to other reported approaches.

In our study, we safely delivered up to 73 Gy (an estimated 2-Gy BED) to the tumor itself, augmenting the dose usually delivered to the LBM and optimizing LC while, as an important concurrent benefit, theoretically minimizing the overall amount of normal brain exposed to radiation. In fact, at the time of second SSRS, most LBM were smaller (67% demonstrated $> 30\%$ decrease in volume) than at the start of treatment. There was a median decrease in these lesions of 2.0 cm³ (range 19.6 cm³ decrease to 6.7 cm³ increase), which corresponds to a median decrease of 17%.

These data are similar to findings reported in other 2-SSRS series.⁷⁴ Our data support the stated rationale of this approach to potentially mitigate the toxicity associated with LBM treatment through irradiation of a smaller volume of surrounding normal brain. Minimizing the volume of normal brain exposed to radiation may make 2-SSRS a particularly valuable approach for treating tumors in eloquent brain or near critical structures, where the radiation-related toxicity is especially problematic.

We further suggest that using this approach may allow for deferral of WBRT in patients who are not surgical candidates or who wish to avoid the recovery period and potential morbidities of surgery. Alternatively, 2-SSRS provides a treatment option for patients who are not surgical candidates and who have already undergone WBRT in the management of their intracranial disease and otherwise have limited treatment options. Of note, 2-SSRS has the additional advantage of being independent of delivery platform, obviating the current limitations to FSRS with frame-based approaches. Finally, because most patients with brain metastases are on systemic therapy and often succumb to systemic progression, 2-SSRS has the advantage of potentially being the least disruptive modality in terms of the patient's overall care and outcome.

From a radiobiological perspective, 2-SSRS may offer possible advantages compared with other options in several ways. First, the high doses per session may further enhance killing of tumor cells through endothelial cell apoptosis, microvascular dysfunction, and the disruption of tumor perfusion, an effect that arises at a threshold dose of 10 Gy

and is typically not achieved with FSRS, where delivered doses are typically 5–9 Gy per session.⁵ Second, although 2-SSRS is a dose-dense regimen as required for tumor control, the time frame from the first to the second session probably allows for repair and repopulation of normal cells, thereby improving the overall safety of the treatment. According to Bender,⁷ the repair half-time for late radiation effects in the brain can be as long as 76 hours; therefore, we chose a 30-day interval between stages to allow for 10 half-lives for repair and to minimize the risk of RN. Third, if the tumor decreases in size from the first session, this may result in improved oxygenation to the remaining tumor cells and enhanced radiation sensitivity compared with the cytotoxicity manifested in a tumor with a greater hypoxic component. Moreover, this may also allow for re-assortment of the remaining tumor cells into the G2-M phase of the cell cycle, further augmenting the efficacy of treatment.

Although the data are encouraging, we acknowledge that study limitations exist, specifically those that are inherent in the retrospective study design and unknown bias in patient selection for this treatment strategy. An additional study limitation may be related to the diagnosis of RN using radiographic features alone, which could affect determination of the overall LC rate if enlarging lesions contain both viable tumor and necrotic tissue. Moreover, toxicities between trials are variably reported, and direct comparisons are challenging. Limitations may also exist with trying to model single-session SRS, FSRS, 3-SSRS, and 2-SSRS using a standard BED equation; however, this is debatable and beyond the nature of this study, which focused on clinical outcomes. That said, the clinical outcomes seem to be consistent with our expectations by simply using the standard BED equation. Finally, we suggest that larger trials with prospectively collected toxicities are warranted to confirm these initial results and to compare the effectiveness of 2-SSRS with alternative management strategies for LBM.

Conclusions

This series suggests that 2-SSRS is a feasible, safe, and effective treatment modality with an excellent LC rate (88% at 6 months) and similar or better OS and toxicity compared with many other series where LBM were treated with SRS or FSRS. We further demonstrated that multiple LBMs can be concurrently treated with a 2-SSRS strategy and that LBM arising from traditionally radio-resistant pathology can also be effectively treated in this manner. Finally, we propose a prognostic model allowing patients to be separated into favorable and unfavorable response groups that are stratified based upon KPS score, global intracranial disease, and response of LBM to the initial radiosurgical treatment, which can serve to guide clinical decision making.

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Disclosures

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Conception and design: Angelov, Barnett. Acquisition of data: Angelov, Mohammadi, Bennett, Abbassy, Elson, Montgomery, Habboub. Analysis and interpretation of data: all authors. Drafting the article: Angelov. Critically revising the article: all authors. Reviewed submitted version of manuscript: Angelov, Barnett, Mohammadi, Bennett, Abbassy, Chao, Montgomery, Habboub, Vogelbaum, Suh, Murphy, Ahluwalia, Nagel. Approved the final version of the manuscript on behalf of all authors: Angelov, Barnett. Statistical analysis: Elson. Study supervision: Angelov, Barnett.

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