Scientific Article

Safety and Feasibility of Stereotactic Radiosurgery for Patients with 15 or more Brain Metastases

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Background: Current standard of care treatment for patients with ≥15 brain metastases (BM) is whole brain radiation therapy (WBRT), despite poor neurocognitive outcomes. We analyzed our institutional experience of treating these patients with stereotactic radiosurgery (SRS), with the aim of evaluating safety, cognitive outcomes, and survival metrics.
Methods: Patients who received SRS for ≥15 BMs in 1 to 5 fractions from 2014 to 2022 were included. Cognitive outcomes were objectively evaluated using serial Patient-Reported Outcome Measurement Information System (PROMIS) scores. The Kaplan-Meier method was used for survival analysis and log-rank test for intergroup comparisons.
Results: Overall, 118 patients underwent 124 courses of LINAC-based SRS. The median number of lesions treated per course was 20 (range, 15-94). Most patients received fractionated SRS to a dose of 24 Gy in 3 fractions (81.5%). At the time of SRS, 19.4% patients had received prior WBRT, and 24.2% had received prior SRS. The rate of any grade radiation necrosis (RN) and grade ≥3 RN were 15.3% and 3.2%, respectively. When evaluating longitudinal PROMIS score trends, 25 of 31 patients had a stable/improved PROMIS score. Patients who did not receive prior brain RT had a longer median survival (7.4 months vs 4.6 months, *P* = .034). The 12m local control was 97.6%, and the cumulative incidence of distant intracranial failure, with death as a competing event, was 46% (95% CI, 36%, 55%). One year freedom from neurologic death, leptomeningeal disease, and salvage WBRT were 89%, 94.6%, and 84%, respectively.
Conclusion: We present here one of the largest studies evaluating SRS for patients with ≥15 BMs. SRS was safe, had favorable cognitive outcomes, and had comparable survival outcomes to contemporary studies evaluating WBRT in this population. Treatment-naïve

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patients had a median survival of >6 months, long enough to benefit from cognitive sparing with SRS. Our study supports randomized studies comparing SRS and hippocampal avoidance WBRT approaches for these patients.

Introduction

The prevalence of brain metastases in cancer patients has been steadily rising, driven in part by availability of better imaging, as well as advancements in cancer therapies enabling patients to survive longer with controlled primary tumors. Up to 30% of adult cancer patients develop brain metastases in their lifetime.[1-3] Traditionally, patients with multiple brain metastases have a poor median survival of <6 months and often require whole brain radiation therapy (WBRT). WBRT, although having an important role in controlling multiple brain metastases, often results in neurocognitive decline as early as 3 months after treatment and impairs patients' quality of life due to the indiscriminate impact of conventional WBRT on healthy brain tissue. Stereotactic radiosurgery (SRS) has emerged as a precise and noninvasive radiation modality that offers a unique opportunity to target multiple brain metastases with enhanced precision, sparing surrounding normal brain tissue and reducing the risk of cognitive decline. SRS is associated with excellent local tumor control with minimal side effects and is now considered the standard of care in management of patients with 1 to 4 brain metastases.[4,5]

Over the past few years, significant progress has been made in the field of SRS, driven by advanced imaging modalities, treatment planning, and intrafraction image guidance. Although SRS has been traditionally considered in patients with up to 4 brain metastases, it is being increasingly used for patients with 5 or more lesions. Recent studies have shown the effectiveness of SRS in treating patients with 5 or more brain metastases.[6-10] These studies also suggest the hypothesis that the total tumor volume and not the number of metastases may be the driver in determining the outcomes for patients with multiple brain metastases.[11] Several smaller series have now confirmed that higher intracranial burden (higher volume of brain metastases within the brain) rather than the number of metastases predicts poorer outcomes.[12-17]

However, despite the promising potential of SRS, evidence validating the use of SRS in the management of patients with multiple brain metastases is lacking, and most patients with 15 or more metastases continue to be treated with WBRT. With the aim of further broadening the indications of SRS in this group of patients, we analyzed our institutional experience of treating patients with 15 or more BMs with SRS. We intend to shed light on the efficacy, safety, and clinical considerations related to SRS in this patient cohort. Furthermore, we aim to identify predictors of long-term survival in this group of patients, which can further help in selecting a group of patients who may be best suited for SRS instead of WBRT.

Methods

Patient selection

After approval from our Institutional Review Board and data monitoring committee, we identified all patients treated with SRS for brain metastases at our institution from January 2014 to December 2022. Study inclusion criteria included: (1) patients receiving SRS for 15 or more discrete brain metastases in one course; and (2) single-fraction or multifraction SRS defined as a dose of at least 5 Gy per fraction given in 5 fractions or fewer. Patients undergoing split course or staged SRS treating a total of 15 or more lesions over multiple courses were excluded.

Radiation simulation and treatment planning

All patients had a thin-slice volumetric postcontrast MRI imaging with at least 1.5T and were discussed in multidisciplinary conference before proceeding with radiosurgery. Patients were treated on a Varian Edge linear accelerator using noncoplanar volumetric modulated arc therapy (VMAT) or HyperArc. Patients were simulated supine with a Qfix Encompass thermoplastic mask and treated on a robotic couch with 6° of freedom, daily kV cone beam CT image guidance, and surface-guided radiation therapy using the Varian Optical Surface Monitoring System. Gross tumor volume (GTV) was contoured on fused contrast-enhanced MRI images obtained within 2 to 3 weeks of SRS treatment. Typical planning target volume (PTV) margin used was 2 mm, although a smaller margin of 1 mm was used for tumors close to the critical structures such as the brain stem and optic structures. The volume for each lesion was determined from physician-defined contours and collected from the treatment planning software. Radiation was planned using a single-isocenter multitarget (SIMT) approach, which permits rapid delivery of focal therapy to multiple brain metastases simultaneously using VMAT.[18] Typical radiation dose prescribed was dependent on fractionation, but for the majority of patients treated in 3 fractions, the marginal dose was 24 Gy to the PTV with a simultaneous integrated boost to 27 Gy to the GTV.

Follow-up

Patients were followed every 2 to 3 months after SRS with contrast-enhanced MRI brain, including MRI with perfusion. If local or distant treatment failure was diagnosed, patients underwent salvage therapy with surgical resection, additional SRS, or WBRT, based on their disease and clinical performance status. The last clinic visit, imaging, or date of contact was used for censoring patients alive at the time of analysis. Patient-level and tumor-level data for each course were extracted. If a patient underwent multiple courses of SRS, all courses were included separately. Dosimetric data, including GTV and PTV volumes, were also collected. Follow-up data collected included local treatment failure, intracranial progression, leptomeningeal failure, overall survival (OS), salvage WBRT, time to salvage WBRT, radiation necrosis (RN), and time to development of RN. Local tumor control was assessed using the Response Assessment in Neuro-Oncology-Brain Metastases guidelines (RANO-BM).[19] New lesions requiring further courses of RT were classified as intracranial progression. Local treatment failure of the treated lesion(s) was classified separately. RN was defined using surgical pathology or MRI with perfusion and diffusion as available and graded using the National Cancer Institute's CTCAE version 5.0 (grade 1: asymptomatic; grade 2: moderate symptoms, corticosteroids indicated; grade 3: severe symptoms, medical intervention indicated; grade 4: life-threatening, urgent intervention; and grade 5: death). Other adverse events were also graded using CTCAE version 5.0.[20] Follow-up details were extracted from the electronic medical record (EMR), and individual MRI images were reviewed to determine which of the treated metastases were associated with RN or local progression. Data regarding systemic therapy were also collected, including cytotoxic chemotherapy, immunotherapy (any immune checkpoint inhibitors), and/or oral targeted therapies. Diagnosis-specific Graded Prognostic Assessment (dsGPA) score was calculated for patients with primary breast, lung, renal, and gastrointestinal cancers and melanoma based on previously described methodology.[21,22]

Cognitive outcomes

Cognitive outcomes were objectively evaluated using serial NIH Patient-Reported Outcome Measurement Information System (PROMIS)-8 short-form scores—using the cognitive function toolkit of the Quality of Life in Neurologic Disorders (Neuro-QoL) measurement system.[23-25] The PROMIS short-form items target positive self-assessments of cognitive functioning such as "My memory has been as good as usual" and "I have been able to concentrate." The Cognitive Concerns items are worded negatively and express concerns in the same areas such as "My thinking has been slow" and "I have had trouble shifting back and forth between different activities that require thinking." Items on both subscales use a 5-point rating from "not at all" to "very much." Items are summed to create a total score for each subscale. PROMIS cognitive scales have been shown to be short, reliable, and psychometrically sound measures to assess functioning and health for people with neurologic disorders.[26]

Specific aims/endpoints

Our primary endpoint was grade 3 or higher radiation necrosis (RN). Secondary endpoints were neurocognitive decline >5 points using serial PROMIS8 scores,[27] local control, intracranial progression-free survival (PFS), and overall survival (OS).

Statistical analysis

Summary statistics for patient characteristics and brain volumetric doses are presented as both mean and standard deviation (SD) as well as median and interquartile ranges (IQR). The Pearson χ^2 test was used to assess measures of association in frequency tables. Actuarial incidence of RN was estimated per patient using the Kaplan-Meier method, with lesions censored at time of resection or last brain MRI. Kaplan-Meier curves were used for survival analysis, and the log-rank test was used for intergroup comparisons. OS was defined as the time between initial SRS and death from any cause, with censoring of patients who were lost to follow-up. Intracranial PFS was defined from the date of SRS to the date of first intracranial progression or death. Local control was defined on a per patient basis, with censoring of all patients at the date of last follow-up or MRI. Fine and Gray competing risks regression was used to summarize cumulative incidence of outcomes, where death without the outcome was a competing event. Univariate and multivariable logistic regression analyses using Cox proportional hazards models were conducted to evaluate the associations between the clinical or dosimetric factors and survival. Logistic regression analyses were summarized using odds ratios and their 95% confidence intervals (CI). A *P* value of .05 or less was considered statistically significant. Statistical tests were based on a 2-sided significance level. All statistical analyses were performed using R v4.2.2 (R Core Team) and SPSS v23.0 (Armonk).

Results

From January 2014 to December 2022, a total of 118 patients underwent 124 courses of SRS treating 15 or more brain metastases per course. The mean and median

number of lesions treated per patient was 24.8 and 20, respectively (range, 15-94). Patient characteristics are detailed in Table 1. Median age of patients at RT was 61.6 years (IQR 51.4-69.5). The most common primary tumor histologies were lung (47.6%) followed by melanoma (21.0%) and breast (14.5%). The median SRS dose used was 24 Gy (range, 18−30 Gy), with 87.9% patients receiving the total radiation dose in 3 daily fractions. A total of 43.5% of patients had brain metastases at diagnoses, and 29.0% patients had no or controlled systemic disease at the time of SRS. A total of 22.6% patients also underwent surgery for 1 or more BMs (39.3% preop RT and 60.7% postop RT), whereas 89.5% patients received systemic therapy after SRS.

At the time of SRS, 19.4% patients had received prior WBRT and 24.2% had received at least 1 prior SRS course, with 79 patients not receiving any prior brain RT ("brain RT naïve"). Patients receiving salvage SRS had a median brain metastases velocity of 22/y. We then divided the cohort into brain RT naïve patients, that is, those who received upfront SRS to ≥15 metastases (n = 79), and those who had received any prior brain RT (WBRT or SRS) before SRS to ≥15 metastases (n = 39) (Table 1). Brain RT naïve patients had a higher median age at brain metastases diagnosis (P = .016), less % controlled extracranial disease at SRS (P = .004), and a higher median total GTV volume (P < .001). This group of patients also underwent surgery for brain metastases more frequently (P < .001). The median dsGPA score was 1.5 among all patients where dsGPA is defined (n = 118; lung − 1.5; breast − 1.75; melanoma − 1.5; renal − 1.75; and gastrointestinal − 1.5). Overall, 45 (38.1%) patients had a dsGPA of 1.0 or lower.

Treatment-related adverse events and cognitive outcomes

Table 2 reports treatment related toxicities. At a median follow-up of 5.1 months, the rates of any grade RN and grade 3 or higher RN were 15.3% and 3.2%, respectively. The actuarial incidence of any grade RN at 6 and 12 months was 10.8% and 28%, respectively, whereas symptomatic (grade 2 or higher RN) was 3.1% and 13.2%, respectively. New-onset seizures after RT (grade 3) were seen in 3 patients (2.4%), grade 1 alopecia in 3 patients (2.4%), and subjective cognitive decline in 5 patients (4.0%).

Objective cognitive data were available for 38 patients (Supplementary Table E1). Mean PROMIS scores at baseline, 3m, 6m, and 9m after SRS were 32.0, 31.6, 30.4, and 28.7 out of 40, respectively (Figure 1). When longitudinal trends for 6 months were available, 25 of 31 patients (80.6%) had a stable (n = 20) or improved (n = 5) PROMIS score. Overall, 6 patients had a decline of >5 points on PROMIS, of whom 2 patients had tumor progression, whereas one each had radiation necrosis, salvage WBRT, and decline on lurbinectedin; 47.4% patients had a PROMIS score of >35 at last follow-up.

Local control and survival outcomes

The median follow-up for the entire cohort was 5.1 months, whereas for patients still alive at the last follow-up, it was 8.9 months. Median follow-up by reverse Kaplan-Meier method was 17.8 months (95% CI, 10.5-25.1 months). Patterns of treatment failure are described in Table 3. The median overall survival from SRS for the entire cohort was 5.8 months (95% CI, 4.6-7.8 months; Fig. 2A), with a 12-month OS of 29.7%. Brain RT naïve patients had a significantly higher median OS (7.4 months vs 4.6 months, P = .034; Fig. 2C). When calculating from the date of brain metastases diagnosis, median OS was 11.3 months (95% CI, 7.2-15.3) overall, and 9.2 months (6.5-11.8) for brain RT naïve patients. Table 3 also describes the median OS by primary histology.

Table 4 demonstrates the results of univariate Cox regression analyses of the predictors of OS. In the entire cohort, no prior WBRT or SRS (P = .038), higher KPS (P = .002), and systemic therapy after SRS (P < .001) predicted for improved OS. For brain RT naïve patients, age at RT (P = .038) and immunotherapy use (P = .035) also predicted for OS. There was no impact of the number of lesions, GTV volume, or PTV volume on survival outcomes. On multivariable modeling of confounding predictors of interest, prior brain RT (HR, 1.87, 95% CI, 1.17-2.99; P = .009) and KPS ≥80 (HR, 0.48, 95% CI, 0.28-0.83; P = .012) continued to be significant predictors of survival (Supplementary Table E2).

The 12-month actuarial local control was 95.2% (95% CI, 92.3%-98.1%), whereas the cumulative incidence of distant intracranial failure at 12 months, with death as a competing event, was 46% (95% CI, 36%, 55%). Median intracranial progression-free survival after SRS was 2.7 months (95% CI, 2.1-3.8; Fig. 2B). A total of 6.5% of patients had leptomeningeal disease progression, and 19.4% patients required salvage WBRT. On Fine and Gray competing risk analyses with death as a competing factor, 12-month freedom from neurologic death, leptomeningeal disease, and salvage WBRT were 89%, 94.6%, and 84%, respectively. Supplementary Tables E3-6 demonstrate univariate regression models estimating the hazard ratios for neurologic death, leptomeningeal disease, salvage WBRT, and distant intracranial progression, where death without respective events was a competing event. Patients with extracranial control at RT were at significantly lower risk of neurologic deaths (HR, 0.35; 95% CI, 0.14-0.89; P = .028), whereas those who received prior brain RT were at significantly higher risk of distant intracranial progression (HR, 2.15; 95% CI, 1.24-3.73; P = .006).

Table 1   Patient characteristics

Characteristics	All patients	Brain RT naïve patients	P value (prior RT vs no prior RT)
Number of patients	118	79	NA
Number of courses	124	79	NA
Total number of BM lesions	3071	1931	NA
Median number of lesions per patient (IQR)	20 (17, 27)	20 (17, 30)	.8
Median age at brain metastases diagnosis (IQR)	61.7 y (52.1, 70.7 y)	64 y (56, 72 y)	**.016**
Median age at RT (IQR)	63 y (52.1, 70.9 y)	64 y (56, 73 y)	.068
Sex			.2
Male	71 (57.3%)	49 (62%)	
Female	53 (42.7%)	30 (38%)	
Primary tumor histology			.2
Lung	59 (47.6%)	32 (41%)	
Melanoma	26 (21.0%)	20 (25%)	
Breast	18 (14.5%)	11 (14%)	
Genitourinary	10 (8.1%)	9 (11%)	
Gastrointestinal	5 (4.0%)	3 (3.8%)	
Head and neck	4 (3.2%)	3 (3.8%)	
Gynecologic	2 (1.6%)	1 (1.3%)	
Brain metastases at initial diagnosis			.3
Yes	54 (43.5%)	37 (47%)	
Extracranial disease status at SRS			**.004**
Controlled	36 (29.0%)	16 (20%)	
Progressive	88 (71.0%)	63 (80%)	
KPS at RT			.14
90-100	55 (44.4%)	40 (50.9%)	
70-80	62 (50.0%)	33 (42%)	
<70	7 (5.6%)	14 (7.6%)	
Diagnosis-Specific GPA			.3
0-1	45 (38.1%)	30 (40.0%)	
1.5-2.0	54 (45.8%)	34 (45.3%)	
2.5-3.0	18 (15.3%)	11 (14.7%)	
3.5-4.0	1 (0.8%)	0	
Prior WBRT	24 (19.4%)	0	NA
Prior SRS	30 (24.2%)	0	NA
Median marginal SRS dose % receiving 24 Gy in 3 fractions	24 Gy (18, 30 Gy) 81.5%	24 Gy (18, 30 Gy) 80.0%	.2
No. of fractions			.3
1	6 (4.8%)	5 (67%)	
3	109 (87.9%)	67 (85%)	
4	1 (0.8%)	0	
5	8 (6.4%)	7 (8.9%)	
Median total GTV in cc (IQR)	7 (2,16)	11 (4,26)	**<.001**

Table 1 (*Continued*)

Characteristics	All patients	Brain RT naïve patients	*P* value (prior RT vs no prior RT)
Median total PTV in cc (IQR)	26 (15, 49)	33 (21, 64)	**<.001**
Time from diagnosis to SRS (months)	1 (0, 7)	0 (0, 1)	NA
Systemic therapy after RT			
Yes	111 (89.5%)	67 (85%)	**.031**
Immunotherapy	30 (24.2%)	22 (28%)	.2
Oral targeted therapies	18 (14.5%)	11 (14%)	.8
Surgery for brain metastasis			
Yes	28 (22.6%)	28 (35%)	**<.001**
Surgery after SRS (preop SRS)	11 (39.3%)	11 (39.3%)	
Postop SRS	17 (60.7%)	17 (60.7%)	

Abbreviations: WBRT = whole-brain radiation therapy; SRS = stereotactic radiosurgery; RT = radiation therapy; BM = brain metastases; NA = not applicable; IQR = interquartile range; KPS = Karnofsky Performance Score; GTV = gross tumor volume; PTV = planning tumor volume; y = years.

Long-term survivors

Overall, 24 patients (19.3%) in our cohort survived >1 year, with a median OS of 21.4 months. This group had a median of 18 brain metastases treated (range, 15-32). Among these patients, cognitively 8 of 9 patients (89%) did not have any decrease in their PROMIS scores over time. On univariate analysis, a significantly higher number of these long-term survivors were younger (median age 59 years vs 64 years, *P* = .048), had a KPS of 90 to 100 (66.7% vs 39%, *P* = .003), received systemic therapy (100% vs 87%, *P* = .052), and developed RN (any grade RN 37.5% vs 10%; grade 3 RN 16.7% vs 0%; *P* = .002). There was no difference by SRS dose, number of brain metastases treated, sex, primary tumor histology, or extracranial control at time of SRS (Supplementary Table E7).

Discussion

Our study represents one of the largest analyses of patients with 15 or more brain metastases treated with SRS alone. Our results demonstrate that SRS for this patient population is safe, with low rates of grade 3 or higher adverse events. Only 5% patients experienced grade 3 or higher RN at 12 months, which is comparable to other historical studies evaluating SRS.[28,29] The median OS in our cohort was 5.8 months, whereas that in treatment-naïve patients was 7.4 months. The median dsGPA score in our study was 1.5, which corresponds to a median survival of 6.5 months (lung), 9.4 months (breast), 7.3 months (renal), and 4.7 months (melanoma) from the time of initial treatment of brain metastases.[22] Our patients had a similar median OS when evaluating by primary histology (Table 3).

Prior randomized studies by Chang et al and Brown et al evaluating SRS or SRS with WBRT in patients with 1 to 3 newly diagnosed brain metastases observed a median OS of 7.4 to 10.4 months. Multiple trials have since demonstrated similar OS among patients with up to 10 metastases treated with SRS alone. Yamamoto et al evaluated their experience of treating nearly 1200 patients with 1 to 10 brain metastases, demonstrating no difference in OS in patients who had 2 to 4 brain metastases versus 5 or more brain metastases when treated with SRS alone.[8] The median overall survival after SRS was 10.8 months in both patient groups. A retrospective study by the same group reported a median survival of 6.8 months for patients with 2 to 9 lesions versus 6.0 months for those with ≥10 lesions.[30] In another study including 981 patients with >10

Table 2 Adverse events

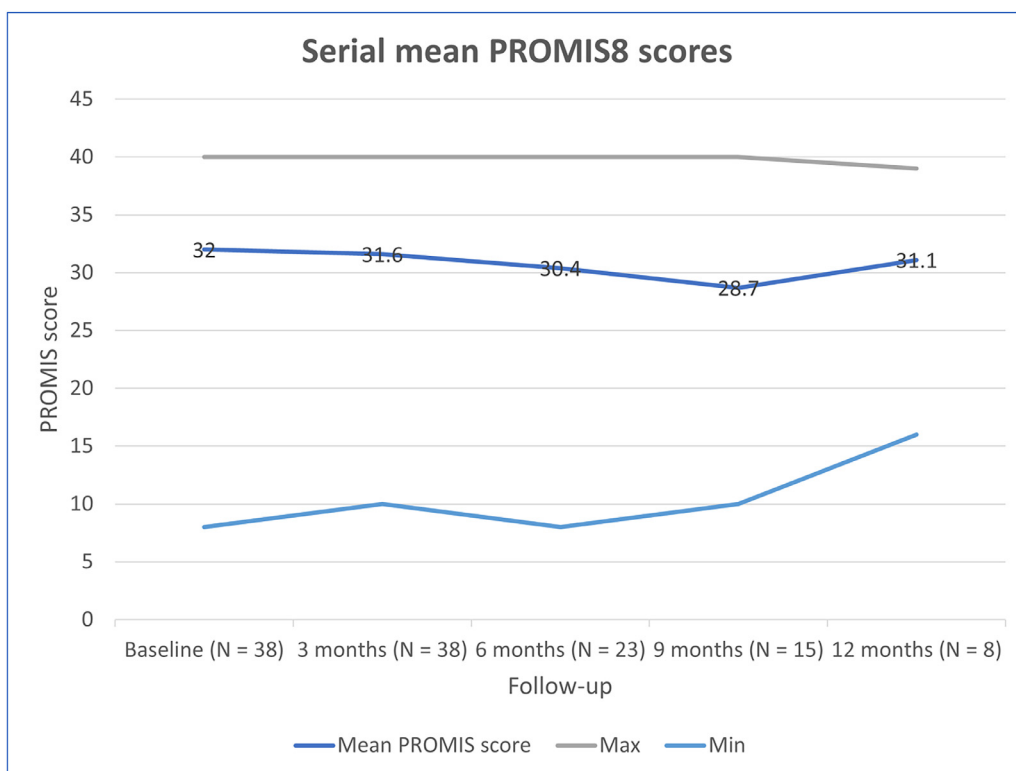| Toxicity	N (%)	
Radiation necrosis (RN)		
Any grade	19 (15.3%)	
1	9 (7.3%)	
2	6 (4.8%)	
3	4 (3.2%)	
Actuarial incidence of RN per patient	6 months	12 months
Any grade	10.8%	28.0%
Symptomatic RN (grade 2+)	3.1%	13.2%
grade 3+ RN	2.4%	5.0%
New onset seizures (grade 3)	3 (2.4%)	
Alopecia (all grade 1)	3 (2.4%)	
Subjective cognitive decline	5 (4.0%)	

Figure 1   Cognitive outcomes: Serial mean NIH PROMIS8 scores.

SRS-treated brain metastases, median survival was 5.5 months, similar to our study.[31] A recent meta-analysis including 2360 patients with 10+ brain metastases treated with SRS reported a pooled 12-month OS of 30.5% (95% CI, 20.5%-42.7%).[32] Of note, none of these studies describe outcomes in patients with >15 metastases specifically.

A pertinent finding in these aforementioned studies was that SRS was better than SRS with WBRT in terms of cognitive decline by almost 30% at 4 months (52% vs 24%). The N0574 study showed that cognitive decline was higher with WBRT (52.9% vs 20%).[5] RTOG 0933 showed that the probability of cognitive decline (delayed recall) with HA-WBRT was 33% at 4 months, which was significantly lower compared with WBRT historical controls.[33] In the Japanese single-arm study of SRS, patients with fewer than 5 metastases had similar MMSE scores and long-term complication rates as those with or 5 to 10 metastases.[7] Palmer et al recently performed a secondary analysis of the N107C clinical trial comparing SRS and WBRT for <5 resected brain metastases and found that cognitive deterioration was less frequent with SRS (37%-60%) compared with WBRT (75%-91%) at all time points.[34] The difference in cognitive deterioration started as early as 3 months after RT, and, in fact, the difference between SRS and WBRT was highest at 3 months (37% vs 88.9%). Although NIH PROMIS scores have been relatively less commonly used in trials evaluating neurocognitive outcomes, implementation of this questionnaire in regular clinical practice is relatively easy, with minimal

additional testing time required.[35] Recent studies have also validated PROMIS function scores in cancer care and provided guidance for interpreting the clinical meaning of scores.[27] The rate of significant cognitive decline in our cohort using these scores was <20% at a median follow-up of 5.1 months, although the serial data were available for a limited number of patients.

More recent studies are evaluating SRS versus WBRT in patients with 4 to 15 BMs. Li et al recently presented early results from a phase III RCT comparing SRS versus WBRT for patients with 4 to 15 nonmelanoma BMs at ASTRO 2020.[10] Although the study was terminated early, they reported a clinically meaningful and statistically significant benefit in memory function change with SRS at 1 month ($P = .033$), 4 months ($P = .041$), and 6 months ($P = .012$), using the HVLT total recall test and global cognitive function measure. Of the patients evaluable for survival, median OS (7.8 months vs 8.9 months), local control (95% vs 87%), and distant brain control (60% vs 80%) were statistically similar between SRS versus WBRT groups, respectively. In another study, Zindler et al and the MAASTRO group in the Netherlands randomized patients with 4 to 10 BM with a maximum lesional diameter of 2.5 cm and a maximum cumulative lesional volume of 30 cm^3 to WBRT (20 Gy in 5 fractions) or SRS (15-24 Gy in 1 fraction) and found a 1-year survival of 57% for SRS versus 31% for WBRT, with patients in the SRS group maintaining a persistently higher quality of life than those in the WBRT group.[9,36,37] The trial closed prematurely

Table 3   Patterns of failure and survival outcomes

Outcomes	All patients	Brain RT naïve patients	*P* value (prior RT vs no prior RT)
Median follow-up (IQR)	5.1 mo (2.5, 9.2)	5.7 mo (2.6, 11.3)	
Deaths	96 (77.4%)	55 (70%)	**.006**
Long-term survivors >1 year	24 (19.4%)	18 (22.8%)	.2
Neurologic death	17 (13.7%)	10 (13%)	.7
Cumulative incidence at 1 year (95% CI)	11% (5.7, 17%)	10% (4.4, 19%)	
Intracranial progression	65 (52.4%)	28 (48.5%)	.4
Distant intracranial	62 (50.0%)	36 (46%)	
Progression of treated met	3 (2.4%)	2 (2.5%)	
PFS after RT			.8
Median (95% CI)	2.7 mo (2.1, 3.8)	3.0 mo (2.1, 3.8)	
Cumulative incidence of distant progression at 1 year (95% CI)	46% (36, 55%)	37% (24, 50%)	
Leptomeningeal disease progression	8 (6.5%)	7 (8.9%)	.3
Cumulative incidence at 1 year (95% CI)	5.4% (2.2, 11%)	7.4% (2.7, 16%)	
Salvage WBRT	24 (19.4%)	20 (25%)	**.026**
Cumulative incidence at 1 year (95% CI)	16% (9.6, 23%)	21% (12, 32%)	
Overall survival after SRS			**.034**
Median (95% CI)	5.8 mo (4.6, 7.8)	7.4 mo (5.7, 13.8)	
6-month OS	49.7%	57.2%	
1-year OS	29.7%	36.6%	
Overall survival after SRS by primary histology: median (95% CI)			.8
Lung	5.0 mo (3.3-6.6)	7.0 mo (3.6-10.4)	
Melanoma	5.7 mo (1.1-10.3)	5.7 mo (0.0-11.9)	
Breast	7.9 mo (3.9-11.9)	9.0 mo (1.3-16.7)	
Genitourinary	7.1 mo (2.7-11.5)	7.1 mo (5.1-10.0)	
Overall survival from BM diagnosis			.4
Median (95% CI)	11.3 mo (7.2-15.3)	9.2 mo (6.5-11.8)	
6-month OS	72.3%	61.5%	
1-year OS	49.7%	39.8%	
Overall survival from BM diagnosis by primary histology: median (95% CI)			.3
Lung	15.6 mo (11.3-19.9)	8.3 mo (4.0-12.6)	
Melanoma	9.3 mo (3.6-15.0)	6.4 mo (0.0-13.0)	
Breast	10.0 mo (1.1-18.9)	9.4 mo (1.6-17.2)	
Genitourinary	14.4 mo (4.2-24.7)	7.6 mo (0.0-16.9)	

due to poor accrual resulting from patients' and referrers' preference for SRS. In another recent study by Minniti et al, investigators treated 40 patients with 10 or more brain metastases with single-isocenter multiple-target technique (SIMT) SRS alone (median number of lesions 13, range, 10-21) and showed 1-year survival and local control rates of 65% and 86%, respectively.[29] Radiation necrosis was seen in 7 patients. Our patient population harbored more unfavorable characteristics than those in these studies, with a median number of lesions per patient of 20 (range, 15−94); hence, our survival outcomes are expected to be somewhat lower than these patient populations.

The cumulative incidence of distant intracranial failure at 1 year in our study was 46%. This is similar to the
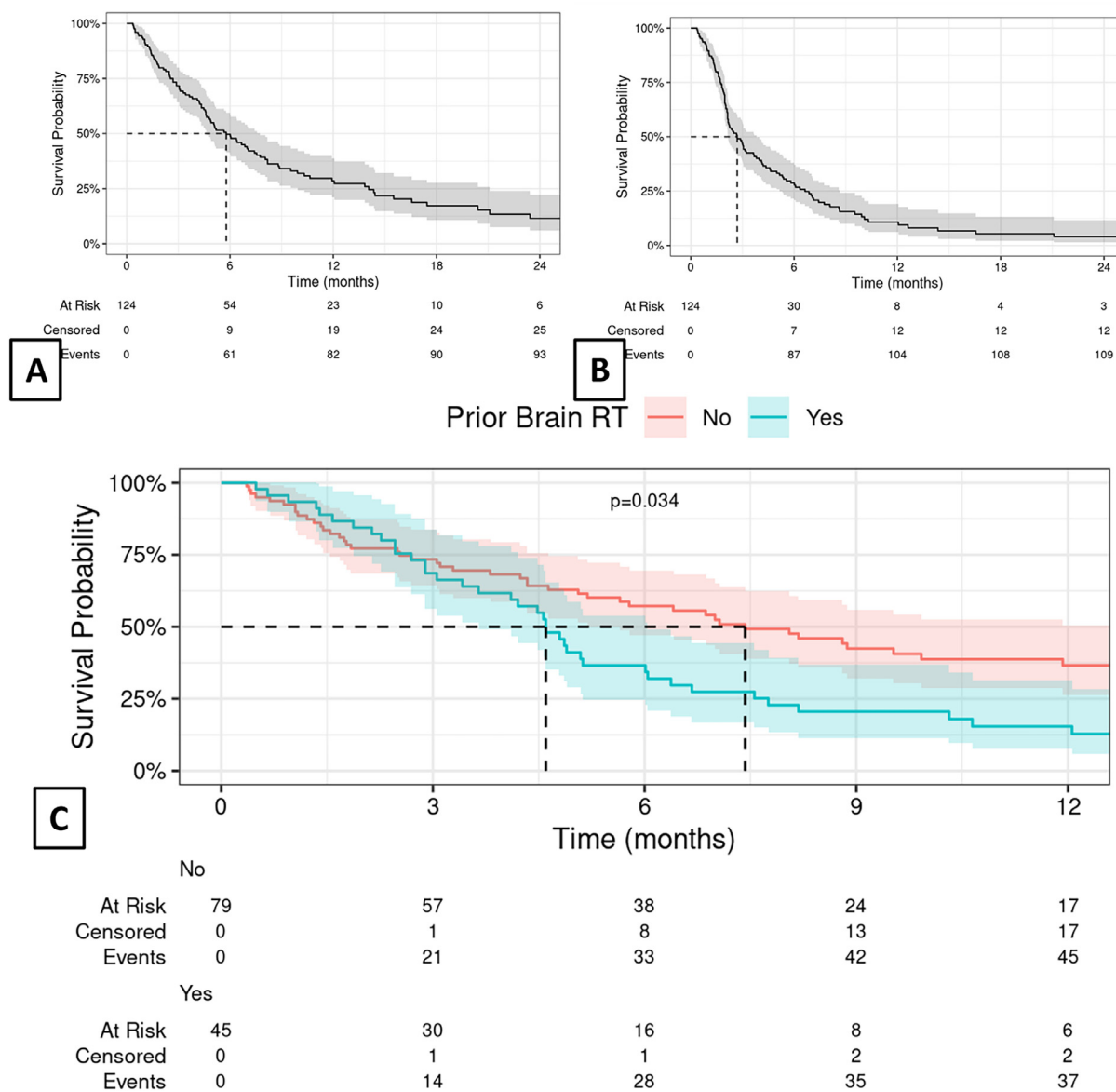
Figure 2 Kaplan-Meier curve for survival outcomes for (A) overall survival for all patients; (B) progression-free survival for all patients; and (C) overall survival stratified by prior brain RT.

earlier randomized studies evaluating SRS for 1 to 3 metastases. Chang et al reported a 1-year freedom from CNS recurrence of 27% with SRS alone versus 73% with SRS plus WBRT (P = .0003), whereas the total intracranial control at 1 year in the secondary analyses of N107C was 40.7% with SRS alone versus 81.5% with WBRT (P = .003). Although the benefit in intracranial control with WBRT is clear, it does not provide any additional survival benefit. We also observed that the rates of 1 year freedom from neurologic death and leptomeningeal disease were quite high, at 89% and 94.6%, respectively. Patients with controlled extracranial disease at RT were at significantly lower risk of neurologic death.

Many recent and ongoing clinical trials have typically focused on using an arbitrary number of lesions as a criterion for SRS eligibility. Recent reports have demonstrated that the total treatment volume rather than the absolute number of metastases could be the most significant predictor of survival.[12] Likhacheva et al reported that the tumor volume was predictive of local control, with a HR of 4.56 for total volume >2 cc,[16] and Kim et al reported correlation of unfavorable outcomes with cumulative tumor volume greater than the median volume of 7 cc.[13] However, the median number of metastases treated in both these studies were 2 (range, 1-13). The median total GTV per patient in our study was 7 cc (interquartile range, 2-16 cc, range, 0.4-98.5 cc). We did not observe a difference in survival based on number or volume of lesions treated.

A few ongoing trials are evaluating SRS and WBRT. The CCTG/Alliance CE7 is an ongoing intergroup phase

Table 4 Univariate analysis of factors affecting overall survival

Characteristic	All patients (N = 124)			Patients with no prior RT (N = 79)		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Total SRS dose	0.96	0.84, 1.09	.5	0.99	0.83, 1.17	.9
Number of BMs treated	1.00	0.98, 1.02	>.9	1.01	0.98, 1.03	.6
Prior brain RT = Yes	1.55	1.03, 2.33	**.038**			NA
Total GTV	1.01	0.99, 1.02	.4	1.01	1.00, 1.03	.090
Total PTV	1.00	1.00, 1.01	.5	1.01	1.00, 1.01	.12
Sex = Female	1.09	0.72, 1.64	.7	0.98	0.56, 1.73	>.9
Primary location (vs lung)	0.90	0.53, 1.53	>.9	0.87	0.44, 1.73	>.9
Brain metastases at diagnosis = Yes	0.90	0.60, 1.36	.6	0.92	0.53, 1.58	.8
Age at RT	1.01	1.00, 1.03	.055	1.02	1.00, 1.04	**.038**
KPS at RT			**.002**			**.043**
70	1.27	0.46, 3.52		1.43	0.42, 4.89	
80	0.79	0.31, 2.02		0.70	0.23, 2.11	
90	0.44	0.17, 1.13		0.53	0.18, 1.55	
100	0.26	0.07, 0.97		0.18	0.03, 1.01	
KPS ≥80 = Yes	0.47	0.28, 0.78	**.007**	0.43	0.22, 0.86	**.027**
Extracranial control at RT = Yes	1.44	0.92, 2.27	.11	1.68	0.82, 3.43	.14
Systemic therapy after RT = Yes	0.12	0.06, 0.23	**<.001**	0.10	0.04, 0.21	**<.001**
Surgery = Yes	0.96	0.58, 1.58	.9	1.28	0.73, 2.25	.4
RT timing = postop RT	0.85	0.35, 2.10	>.9	0.81	0.33, 2.02	.6
Immunotherapy = Yes	0.67	0.41, 1.10	.10	0.52	0.27, 0.99	**.035**
TKI	1.05	0.60, 1.82	.9	0.81	0.37, 1.80	.6

Abbreviations: HR = hazard ratio; CI = confidence interval.

III clinical trial evaluating SRS and WBRT for patients with 5 or more brain metastases (NCT03550391).[38] Another ongoing trial, Whole Brain Irradiation or Stereotactic RadioSurgery for 5 or more brain metastases (WHOBI-STER), is comparing neurocognitive outcomes and level of autonomy in daily activities between SRS and WBRT (NCT04891471).[39,40] The phase III NRG BN-009 trial is currently enrolling patients with distant intracranial progression with a brain metastases velocity of ≥4 per year and randomizing them to salvage SRS alone or SRS + hippocampal-avoidant WBRT. Our patient population receiving salvage SRS after prior RT had a median brain metastases velocity of 22/y.

There are several limitations to our study, including the inherent retrospective design and a heterogenous patient population. Another limitation is the inclusion of patients who had received prior brain radiation to maintain a reasonable sample size, although we tried to dichotomize the results based on receipt of prior brain radiation. Also, a limited number of our patients had objective cognitive data available for analysis. We routinely started using PROMIS8 scores for neurocognitive assessments in 2019 to 2020; hence, patients treated before this did not have neurocognitive data available for review. In addition, given the retrospective nature of the study, filling out neurocognitive questionnaire was not mandatory for the patients, and there were several potential reasons for patients not filling out the questionnaires, including patient choice.

In conclusion, the integration of radiosurgery into the multidisciplinary approach for managing patients with 15 or more metastases holds promise, and these patients are expected to survive long enough to benefit from the cognitive sparing effects of SRS over WBRT. Improved MRI-based imaging has proven to be a highly sensitive test for determining the true extent of intracranial disease. The significant possibility of cognitive decline after WBRT and the lack of good treatment options to improve cognition is problematic in light of longer patient survival. All of our patients were treated with frameless LINAC-based SRS using a single-isocenter technique that permits non-invasive, fast, and accurate targeting of multiple metastases simultaneously. With further research and clinical investigations, we hope to appropriately select patients

who are good candidates for SRS to improve patient outcomes, ultimately leading to better quality of life and prolonged survival for these individuals grappling with the challenges of advanced cancer and brain metastases.

Conclusions

We present here one of the largest studies evaluating SRS for patients with ≥15 BMs. We found that SRS was safe, had excellent subjective cognitive outcomes, and had comparable survival outcomes to contemporary studies evaluating WBRT in this patient population. Treatment-naïve patients had a median survival of >6 months, long enough to benefit from cognitive sparing with SRS. The historical practice of directing patients with 15 or more lesions to treatment with WBRT alone is not supported by our findings. Our study supports further randomized studies comparing SRS and hippocampal avoidance WBRT approaches in this group of patients.

Disclosures

Dr Palmer reports serving on Novocure Advisory Board, consulting fees from More Health and Huron consultant, and grant funding from Varian Medical Systems, Genentech, and NIH R702 and NIH R01 outside the submitted work. None of the other authors have relevant conflicts of interest.

Supplementary materials

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