

Outcomes and Prognostic Factors for Patients With Brainstem Metastases Undergoing Stereotactic Radiosurgery

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BACKGROUND: Treatment of tumors metastatic to the brainstem with stereotactic radiosurgery (SRS) has not been widely studied.

OBJECTIVE: To identify the effects of SRS on patients with brainstem metastases by assessing duration of local progression-free survival (LPFS) and overall survival.

METHODS: We retrospectively reviewed clinical data collected from 60 patients undergoing linear accelerator-based SRS for tumors metastatic to the brainstem between August 1994 and December 2007. The LPFS and overall survival were calculated with the Kaplan-Meier method. Prognostic factors were evaluated with the log-rank test and Cox proportional hazards model.

RESULTS: The median age of patients was 61 years (range, 39-85 years); the median treated lesion volume was 1.0 mL (range, 0.1-8.7 mL); and the median SRS dose was 15 Gy (range, 8-18 Gy). The median overall survival interval after SRS was 4 months (95% confidence interval, 3.4-4.9 months); crude local tumor control was 76%; and median LPFS was 5.7 months (95% confidence interval, 3.0-8.4 months). Shorter overall survival was associated with a pretreatment tumor volume ≥ 4 mL ($P < .001$) and male sex ($P = .03$). Shorter LPFS was associated with a pretreatment tumor volume ≥ 4 mL ($P = .008$), a melanoma primary tumor ($P = .002$), and the presence of necrosis in pre-SRS magnetic resonance imaging ($P = .04$). A Basic Score for Brain Metastases of 2 to 3 vs 1 ($P = .007$) and a Score Index for Radiosurgery > 5 ($P = .003$) were significantly associated with longer survival. Twelve patients (20%) developed SRS-related complications.

CONCLUSION: Stereotactic radiosurgery provides noninvasive treatment and favorable local tumor control for patients with brainstem metastases.

KEY WORDS: Brainstem, Metastasis, Outcomes, Stereotactic radiosurgery

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Metastases to the brainstem are relatively uncommon, constituting 5% to 7% of metastatic brain lesions.^{1,2} Regardless of diverse pathological features, metastatic brainstem lesions present a high risk of significant neurological deficit owing to surrounding critical neuronal structures. Although microsurgical

techniques provide access to the brainstem, surgical resection of lesions metastatic to the brainstem is not routinely recommended because of the perceived high risk of morbidity and mortality.¹

The effects of whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) are well described for the treatment of patients with brain metastases.³⁻⁶ The survival time of patients with brain metastases increases from 1 to between 3 and 4 months after treatment with WBRT.⁶ To determine the effect of SRS on the treatment of tumors metastatic to the brain, Andrews et al⁵ conducted randomized controlled trial 9508 of the Radiation Therapy Oncology Group, which showed a significant improvement in median survival time of patients receiving SRS

ABBREVIATIONS: **BSBM**, Basic Score for Brain Metastases; **CI**, confidence interval; **GPA**, Graded Prognostic Assessment; **KPS**, Karnofsky Performance Scale; **LPFS**, local progression-free survival; **RPA**, recursive partitioning analysis; **SIR**, Score Index for Radiosurgery; **SRS**, stereotactic radiosurgery; **WBRT**, whole-brain radiation therapy

plus WBRT compared with WBRT alone. Recently, the use of SRS alone to treat brain metastasis has increased. A randomized clinical trial by Aoyama et al⁷ comparing patients who underwent SRS alone with those undergoing SRS followed by WBRT revealed that there was no difference between the 2 groups in survival, cause of death, toxic effects of radiation, or preservation of neurological function, although the local control failure rate was higher in the group receiving SRS alone. However, little attention has been paid to the management of brainstem metastases because of their rarity and the anticipated poor outcome of afflicted patients. Only a few studies with small numbers of patients have assessed the use of SRS for brainstem metastases.^{1,8-14} Five of these reports evaluated the prognostic factors for overall survival,^{1,9,10,13,14} and factors for local tumor control were assessed in only 1 report.⁹

The purpose of our study was to identify the effects of SRS on brainstem metastases by assessing local progression-free survival (LPFS) time and overall survival duration of the patients. We tried to identify factors independently associated with LPFS and overall survival time. We also assessed the treatment complications. To the best of our knowledge, this study represents the largest series of patients treated with SRS for tumors metastatic to the brainstem.

MATERIALS AND METHODS

Patient Data

Patients undergoing linear accelerator-based SRS for brainstem metastases at The University of Texas MD Anderson Cancer Center between August 1994 and December 2007 were included in this study. The patients' characteristics, including disease and treatment data used in this report, were collected prospectively and reviewed in a retrospective fashion. The date of local tumor control failure, dates of the last clinical and imaging follow-up, and the date and cause of death were recorded. Some patients received WBRT before SRS. Patients were selected for WBRT before SRS if they had >3 to 4 total brain metastases, if they had a generally poorer Karnofsky Performance Scale (KPS) score, and if it was the preference of both physician and patient. Because Chang et al¹⁵ recently showed that patients treated for brain metastases with SRS had better neurocognitive outcomes than those treated with WBRT, we tend to treat multiple lesions with SRS and to delay WBRT. The study was approved by the institutional review board under protocol number DR07-0963.

Radiation Technique

Patients underwent SRS using either the Varian linear accelerator (Palo Alto, California) or, after 1999, a dedicated PRIMART linear accelerator (Siemens Oncology Care, Concord, California). After administration of local anesthesia, a Brown-Robert-Wells stereotactic head frame (Integra Radionics, Burlington, Massachusetts) was used for immobilization and intracranial target localization. Contrast-enhanced computed tomography (CT) images (at 1.5-mm thickness) were obtained on the same day with a CT scanner in all cases. The scans were transferred to a workstation by a Digital Imaging and Communication in Medicine link for treatment planning with X-knife software (versions 3 and 4; Integra Radionics). The volume of the targeted lesion was measured with the treatment planning computer. All cases were planned with a CT-based radiosurgical treatment planning system, the Radionics

X-Knife system. Lesions well visualized on CT were contoured on CT only. Smaller lesions required the acquisition of volumetric thin-slice magnetic resonance imaging (MRI) for fusion with the planning CT for target delineation purposes. After treatment planning was completed, SRS was performed on the same day with an appropriate cone (selected from cone sizes ranging from 0.75-4 cm in diameter) or multiple small rectangular fields collimated with a mini-multileaf collimator (4-mm-thick leaves), typically prescribed to the 90% to 95% isodose line to ensure 100% coverage of the tumor volume, and 1 isocenter per target. The gross target volume was defined as just the contrast-enhancing lesion without any margin. No additional margins were applied for setup uncertainty. Treatment setups were all verified with the use of patient-specific quality assurance procedures following the Winston-Lutz test. Single-fraction SRS was used in all cases.

Patient Follow-up

As part of standard care, the patients receiving SRS underwent routine clinical evaluations and MRI during their follow-up visits every 1 to 3 months. Volumetric tumor measurements were performed prospectively with Vitrea2 software (version 2.2; Vital Images, Plymouth, Minnesota). The patients' neurological symptoms and KPS scores before SRS were recorded. The response of the brainstem metastases to the SRS was obtained by comparing follow-up MRI scans with pre-SRS MRI scans. Local treatment was considered to have failed if there was an increase in tumor volume of $\geq 25\%$ compared with the pre-SRS volume. Any clinical symptoms such as headache, nausea and vomiting, new neurological deficits, or worsening deficits during the follow-up period related to the SRS procedure and any imaging findings such as significant edema, hemorrhage, and necrosis were considered to be SRS-related complications.

Outcome Measures

The end points of the study were survival time, local tumor control, and treatment complications. Overall survival time and LPFS time were calculated in months from the dates of each patient's SRS procedure. The date of last follow-up was used to compute survival time, and the last imaging date was used to determine local tumor control. For LPFS, patients with a lapse in imaging information before death were censored at the time of last imaging, not at the time of death, even if death information was available. Those who underwent salvage WBRT were censored at the time of the salvage WBRT. Crude local control was defined as the absence of local control failure. We assessed the following factors for their impact on survival and local tumor control: age and sex of the patient, primary tumor site, tumor location in the brainstem, status of the primary cancer (controlled or uncontrolled), status of extracranial systemic metastasis (present or absent), presence of symptoms before SRS, KPS score, number of brain metastases (single or multiple), brainstem lesion characteristics on MRI (presence of edema, tumor volume, tumor hemorrhage, and necrosis), SRS dose, and adjuvant WBRT.

Statistical Analysis

Frequencies and descriptive statistics were obtained for the various entities under study. Continuous and ordinal variables were tested with Student's *t* test or a nonparametric test, respectively, as appropriate.

Kaplan-Meier estimates of survival were obtained, and differences in the survival curves among various subgroups were compared with a log-rank test. The Cox proportional hazards method was used to identify

independent factors associated with LPFS and overall survival using a backward stepwise selection method, with adjuvant WBRT considered a time-dependent covariate. Crude hazard ratios (HRs) and HRs adjusted for the various covariates and the corresponding 95% confidence intervals (CIs) were obtained. Analyses were performed for all patients and for the subgroup of patients who did not receive any treatment for their brainstem metastases before SRS. In a secondary analysis, we stratified the patients using 4 additional grading systems: the Radiation Therapy Oncology Group's recursive partitioning analysis (RPA),¹⁶ the Score Index for Radiosurgery (SIR),¹⁷ the Basic Score for Brain Metastases (BSBM),¹⁸ and the Graded Prognostic Assessment (GPA).¹⁹ We further investigated which of those grading systems was associated with overall survival time for patients with metastatic brainstem lesions. A value of $P \leq .05$ was considered statistically significant. All tests were 2 tailed. SPSS version 16.0 and STATA 10 were used for the analyses.

RESULTS

Patient Characteristics

During the study period, 1440 patients with brain metastases were treated with SRS. From these, we identified 71 consecutive patients (5%) who underwent SRS for metastases to the brainstem. Nine patients for whom pre-SRS imaging was unavailable and 2 patients who developed leptomeningeal disease before the index SRS procedure were excluded. Therefore, 60 patients were included in the present study. Twenty-nine patients (48%) were female and 31 patients (52%) were male. The median age of patients at the time of SRS was 61 years (range, 39-85 years). The median KPS score was 90 (range, 50-100). Forty-three patients (72%) had symptoms related to the brainstem metastases. The most frequent presenting symptom was cranial nerve deficit (38% of patients). Brainstem lesions were most frequently found in patients with primary lung cancer (33%), followed by melanoma (24%) and breast cancer (18%). Among the patients with lung cancer metastasis to the brainstem, 18 had non-small-cell lung cancer and 2 had small-cell lung cancer. The patients with small-cell lung cancer had received WBRT for other brain metastases before the SRS treatment for brainstem metastasis.

The median number of total intracranial metastases including brainstem lesions at the time of SRS was 2 (range, 1-9). Uncontrolled primary disease was noted in 13 patients (22%), whereas 47 patients (78%) had no active primary disease or stable primary disease. Extracranial systemic metastasis was observed in 41 patients (68%). The median interval between the diagnosis of the primary cancer and the brainstem metastasis was 22 months (range, 0-267 months), and the median time between the diagnosis of the brainstem metastasis and SRS treatment was 18 days (range, 1-344 days). Table 1 details the characteristics of the patients and their lesions.

Radiosurgical Planning

The median treatment volume was 1.0 mL (range, 0.1-8.7 mL). The median prescribed dose was 15 Gy (range, 8-18 Gy) treated at the 77% to 95% isodose contour (median, 85%). Our dose-prescribing practices have generally been more conservative for

TABLE 1. Characteristics of Patients With or Without Prior Treatment of Brainstem Metastases^a

Characteristic	Value
Patients (F/M), n	60 (29/31)
Median age (range), y	61 (39-85)
Primary malignancy, n (%)	
Lung	20 (33)
Melanoma	14 (24)
Breast	11 (18)
Kidney	7 (12)
Other ^b	8 (13)
Symptoms and findings, n (%)	
Cranial nerve palsies	23 (38)
Ataxia	17 (28)
Hemiparesis	9 (15)
Headache	3 (5)
Hydrocephalus	2 (3)
None	17 (28)
Median KPS score (range)	90 (50-100)
RPA class, n (%)	
I	8 (13)
II	47 (78)
III	5 (9)
Other intracranial metastases at the time of SRS, n (%)	25 (42)
Uncontrolled primary cancer at the time of SRS, n (%)	13 (22)
Extracranial metastases at the time of SRS, n (%)	41 (68)
Median interval between primary cancer diagnosis and brainstem metastasis diagnosis (range), mo	21.7 (0-266.8)
Median interval between brainstem metastasis diagnosis and SRS (range), d	18 (1-344)
Median tumor volume (range), mL	1.0 (0.1-8.7)
Location of treated brainstem metastasis, n (%)	
Midbrain	15 (25)
Pons	39 (65)
Medulla	6 (10)
Pre-SRS MRI finding, n (%)	
Contrast enhancement	60 (100)
Hemorrhage	8 (13)
Edema	25 (42)
Necrosis	18 (30)
WBRT for brainstem metastasis before SRS	9 (15)
Median SRS dose (range), Gy	15 (8-18)
Median isodose, %	85 (77-95)
Median cone diameter (range), cm	1.5 (0.75-3.5)

^aKPS, Karnofsky Performance Scale; MRI, magnetic resonance imaging; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

^bOther primary tumors included primary unknown (adenocarcinoma), 3 patients; endometrial carcinoma, 1 patient; sarcoma, 1 patient; bladder cancer, 1 patient; colon cancer, 1 patient; and uterine cancer, 1 patient.

brainstem metastases than typical size-based prescription guidelines to minimize the risk of the development of radionecrosis of the brainstem and potentially serious associated complications. Radiosurgery was applied with cones ranging from 0.75 to 3.5 cm

in diameter (median, 1.5 cm) or mini-multileaf collimator-shaped rectangular fields for irregularly shaped targets or targets very close to critical structures. Figure 1 demonstrates the SRS planning schema of a metastatic brainstem lesion.

Clinical Outcome and Follow-up

The median follow-up time after radiosurgery among patients still alive at the end of the study was 12.8 months (range, 1.4-32.4 months). The median imaging follow-up time after radiosurgery was 5.3 months (range, 0.3-27.0 months). Treatments and outcomes of the patients are detailed in Table 2. Tumor regression was apparent after SRS in 13 patients (22%) with brainstem metastases. These patients remained neurologically stable. Two patients whose brainstem lesions remained stable in size showed neurological improvement after SRS. No correlation was found between tumor regression and neurological improvement after SRS.

Twelve patients (20%) developed a total of 15 complications related to SRS. Nine complications developed within 1 month after radiosurgery, and 6 developed after that. Among these 15 complications, there were 4 instances of hemiparesis, 2 instances of cranial nerve deficit, 3 instances of headache, 4 instances of nausea/vomiting, and 2 instances of hemorrhage in the radio-surgically treated lesion. Among the patients who developed a hemorrhagic complication, 1 patient had a diagnosis of a lung cancer primary and also showed neurological worsening, including hemiparesis and a cranial nerve deficit, and the other patient (with a breast cancer primary) showed a stable neurological examination. Neurological complications were major in 2 patients, including hemiparesis in 1 patient and hemiparesis and cranial nerve deficit with hemorrhage in another patient. Other complications were mild and temporary. No patient experienced a seizure related to the SRS procedure.

Twenty-nine patients (48%) were newly diagnosed with brainstem metastases and did not receive any treatment of the brainstem before undergoing SRS. Nine patients (15%) received WBRT for the brainstem lesion at least 1 month before SRS. Adjuvant WBRT was administered to 6 patients (10%) within 1 month after SRS at a median dose of 30 Gy (range, 30-35 Gy).

LPFS Time

Eleven patients (18%) did not have an imaging follow-up visit, either because they were in poor health or because they did not survive long after SRS. The other 49 patients (82%) underwent at least 1 post-SRS follow-up imaging study. For these patients, the median time of follow-up imaging was 3.5 months (range, 0.2-36.1 months), and crude local control was achieved in 76% of their tumors at the last follow-up. The rate of LPFS was 44% at 6 months (95% CI, 26-63) and 35% at 1 year (95% CI, 16-53), with a median LPFS time of 5.7 months (95% CI, 3.0-8.4 months; Figure 2).

In univariate testing, a brainstem tumor volume ≥ 4 mL (HR, 6.1; 95% CI, 1.8-20.5; $P = .003$), an SRS dose < 14 Gy (HR, 3.8; 95% CI, 1.0-14.1; $P = .049$), the presence of necrosis (HR, 2.8; 95% CI, 1.1-7.1; $P = .03$), a melanoma primary (HR = 2.8; 95%

CI, 1.1-6.9; $P = .03$), and male sex (HR = 2.5; 95% CI, 1.0-6.3; $P = .05$) were significantly associated with a shorter LPFS duration (Table 3). Although there was a difference in the median LPFS time between the patients with a KPS score < 80 and those with a KPS score ≥ 80 (2.3 and 5.7 months, respectively), this difference was not statistically significant ($P = .06$). Similarly, there was a difference in the median LPFS duration between the patients with an additional intracranial metastasis not located in the brainstem and those without (3.7 and 9.4 months, respectively) and between patients with a breast primary tumor and those with other types of primaries (median not reached and 4.1 months, respectively), but these differences also achieved only borderline statistical significance ($P = .06$ and $P = .07$, respectively). In the multivariate Cox proportional hazards analysis, pre-SRS tumor volume (adjusted HR, 6.2; 95% CI, 1.6-24.0; $P = .008$), a melanoma primary (adjusted HR, 4.9; 95% CI, 1.8-13.6; $P = .002$), and necrosis observed in pre-SRS MRI studies (adjusted HR, 3.1; 95% CI, 1.1-9.1; $P = .04$) were associated with a significantly shorter LPFS.

We further analyzed the characteristics and outcomes of the patients who did not receive any treatment of the brainstem before the SRS procedure. In this patient subgroup, a diagnosis of melanoma, the presence of pre-SRS necrosis, and KPS score were significantly associated with LPFS. Only 8 patients had a tumor volume ≥ 4 mL; probably as a result of this small number, that factor, which had a strong HR of 27.9, had a value of only $P = .20$.

Overall Survival Time

Fifty-five patients (92%) died during the follow-up period. Death was related to systemic disease progression in 39 (71%), progression of other cerebral metastases in 4 (7%), and brainstem lesion progression in 1 (2%). The cause of death was unknown in 11 patients (20%). A diagnosis of leptomeningeal disease is an established strong negative prognostic factor for survival. Given our inability to statistically control for its effect in this sample, we excluded 2 patients from the outcome analysis who developed leptomeningeal disease after undergoing SRS. Among the remaining 58 patients, the median survival time after SRS for a brainstem metastasis was 4.0 months (95% CI, 3.4-4.9 months; Figure 3). The median survival times among patients with various characteristics are listed in Table 4.

We sought to determine factors associated with a shorter survival duration. In the univariate analysis, a brainstem tumor volume of ≥ 4 mL (HR, 4.3; 95% CI, 2.0-9.1; $P < .001$), an SRS dose of < 14 Gy (HR, 2.9; 95% CI, 1.5-5.7; $P = .003$), a KPS score of < 80 (HR, 2.4; 95% CI, 1.2-5.3; $P = .02$), and male sex (HR = 1.8; 95% CI, 1.0-3.2; $P = .05$) were significantly associated with a shorter survival duration. Although there was a difference in median overall survival time between the patients with controlled and uncontrolled primary cancer (5.4 and 2.9 months, respectively), this difference was not statistically significant ($P = .06$). Similarly, there was a difference in median overall survival time between the patients with a breast primary tumor and those with other types of primary tumors (5.4 and 2.9 months, respectively), but the difference did not reach

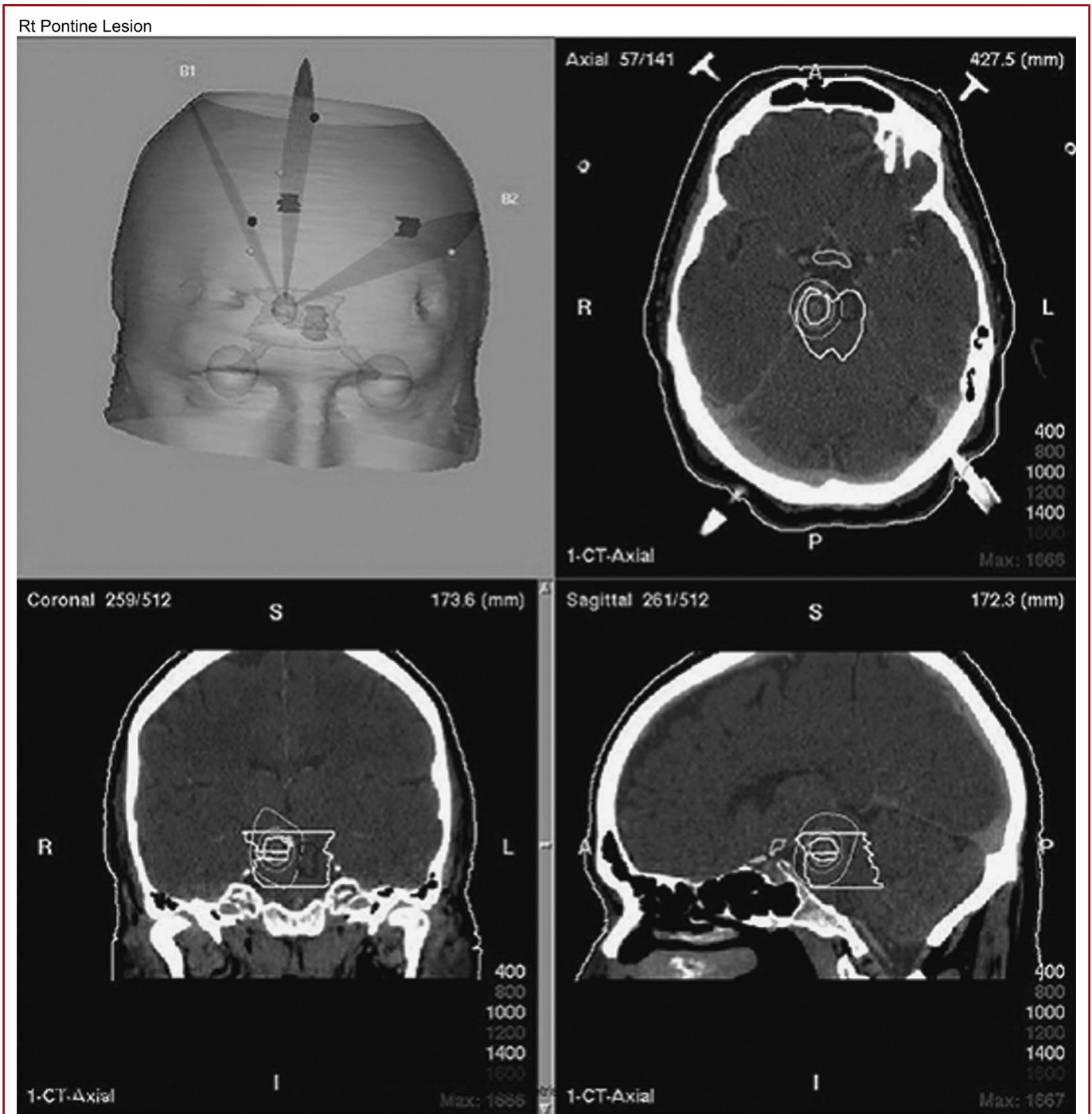


FIGURE 1. Stereotactic radiosurgery planning schema of a metastatic brainstem lesion for a patient with renal cell carcinoma. The treatment dose was 14 Gy to the 84% isodose line using 3 noncoplanar arcs and a 1.5-cm cone.

TABLE 2. Treatments and Outcomes in Patients After Stereotactic Radiosurgery for Brainstem Metastases^a

Treatment or Outcome	Value
Adjuvant WBRT within 30 d of SRS, n (%)	6 (10)
Neurologic condition after SRS, n (%)	
Stable/improved	49 (82)
Worsened	9 (15)
Unknown	2 (3)
Post-SRS complication, n (%) ^b	
Hemiparesis	4 (7)
Nausea/vomiting	4 (7)
Headache	3 (5)
Cranial nerve deficit	2 (3)
Hemorrhage	2 (3)
None	48 (80)
Median imaging follow-up time after SRS (range), mo	5.3 (0.3-27.0)
Local tumor control failure, n (%) ^c	12/49 (24)
Dead at the end of follow-up, n (%)	55 (92)
Cause of death, n (%)	
Systemic cancer	39 (71)
Other brain metastasis	4 (7)
Brainstem metastasis	1 (2)
Unknown	11 (20)
Median follow-up time after SRS (range), mo ^d	12.8 (1.4-32.4)

^aSRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

^bTwelve patients developed an SRS-related complication; 1 patient developed headache and nausea/vomiting, and 1 patient developed a hemorrhage in the treated lesion plus hemiparesis and cranial nerve deficit.

^cEleven patients underwent no post-SRS imaging studies.

^dAmong those alive at the end of the study period.

statistical significance ($P = .09$). No correlation was noted between total number of brain metastases and overall survival time.

In a confirmatory analysis, we compared the characteristics of short-term survivors (patients who survived <2 months; $n = 12$) and long-term survivors (those who survived >12 months; $n = 10$). Although patients with a breast primary tumor showed a trend for longer survival, those with a melanoma primary, uncontrolled primary cancer, a tumor volume ≥ 4 mL, or a KPS score <80 or receiving an SRS dose <14 Gy were more likely to have shorter survival times.

In the multivariate Cox proportional hazards analysis, pre-SRS tumor volume (adjusted HR, 4.6; 95% CI, 2.2-9.7; $P < .001$; Figure 4) and male sex (adjusted HR, 1.9; 95% CI, 1.1-3.4; $P = .03$) were associated with a significantly shorter overall survival interval.

We further analyzed the characteristics and survival of the patients who did not receive any treatment of the brainstem before the SRS procedure and identified the median overall survival time and significant factors associated with survival time. We found that the overall survival time and factors associated with it in this group of patients were consistent with these same parameters in the whole study group (data not shown).

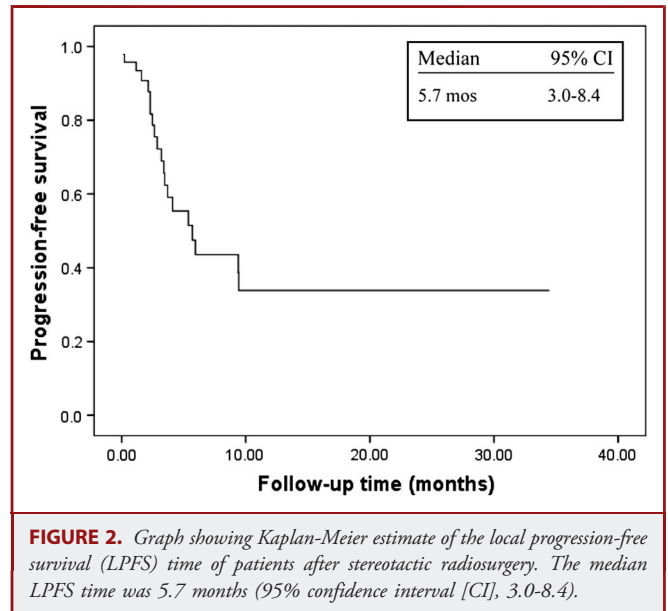


FIGURE 2. Graph showing Kaplan-Meier estimate of the local progression-free survival (LPFS) time of patients after stereotactic radiosurgery. The median LPFS time was 5.7 months (95% confidence interval [CI], 3.0-8.4).

Prognostic Scales

The association between the patients' scores on 4 accepted grading systems and their overall survival times was assessed. Patients with a BSBM of 2 to 3 survived significantly longer than those with a score of 1 (5.4 and 2.3 months, respectively; HR, 2.4; 95% CI, 1.3-4.5; $P = .007$). Similarly, patients who had an SIR of >5 survived significantly longer than those scoring ≤ 5 (5.5 and 2.9 months, respectively; HR, 2.5; 95% CI, 1.4-4.5; $P = .003$; Figure 5A and 5B). The RPA and GPA scoring systems were not found to be significantly associated with survival.

DISCUSSION

Here, we reviewed the patients who received SRS for metastatic brainstem lesions and evaluated the effect of SRS on local tumor control and overall survival duration. We also identified the factors associated with LPFS and overall survival time. We found a significant association between pre-SRS tumor volume and male sex and the overall survival duration. Furthermore, 4 prognostic scales were applied to our brainstem metastasis data set, and the BSBM and SIR scales were found to be strongly prognostic for overall survival. There were too few patients in RPA class 3 to detect a significant difference in survival between them and those in RPA class 1 or 2.

Similar to our results, Shuto et al¹² reported an overall median survival time of 4.9 months in patients with tumors metastatic to the brainstem. Surprisingly, some other studies using SRS for metastatic brainstem lesions have observed median survival times ranging from 8.5 to 12 months, which is longer than is generally expected in patients with brain metastases^{1,8-11,13} (Table 5).

TABLE 3. Univariate Analysis of Characteristics in Patients Undergoing Stereotactic Radiosurgery for Brainstem Metastases in Relation to Local Tumor Progression-Free Survival^a

Characteristic	n	Median		HR	95% CI	P
		Survival, mo	95% CI			
Age at time of SRS				1.0	0.96-1.1	.92
Sex						
Female	23	NR		1.0		
Male	24	3.7	2.2-5.2	2.5	1.0-6.3	.05
Breast primary tumor						
No	37	4.1	1.5-6.7	3.9	0.9-16.7	.07
Yes	10	NR		1.0		
Kidney primary tumor						
No	41	5.7	3.0-8.4	3.2	0.4-25.0	.26
Yes	6	NR		1.0		
Lung primary tumor						
No	34	5.4	0.0-12.6	1.0	0.4-2.6	.98
Yes	13	5.9	3.0-8.9	1.0		
Melanoma primary tumor ^b						
No	34	9.4	ND	1.0		
Yes	13	2.9	2.1-3.6	2.8	1.1-6.9	.03
Tumor location						
Pons	31	5.9	0.0-12.6	1.0		
Medulla	4	5.4	0.5-10.3	1.1	0.25-4.8	.92
Midbrain	12	3.4	ND	1.24	0.4-3.8	.71
Hemorrhage seen on MRI scans						
No	39	5.7	3.0-8.4	1.0		
Yes	8	2.5	1.8-3.1	2.0	0.7-5.9	.24
Edema						
No	25	5.9	ND	1.0		
Yes	22	3.7	0.0-7.5	1.5	0.64-3.7	.34
Necrosis ^b						
No	33	9.4	ND	1.0		
Yes	14	3.5	2.6-4.3	2.8	1.1-7.1	.03
Other intracranial metastases seen at time of SRS						
No	18	9.4	ND	1.0		
Yes	29	3.7	2.6-4.8	2.6	1.0-6.8	.06
Brainstem lesion symptoms at time of SRS						
No	14	5.4	0.0-11.6	1.2	0.4-3.2	.78
Yes	33	5.7	2.8-8.6	1.0		
Activity of primary cancer						
Controlled	37	5.4	3.0-7.8	1.2	0.34-4.0	.8
Uncontrolled	10	9.4	0.0-22.4	1.0		
Extracranial metastasis						
No	16	5.7	2.7-8.7	1.3	0.52-3.2	.58
Yes	31	9.4	0.0-20.1	1.0		
Brainstem tumor volume, mL ^b						
<4	40	5.9	0.4-11.4	1.00		
≥4	7	2.3	0.0-5.3	6.1	1.8-20.5	.003
KPS score						
<80	7	2.3	1.2-3.4	2.9	0.96-9.1	.06
≥80	40	5.7	0.35-11.1	1.0		
Pre-SRS WBRT						
No	31	5.7	2.3-9.2	1.0		
Yes	16	5.4	2.6-8.2	1.2	0.44-3.1	.77
Pre-SRS WBRT for brainstem metastasis						
No	41	5.4	2.9-7.8	3.2	0.4-25.0	.26
Yes	6	9.4	ND	1.0		

(Continues)

TABLE 3. Continued

Characteristic	n	Median		HR	95% CI	P
		Survival, mo	95% CI			
Adjuvant WBRT						
No	41	5.7	3.1-8.3	1.3	0.3-5.9	.71
Yes	6	NR		1.0		
SRS dose, Gy						
<14	6	2.3	2.0-2.6	3.8	1.0-14.1	.049
≥14	41	5.9	0.4-11.4	1.0		

^aCI, confidence interval; HR, hazard ratio; KPS, Karnofsky Performance Scale; MRI, magnetic resonance imaging; ND, not defined; NR, not reached; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

^bPre-SRS tumor volume (adjusted HR, 6.2; 95% CI, 1.6-24.0; $P = .008$), the presence of a melanoma primary (adjusted HR, 4.9; 95% CI, 1.8-13.6; $P = .002$), and the observation of necrosis on pre-SRS MRI scans (adjusted HR, 3.1; 95% CI, 1.1-9.1; $P = .04$) were associated with local tumor progression-free survival time in the multivariate analysis after adjustment for other variables.

These studies also differ from ours with respect to factors considered to be associated with survival, although the average values of a patient's age, KPS score, tumor volume, and SRS dose are close across studies. Nevertheless, patient selection criteria with respect to the status of a patient's primary tumor control and extracranial systemic disease, both ill defined in earlier studies, may play an important role in these differences. The rate of active extracranial disease and uncontrolled primary cancer is presumably higher in our study. The small sizes of series of patients with brainstem metastases may also explain some of these differences.

The crude local tumor control rate in our study was consistent with that achieved for brain metastases in other locations.^{5,18,20,21} Although Shuto et al¹² reported a local control rate (77%) similar

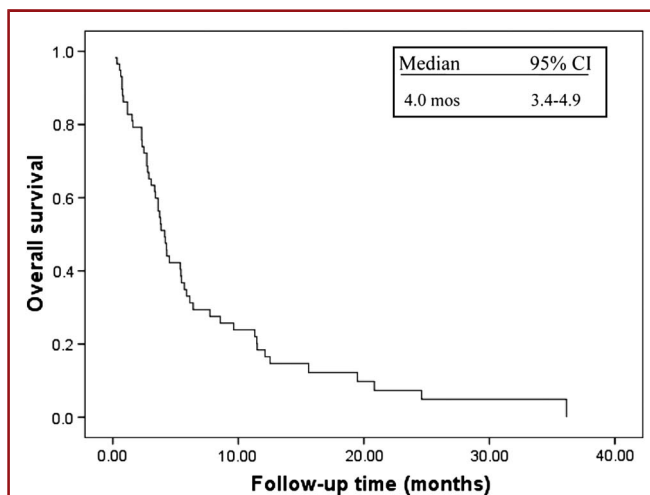


FIGURE 3. Graph showing Kaplan-Meier estimate of overall survival duration of patients after stereotactic radiosurgery. The median overall survival time was 4.0 months (95% confidence interval [CI], 3.4-4.9).

TABLE 4. Analysis of Characteristics Prognostic for Overall Survival in Patients Undergoing Stereotactic Radiosurgery for Brainstem Metastases^a

Characteristic	n	Median		HR	95% CI	P
		Survival, mo	95% CI			
Age at SRS				1.0	1.0-1.0	.99
Sex ^b						
Female	27	5.7	3.0-8.45	1.0		
Male	31	3.7	2.1-5.3	1.8	1.0-3.2	.05
Breast primary tumor						
No	48	3.8	2.6-5.0	1.9	0.9-3.9	.09
Yes	10	9.6	0.0-21.2	1.0		
Kidney primary tumor						
No	51	3.8	3.1-4.6	1.8	0.7-4.6	.21
Yes	7	5.5	2.4-8.6	1.0		
Lung primary tumor						
No	39	4.3	1.7-6.9	1.0		
Yes	19	4.1	3.3-5.0	1.2	0.7-2.1	.62
Melanoma primary tumor						
No	44	4.1	3.4-4.9	1.0		
Yes	14	3.7	1.0-6.5	1.4	0.71-2.7	.35
Tumor location						
Pons	38	4.3	2.4-6.2	1.0		
Medulla	6	2.3	1.0-3.6	1.7	0.7-4.0	.25
Midbrain	14	3.6	2.2-5.0	1.4	0.74-2.7	.30
Hemorrhage seen on MRI before SRS						
No	50	4.2	2.3-6.0	1.0		
Yes	8	3.6	2.5-4.7	1.3	0.6-2.9	.52
Edema						
No	34	3.8	2.9-4.7	1.0	0.6-1.8	.89
Yes	24	4.3	3.2-5.4	1.0		
Necrosis						
No	40	4.2	2.2-6.1	1.0		
Yes	18	2.9	0.0-5.7	1.5	0.84-2.8	.17
Newly diagnosed previously untreated brainstem metastasis						
No	29	4.3	3.5-5.0	1.2	0.7-2.0	.63
Yes	29	3.8	2.0-5.7	1.0		
Other intracranial metastases at the time of SRS						
No	24	3.8	1.3-6.4	1.2	0.7-2.1	.54
Yes	34	4.2	3.2-5.2	1.0		
Brainstem lesion symptoms at the time of SRS						
No	16	2.9	1.0-4.8	1.3	0.64-2.4	.52
Yes	42	4.1	3.5-4.7	1.0		
Activity of primary cancer						
Controlled	45	5.4	3.6-7.1	1.0		
Uncontrolled	13	2.9	0.5-5.2	1.8	1.0-3.4	.06
Extracranial metastasis						
No	19	5.4	2.2-8.6	1.0		
Yes	39	3.8	3.0-4.7	1.1	0.6-1.9	.84
Brainstem tumor volume, mL ^b						
<4	47	5.4	3.8-7.1	1.0		
≥4	11	2.3	0.7-3.9	4.3	2.1-9.1	<.001
KPS score						
<80	10	2.3	1.7-3.0	2.4	1.2-5.3	.02
≥80	48	4.3	2.9-5.8	1.0		
WBRT before SRS						
No	38	3.8	0.7-7.0	1.34	0.74-2.4	.34
Yes	20	4.2	3.4-4.9	1.0		

(Continues)

TABLE 4. Continued

Characteristic	n	Median		HR	95% CI	P
		Survival, mo	95% CI			
WBRT for brainstem metastases before SRS						
No	49	3.8	3.1-4.6	1.0	0.5-2.3	.98
Yes	9	4.3	0.0-8.7	1.0		
Adjuvant WBRT						
No	52	4.1	3.5-4.8	1.0		
Yes	6	3.4	0.0-7.0	1.5	0.6-4.0	.36
SRS dose, Gy						
<14	12	2.3	0.3-4.3	2.9	1.45-5.7	.003
≥14	46	5.4	3.7-7.0	1.0		

^aCI, confidence interval; HR, hazard ratio; KPS, Karnofsky Performance Scale; MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

^bPre-SRS tumor volume (adjusted HR, 4.63; 95% CI, 2.2-9.74; $P < .001$) and male sex (adjusted HR, 1.92; 95% CI, 1.1-3.44; $P = .03$) were significantly correlated with overall survival in the multivariate analysis after adjustment for other variables.

to ours, most previous series show higher rates (range, 85% to 100%). We defined treatment failure as a >25% increase in tumor volume compared with the pre-SRS volume. Use of the definition of a >25% increase in tumor volume could certainly lead to “worse local control” outcomes because other investigators may be inclined to consider increased volume as a treatment-associated effect rather than a failure. There is no uniform standard system in the literature to score tumor control failures after radiosurgery.

Only Kased et al⁹ described the factors associated with LPFS. In that report, the LPFS rate was 90% at 6 months and 77% at 1 year, with the median PFS time not being reached. The authors found that a melanoma primary and an SRS dose of <16 Gy were associated with LPFS. A melanoma primary was found to be a significant predictor of a shorter LPFS time in both the study of Kased et al and the present study. In the study by Kased et al, relatively smaller lesions (median, 0.26 mL) were selected for the SRS procedure. We also found that the presence of necrosis on pre-SRS MRI scans, which has not been evaluated in other studies, was a prognostic factor for shorter LPFS.

Some authors have prescribed mean or median radiosurgical dosages ranging between 13 and 17.6 Gy for metastatic brainstem tumors.^{1,9-12,14} Fuentes et al⁸ and Lorenzoni et al¹³ used higher mean prescribed doses (19.6 and 20 Gy, respectively). There was no significant difference between the 2 groups of studies (low vs high doses) in terms of survival time or local control rate. Thus, the optimal radiation dose for brainstem metastasis treatment remains unclear.

Patients who underwent surgical resection of a brainstem metastasis were not assessed in this study. Patients with brainstem metastasis are evaluated for surgical resection if the lesion is large, if it is in a surgically accessible location, if they have controlled systemic disease and good Karnofsky performance status, and if they are not candidates for SRS treatment. Given the high risk of

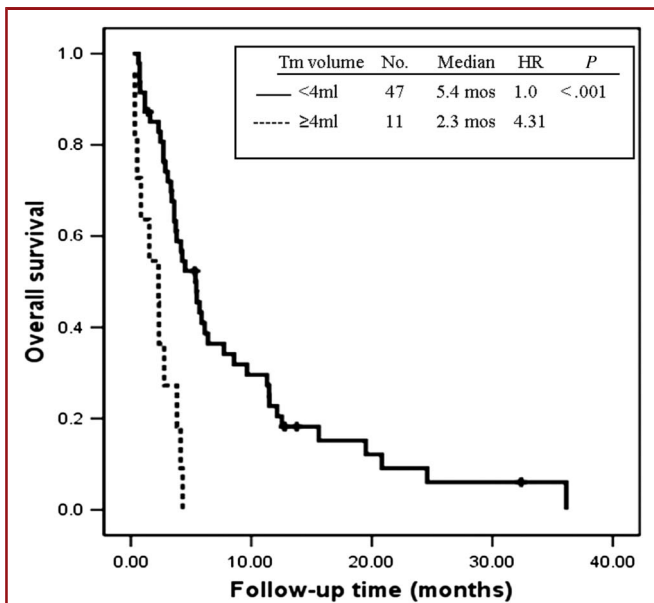


FIGURE 4. Graph showing Kaplan-Meier estimates of overall survival time in relation to brainstem lesion volume. The median survival time was 5.4 months for patients with a tumor (Tm) volume <4 mL and 2.3 months for patients with a tumor volume ≥4 mL (adjusted hazard ratio [HR], 4.3; 95% confidence interval, 2.2-9.7; P < .001).

morbidity and mortality with surgical resection of a metastasis in the brainstem, we tend to treat these lesions with noninvasive options such as SRS. We treated 5 patients with surgical resection for a brainstem lesion during the study period. These patients underwent surgical resection because their lesions were large, exerting mass effect, and surgically accessible. In addition, 4 of these 5 patients underwent surgical resection before 2000, when the efficacy of SRS was not well established. None of the patients who received SRS underwent surgical resection before or after the SRS treatment.

Our reporting of complications of SRS was detailed in this study, and we found an overall complication rate of 20%. This differs from previous studies evaluating brainstem metastases treated with SRS, which have presented lower complication rates or no complications (3 studies).^{8,10,18} This difference may stem from the definition of complication, which was not uniform in various studies; eg, conditions we considered to be complications such as headache and nausea/vomiting were not included as a complication in the earlier series on brainstem metastases. The study of patients with brainstem astrocytomas and vascular malformations by Sharma et al,²² who evaluated radiation safety tolerance limits of the brainstem, noted a new neurological deficit rate of 18.4% related to the SRS treatment. Moreover, their analysis showed that new neurological deficits did not correlate with a marginal dose of >14 Gy, equivalent to the threshold SRS prescription dose for favorable LPFS and overall survival duration

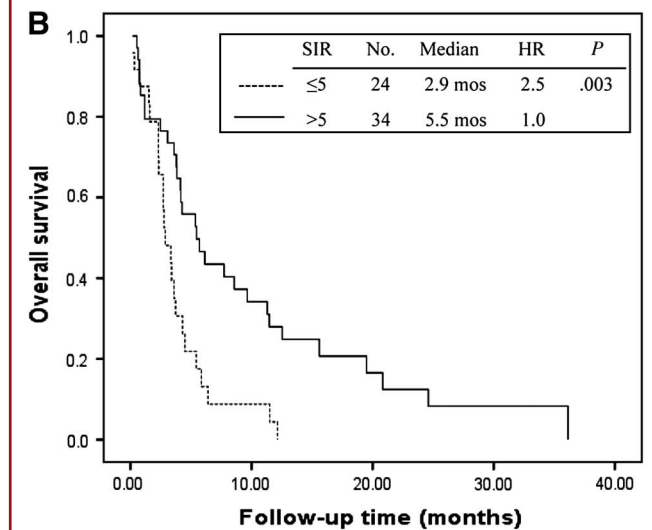
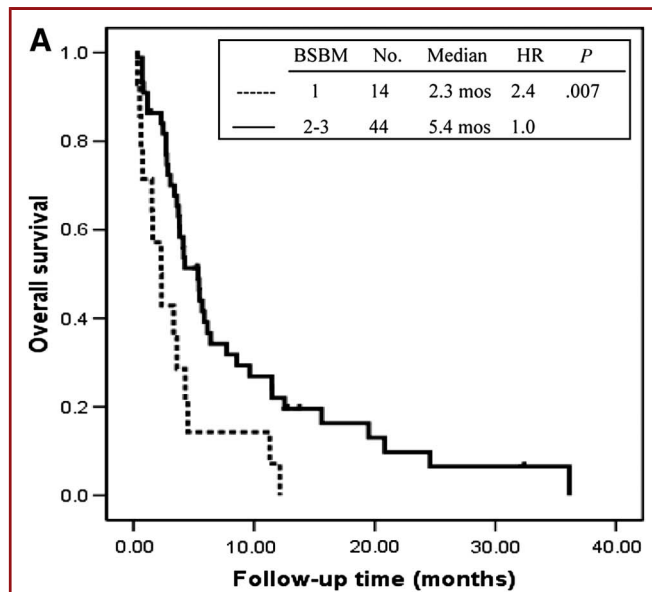


FIGURE 5. A, graph showing Kaplan-Meier estimates of overall survival time in relation to the Basic Score for Brain Metastases (BSBM) in patients after stereotactic radiosurgery. The median overall survival time was 5.4 months for patients with a BSBM of 2 to 3 and 2.3 months for patients with a BSBM of 1 (hazard ratio [HR], 2.4; 95% confidence interval, 1.3-4.5; P = .007). **B,** graph showing Kaplan-Meier estimates of overall survival time in relation to the Score Index for Radiosurgery (SIR) in patients after stereotactic radiosurgery. The median overall survival time was 5.5 months for patients with an SIR >5 and 2.9 months for patients with an SIR ≤5 (HR, 2.5; 95% confidence interval, 1.4-4.5; P = .003).

in our study. Furthermore, the complication rate in our study is consistent with their findings. In addition, it is unlikely that CT-based planning contributed to the complication rate because lesions were generally well delineated on CT and on fused MRI

TABLE 5. Studies of Patients With Brainstem Metastasis Treated With Radiosurgery^a

Study	Patients, n	Median Age, y	Median Tumor Volume, mL	Median Prescribed SRS Dose, Gy	Median Survival, mo	Median PFS, mo	Local Tumor Control, % ^b	Factors Associated With Shorter Survival	Factors Associated With Poor PFS	Complication Rate, %
Huang et al ¹	26	56 (mean)	1.1 (mean)	16	9	N/A	95	Presence of active extracranial disease	N/A	27
Shuto et al ¹²	25	57.1 (mean)	2.1 (mean)	13 (mean)	4.9	N/A	77	N/A	N/A	8
Fuentes et al ⁸	28	57.7 (mean)	2.1 (mean)	19.6 (mean)	12 (median), 10.2 (mean)	N/A	92	N/A	N/A	0
Yen et al ¹⁰	53	57.3 (mean)	2.8 (mean)	17.6 (mean)	11	N/A	87	Presence of active extracranial disease	N/A	0
Hussain et al ¹¹	22	60	0.9	16	8.5	N/A	100	N/A	N/A	5
Kased et al ⁹	42	55	0.26	16	9	N/A	85	Multiple metastasis, melanoma primary	Melanoma primary and SRS dose <16 Gy	9.5
Lorenzoni et al ¹⁸	25	54 (mean)	0.6	20 (mean)	11.1	N/A	95	KPS score <80, uncontrolled primary tumor, radiation therapy, SRS ≥18 Gy	N/A	0
Koyfman et al ¹⁴	43	59	0.37	15	5.8	N/A	85	Lower KPS score, larger tumor volume, SIR, GPA	N/A	12
Present study	60	61	1.0	15	4.2	5.7	76	Tumor volume ≥4 mL, male sex	Tumor volume ≥4 mL, melanoma primary, necrosis in pre-SRS MRI	20

^aGPA, Graded Prognostic Assessment; KPS, Karnofsky Performance Scale; MRI, magnetic resonance imaging; N/A, not available; PFS, progression-free survival; SIR, score index for radiosurgery; SRS, stereotactic radiosurgery.

^bThe definitions of treatment response (local tumor control) are not uniform in the published literature. In the present study, we considered an increase in tumor volume of >25% relative to pre-SRS tumor volume to be local treatment failure.

scans. Currently, we have switched to MRI-based planning since the implementation of Gamma Knife PFXN at MD Anderson.

We have also evaluated the ability of 4 validated stratification systems to predict overall survival time in our patient group. However, our study is limited by its retrospective nature despite prospective data components and by inadequate power despite its relatively larger size. Therefore, our results may not be conclusive, and they should be confirmed in a larger prospective study. Because sample sizes in all brainstem metastasis series are small, pooled analyses among multiple institutions may be necessary to best assess outcomes, prognostic factors, and the ability of grading systems to predict outcomes in patients undergoing SRS for brainstem metastases.

CONCLUSION

Patients with tumors metastatic to the brainstem have a poor prognosis, but SRS provides a noninvasive treatment option and

local tumor control. We have identified prognostic factors for LPFS and overall survival in patients with these lesions. Our findings, in addition to earlier studies on the issue, should be of assistance in the selection of appropriate candidates for treatment of brainstem metastases with SRS.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

In their article, Dr Hatiboglu and colleagues report their experience with linear accelerator–based radiosurgery for the treatment of patients

with brainstem metastasis. They observed an overall local tumor control rate of 76%. Median survival after radiosurgery was 4 months. Twenty percent of patients had radiosurgery-induced complications.

Overall, the authors appear to have used radiosurgery as an upfront treatment for the vast majority of patients with brainstem metastasis at their center. In particular, they cite “the high risks of morbidity and mortality with surgical resection of a metastasis in the brainstem” and the fact “that patients treated with brain metastases with SRS had better neurocognitive outcomes than those treated with WBRT” as justification for the use of radiosurgery in this cohort of brain metastasis patients. Such a treatment paradigm for brainstem metastasis is particularly compelling coming from the MD Anderson group, which is well known for advocating resection for selected patients with brain metastases.^{1,2} The group’s treatment algorithm and findings for brainstem metastasis patients largely mirror those at the University of Virginia.³

In patients with brainstem metastasis, stereotactic radiosurgery should represent the primary treatment for the vast majority of patients. The relative risks and benefits of radiosurgery, whole-brain radiotherapy, and resection are unlikely to ever be rigorously evaluated in a randomized clinical trial of brainstem metastasis patients. Nevertheless, intuitively, radiosurgery is a very appealing approach for these patients. After all, the brainstem is eloquent brain tissue, and in the modern era with ready access to magnetic resonance imaging, brainstem metastases, even if they are symptomatic, are usually small in volume at the time of diagnosis.

Dose planning for such cases requires meticulous attention to detail. The addition of diffusion tensor imaging may be of benefit over standard plans generated with stereotactic magnetic resonance and computed tomography imaging alone. Beyond the traditional dose-volume constraints with radiosurgery, there is a differential radiosensitivity of brainstem tissue dependent on the patient’s age, tumor pathology, comorbidities, and adjacent neuroanatomic structures (eg, tracts and brainstem nuclei). Such factors must be considered when devising the dose plan, thereby striving to achieve delivery of an ideal and conformal dose to the target but also an optimal dose falloff to surrounding brainstem, cranial nerve, and adjacent cerebrovascular structures.⁴ In particular, delivering more dose to the clivus for ventral brainstem metastasis or to the fourth ventricle for dorsal lesions might be preferable than a uniform dose falloff in all directions.

The authors are to be commended for this comprehensive report. It confirms the importance of radiosurgery in the management of patients with brainstem metastasis.

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