

Gamma Knife radiosurgery for brainstem metastases: the UCSF experience

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Received: 29 May 2007 / Accepted: 25 June 2007
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Abstract *Purpose:* To assess clinical and imaging outcomes in patients treated with Gamma Knife stereotactic radiosurgery (SRS) for brainstem metastases. *Materials and methods:* We reviewed all patients with brain metastases treated with SRS at the University of California, San Francisco from 1991–2005 to identify patients who had SRS to a brainstem metastasis. Survival time and freedom from progression (FFP) were calculated from date of SRS using the Kaplan–Meier method. Prognostic factors were evaluated using the log-rank test and Cox proportional hazards model. *Results:* From 1991 through 2005, 42 consecutive patients with brainstem metastases had SRS to 44 lesions (seven midbrain, 31 pontine, and six medullary) in 42 sessions. Primary diagnoses included 14 cases of lung cancer (one small-cell), 10 melanoma, 12 breast cancer, five renal cell, and one unknown. The median age was 55 years (range, 25–79). The median survival time was 9 months after SRS. Longer survival time was associated with single metastasis, non-melanoma histology, and extracranial disease control. The median target volume was 0.26 ml (0.015–2.8 ml) and the median prescribed dose was 16.0 Gy (10.0–19.8 Gy). Brainstem lesion FFP was

90% at 6 months and 77% at 1 year. Four patients had brainstem complications following treatment. Poor brainstem outcome was associated with melanoma and renal cell histology as well as brainstem lesion volume ≥ 1 ml. *Conclusions:* In this series, SRS using a median dose of 16 Gy provided excellent local control with relatively low morbidity in patients with brainstem metastases less than 1 ml or non-melanoma, non-renal cell histology.

Keywords Brain metastasis · Brainstem · Gamma Knife · Stereotactic radiosurgery

Introduction

Brain metastases occur relatively frequently in the setting of systemic malignancy. One autopsy series from the Memorial Sloan Kettering Cancer Center found that 15% of cancer patients had brain metastases and 24% had central nervous system metastases [1]. Indeed, brain metastases are more common than primary brain tumors in adults [2]. Various authors have also reported population-based incidences of brain metastases. In one population-based study conducted in the Netherlands, Schouten et al. reported that within a cohort of 2,724 patients with melanoma, lung, breast, colorectal, or renal cell carcinoma, 8.5% developed brain metastases [3]. The 5-year cumulative incidence of brain metastases was 16.3% in patients with lung cancer, 9.8% in patients with renal cell carcinoma, 7.4% in patients with melanoma, and 5.0% and 1.2% for patients with breast or colorectal carcinoma, respectively. Another group calculated the population-based incidence of brain metastasis for cancer patients diagnosed from 1973 to 2001 within the Metropolitan Detroit Cancer Surveillance System [4]. In this cohort, 9.6% of all lung,

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renal, melanoma, breast, and colorectal cancer patients developed brain metastasis, representing a total of 16,210 new cases. The primary sites with the highest rates of brain metastases were lung (19.9%) and melanoma (6.9%) while 6.5% of renal, 5.1% of breast and 1.8% of colorectal cancer patients developed brain metastases.

Metastasis to the brainstem is relatively uncommon, comprising only 5–7% of brain metastases [5, 6]. Surgical management of these lesions is difficult because of the critical surrounding anatomical structures. While the benefits of whole-brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) for brain metastases are well-established [7–13], the role of these treatment modalities in the management of metastases to the brainstem is less clear. There have been relatively few studies examining brainstem metastasis treated with SRS [14–18]. This study sought to assess clinical and imaging outcomes in patients treated with Gamma Knife SRS for brainstem metastasis at the University of California, San Francisco to better characterize management and outcome issues.

Methods and materials

Patient data collection

We retrospectively reviewed our database of patients who underwent SRS from 1991 through 2005 and searched for patients who were treated for brainstem metastasis. We recorded patient and lesion characteristics and treatment parameters. The study was approved by our institutional review board.

Radiosurgery technique

All patients underwent SRS using the Gamma Knife (Elekta Instruments, Atlanta, GA) [19, 20]. After administration of local anesthesia, the stereotactic head frame was applied and imaging was performed on the day of SRS. Until mid-1992, patients underwent both computed tomography and single-dose gadolinium-enhanced magnetic resonance imaging (MRI), to verify the spatial accuracy of MRI. From mid-1992 to mid-1994, all dose planning and target delineation was conducted using MRI with contiguous 3 mm thick transverse sections. From mid-1994 onward, triple-dose gadolinium-enhanced MRI was used. After target delineation by the radiation oncologist and neurosurgeon, the physicist placed one or more isocenters as needed to create isodose contours conforming to each target using GammaPlan treatment planning software (Elekta, Stockholm). The SRS prescription dose was chosen at the discretion of the treating physicians. A single dose of dexamethasone (10 mg) was given intravenously

on the day of SRS, and patients were discharged home within an hour after SRS. Patients who had been on steroids prior to SRS were given steroid taper schedules.

Treatment response and follow-up

Patients were followed with serial imaging (contrast-enhanced MRI at 3 month intervals) when possible, and with periodic clinical examination. Lesions were measured on each MRI scan in the transverse, anterior–posterior, and vertical dimensions and the product of these three diameters was used to track relative changes in tumor volume. Tumor response of the brainstem lesions was determined using pre- and post-SRS MRI scans and was defined as no response (NR) (no change in tumor volume or less than 50% reduction in volume compared with pre-SRS volume), partial response (PR) ($\geq 50\%$ reduction in tumor volume but not complete resolution of the lesion), and complete response (CR) (complete resolution of brainstem lesion). A treatment failure (TF) was defined as $\geq 25\%$ increase in tumor volume of the brainstem lesion when compared with any prior scan, except in cases considered to be radiation necrosis or hemorrhage. Local control was defined as either NR, PR, or CR. Prior to SRS and at each subsequent clinical visit during follow-up, the patient's neurological symptoms and Karnofsky performance status (KPS) were assessed and recorded. Dates of last clinical follow-up, last imaging follow-up, and dates of death were also recorded.

In patients with lesions for which there was diagnostic uncertainty regarding radiation necrosis vs. tumor progression on follow-up MRI scans, ancillary tests were performed at the discretion of the treating physician. These included positron emission tomography (PET), MR perfusion studies, and MR spectroscopy. Operative resection was not attempted for any patient.

Designated endpoints and statistical analysis

All statistical analysis was performed using Stata software (Stata Corporation, College Station, Texas). The main endpoints of analysis were survival time, brainstem lesion freedom from progression (FFP), and freedom from brainstem complications or poor brainstem outcomes calculated from the date of SRS for brainstem metastasis using the Kaplan–Meier method. Duration times in months were calculated by dividing the number of elapsed days by 30.4375 (the average number of days in a month including leap years: 365.25 days/year divided by 12 months/year). Patients were censored at the time of last clinical follow-up for estimating survival time and freedom from complications or poor outcomes and lesions were censored at the time of last imaging follow-up for estimating lesion FFP. The scoring of tumor progression was unclear in one pa-

tient with hemorrhage of a melanoma brainstem metastasis 1.6 months after SRS (Patient 27 from Table 1) and in one patient with lesion growth 4.8 months after SRS secondary to radiation necrosis vs. tumor recurrence (Patient 3). Thus, two analyses of lesion FFP were performed: one used the conservative assumption that both of these cases had tumor progression and the other analysis scored neither of these cases as tumor progression.

In the complications analysis, two categories of patients were assessed: the first, designated “brainstem complications,” included all patients who developed symptoms from brainstem lesion hemorrhage or necrosis after SRS; the second, designated as “poor brainstem outcomes,” included all patients who developed symptomatic brainstem lesion necrosis or hemorrhage as well as patients thought to have symptomatic or asymptomatic tumor progression. This second category was created and analyzed because it was thought to be clinically relevant.

Univariate analyses were performed using the log rank test and multivariate analyses were performed using the Cox proportional hazards model. Primary site, age (<65 years vs. ≥65 years), KPS (<70 vs. ≥70), single vs. multiple brain metastases, newly-diagnosed vs. recurrent brain metastases, and active vs. absent or controlled extracranial disease were assessed for influence on survival. In terms of FFP and SRS-related complications, the following factors were assessed for prognostic value: prescribed dose, tumor volume, adjuvant WBRT, and primary site.

Results

Patient characteristics

From 1991 through 2005, 882 consecutive patients underwent SRS for brain metastasis. Of these, 42 patients (4.8%) had SRS for metastasis in the brainstem. The characteristics of these patients are summarized in Table 1. The median age at the time of SRS for a brainstem metastasis was 55 years (range, 25–79 years) with the patients having a median KPS of 90 (range, 40–90). Eight patients (19%) were RPA class 1, 31 RPA class 2 (74%), and three RPA class 3 at the time of SRS. Seventeen patients had SRS alone, five had SRS boost with WBRT, 19 had SRS for recurrence after prior WBRT, and one had SRS for new brainstem metastasis after prior resection of a non-brainstem metastasis. Thirty-one lesions (70%) were in the pons, seven were in the midbrain (16%), and six were in the medulla (14%). The primary malignancy was non-small-cell lung cancer in 13 patients (31%), breast cancer in 12 patients (29%), melanoma in 10 patients (24%), renal cell carcinoma in five patients (12%), small-cell lung cancer in one patient, and unknown in one patient. Only five patients

had a single brain metastasis, while the remaining 37 patients had multiple brain metastases at the time of SRS. One patient (Patient 20) had three brainstem lesions treated in one SRS session and the remainder of the patients had a single metastatic brainstem lesion treated.

Radiosurgical dosing

The median brainstem target volume was 0.26 ml (range, 0.015–2.8 ml) while the median brainstem treated volume was 0.44 ml (0.014–3.0 ml). The median maximum brainstem tumor diameter was 0.9 cm (0.4–2.1 cm). The median prescribed dose was 16.0 Gy (10.0–19.8 Gy) treated at the 39–90% (median 50%) isodose contour. The median maximal tumor dose was 31.4 Gy (17.8–40.0 Gy) using 1–11 isocenters (median, two isocenters) per lesion. Most brainstem lesions were treated using the 4-mm collimator and/or the 8-mm collimator.

Survival time

The median survival time after SRS for a brainstem metastasis was 9 months with a 1-year survival probability of 31%. To date, 37 patients are known to have expired. The cause of death was known for 19 patients; 12 patients died from systemic disease progression, six from distant intracranial progression, and one from progression of the brainstem metastases. Four patients were lost to follow-up <1, 1.1, 8.1, and 10.6 months after SRS. One patient is known to be alive and her brainstem lesion continues to remain in complete response 28.4 months after SRS (Fig. 1) with subsequent WBRT for suspicion of leptomeningeal disease. The median survival time for patients who were RPA class I was 9.9 months, while for RPA class II patients it was 8.3 months. The three patients who were RPA class III had survival times of 1.5 months, 1.1 month (patient was lost to follow-up), and 28.4 months (patient still alive). The differences in survival among the different RPA classes were not significant ($P = 0.42$). Univariate analyses demonstrated that longer survival time was significantly associated with single metastasis or with extracranial disease control, and that there was a trend toward longer survival time with non-melanoma histology. The median survival times were 29.8 months among five patients with a single metastasis vs. 7.4 months for 37 patients with multiple metastases (log-rank $P = 0.002$) (Fig. 2), 10.1 vs. 6.6 months for patients with controlled vs. active extracranial disease (log-rank $P = 0.029$), and 9.7 vs. 4.9 months for non-melanoma vs. melanoma histology (log-rank $P = 0.071$) (Fig. 3). The median survival from the date of SRS for brainstem metastases was 10.9 months for patients treated with SRS alone for the initial management of newly-diagnosed brain metastases,

Table 1 Patient and brainstem lesion characteristics and treatment parameters

Patient	Age (years)	Gender	Primary	RPA class	SRS setting	Total # of mets	Brainstem lesion location	Brainstem lesion treatment volume (ml)	Brainstem lesion maximum diameter (cm)	SRS dose (Gy)	Response on last imaging	Living status: survival time (mo)
1	38	F	Unknown	1	Boost	8	Pons	3.0	1.8	15.0	NR	Dead; 9.3
2	46	F	Breast	1	Boost	1	Medulla	0.20	0.5	16.0	CR	Dead; 29.8
3	30	M	Melanoma	1	Alone	1	Pons	1.7	1.3	18.5	Necrosis vs. failure	Dead; 15.1
4	40	M	Melanoma	3	Alone	2	Pons	0.22	0.8	15.0	Died before f/u imaging	Dead; 1.5
5	45	F	Breast	2	RecurX	6	Medulla	0.5	0.7	18.4	PR	Dead; 9.0
6	66	M	Melanoma	2	Alone	1	Midbrain	0.45	0.8	19.0	Failure	Dead; 23.4
7	51	F	Breast	2	RecurX	3	Pons	1.0	1.1	17.0	No imaging f/u	Dead; 6.6
8	48	M	Lung	2	Boost	5	Pons	0.26	0.6	18.0	PR	Dead; 17.5
9	40	F	Breast	2	RecurX	4	Pons	– ^a	0.4	19.8	No imaging f/u	Dead; 6.3
10	39	M	Melanoma	2	Boost	8	Pons	0.09	0.4	18.0	PR	Dead; 5.2
11	40	F	Lung	2	RecurX	2	Midbrain	2.7	1.6	15.0	Died before f/u imaging	Dead; 0.5
12	60	F	Lung	2	RecurX	1	Pons	0.76	1.1	14.0	No imaging f/u	Dead; 30.3
13	48	F	Lung	2	Boost	3	Pons	2.0	1.5	14.0	PR	Dead; 6.5
14	67	M	Kidney	2	RecurX	4	Pons	1.0	0.8	16.0	No imaging f/u	Dead; 6.3
15	60	F	Breast	2	RecurX	16	Midbrain	– ^a	0.8	15.1	NR	Dead; 7.0
16	64	M	Lung	2	RecurX	4	Pons	0.65	0.8	16.0	NR	Dead; 6.4
17	64	M	Lung	1	RecurX	2	Pons	0.85	1.0	14.0	PR	Dead; 9.9
18	55	M	Melanoma	2	Alone	4	Pons	0.06	0.4	18.0	Died before f/u imaging	Dead; 0.4
19	59	M	Kidney	2	Alone	2	Pons	1.3	1.4	16.0	Hemorrhage	Dead; 15.4
20	63	M	Lung	1	RecurX	9	Pons	0.05	0.4	13.0	Died before f/u	Dead; 3.4
							Pons	0.05	0.5	15.0	imaging	
							Pons	0.38	1.0	15.0		
21	64	M	Melanoma	2	RecurX	3	Pons	0.57	1.0	16.0	No imaging f/u	Dead; 10.1
22	36	F	Breast	2	RecurX	9	Medulla	0.36	0.7	10.0	No imaging f/u	Dead; 5.8
23	55	M	Kidney	3	Alone	2	Medulla	0.63	1.0	17.5	No imaging f/u	Unknown; 1.1 ^b
24	57	F	Lung	3	Alone	4	Pons	0.12	0.6	16.0	CR	Alive; 28.4
25	25	F	Breast	2	RecurX	19	Medulla	– ^a	0.9	16.0	PR	Dead; 12.2
26	65	F	Kidney	2	Alone	1	Pons	0.88	1.1	16.0	PR	Unknown; 10.6 ^b
27	30	M	Melanoma	2	RecurS	11	Pons	0.23	0.3	18.5	Hemorrhage vs. failure	Dead; 2.4
28	52	F	Kidney	2	Alone	3	Pons	2.1	1.6	12.0	Failure	Dead; 14.8
29	59	F	Breast	2	Alone	7	Pons	0.11	0.4	18.0	CR	Unknown; 8.2 ^b
30	59	F	Breast	2	Alone	13	Midbrain	– ^a	0.5	14.0	CR	Dead; 8.3
31	56	F	Lung	1	RecurX	14	Medulla	0.14	0.4	15.0	NR	Dead; 7.4

Table 1 continued

Patient	Age (years)	Gender	Primary	RPA class	SRS setting	Total # of mets	Brainstem lesion location	Brainstem lesion treatment volume (ml)	Brainstem lesion maximum diameter (cm)	SRS dose (Gy)	Response on last imaging	Living status: survival time (mo)
32	43	F	Breast	2	RecurX	6	Pons	0.57	1.0	15.0	No imaging f/u	Unknown; 0.1 ^b
33	43	F	Breast	2	RecurX	5	Pons	0.14	0.7	16.0	PR	Dead; 11.9
34	54	M	Lung	2	RecurX	5	Pons	0.16	0.6	16.0	PR	Dead; 9.7
35	77	M	Melanoma	2	Alone	10	Pons	0.14	0.6	16.0	Died before f/u imaging	Dead; 4.3
36	79	M	Melanoma	2	Alone	3	Pons	0.16	0.7	16.0	Died before f/u imaging	Dead; 2.4
37	57	M	Lung	1	Alone	4	Midbrain	0.46	1.1	16.0	PR	Dead; 9.9
38	34	M	Lung	2	Alone	2	Pons	0.24	0.7	15.0	NR	Dead; 10.9
39	60	F	Breast	2	Alone	7	Midbrain	0.01	0.3	16.0	CR	Dead; 12.4
40	58	F	Lung	2	RecurX	6	Midbrain	0.14	0.6	18.0	NR	Dead; 1.7
41	62	F	Lung	1	RecurX	10	Pons	0.44	1.2	16.0	CR	Dead; 20.1
42	77	M	Melanoma	2	Alone	2	Pons	0.68	1.1	15.0	No imaging f/u	Dead; 4.9

Abbreviations: F = female; M = male; RPA = recursive partition analysis; SRS = stereotactic radiosurgery; RecurX = SRS for recurrence after prior radiation therapy; RecurS = SRS for recurrence after prior surgery; Alone = SRS alone initially for newly-diagnosed brain metastases; Boost = SRS boost in conjunction with whole brain radiotherapy for newly-diagnosed brain metastases; NR = no response; CR = complete response; PR = partial response; f/u = follow-up

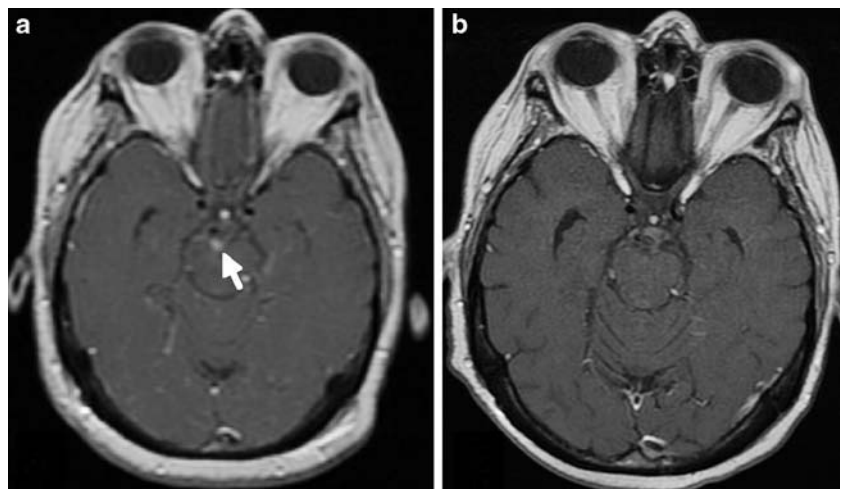
^a Treatment volume for the brainstem lesion was not available when one or more other lesions were included in the same dose matrix with the brainstem lesion

^b The status for patients lost to follow-up is listed as “Unknown” and the duration of known follow-up is shown

9.3 months for patients treated with WBRT plus SRS boost for newly-diagnosed brain metastases, and 7.0 months for patients treated with SRS for recurrent brain metastases. There was no significant survival difference comparing SRS alone to WBRT plus SRS for newly-diagnosed brain metastases ($P = 0.63$) or comparing patients with newly-diagnosed vs. recurrent brain metastases ($P = 0.19$).

Multivariate analysis including age (<65 years vs. ≥ 65 years), KPS (<70 vs. ≥ 70), single vs. multiple metastases, extracranial disease status (controlled vs. active), and non-melanoma vs. melanoma primary stratified by newly-diagnosed vs. recurrent brain metastases confirmed prognostic significance of single brain metastasis (P -value, 0.003; hazard ratio, 0.04), melanoma histology (P -value,

Fig. 1 Axial view of gadolinium-enhanced T1-weighted magnetic resonance (MR) image of a patient with a pontine metastasis prior to radiosurgery (Patient 24) (a). At last imaging follow-up (26 months after radiosurgery), MR scan shows continued complete response of brainstem lesion (b). The patient is still alive at final analysis and the pontine lesion remains in complete response 28.4 months after radiosurgery



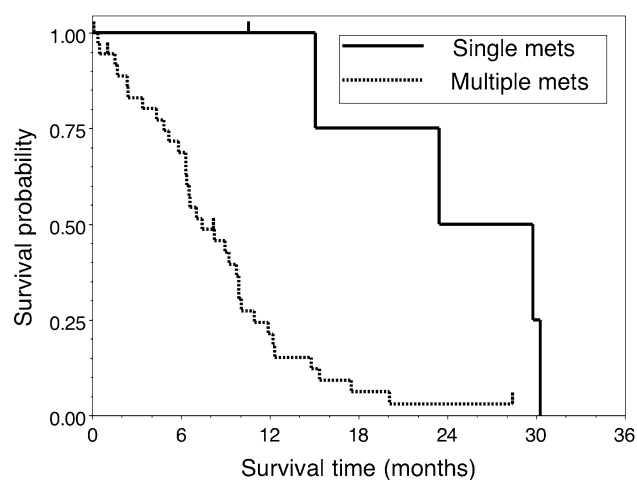


Fig. 2 Actuarial survival. There was a significant association between survival time and single metastasis at the time of SRS for brainstem metastasis (median survival time 29.8 months among five patients with a single metastasis vs. 7.4 months for patients with multiple metastases; log-rank $P = 0.002$)

0.003; hazard ratio, 5.11), and extracranial disease control (P -value, 0.058; hazard ratio, 0.35) (Table 2). Results were similar without stratification.

Freedom from local tumor progression

Follow-up imaging was available for 26 lesions in 26 patients with a median of 6.9 months of imaging follow-up (range, 0.8–28.6 months). Seven patients with nine brainstem lesions had no imaging follow-up because they expired relatively soon (≤ 4.5 months) after SRS. Another nine patients with nine brainstem lesions did not have imaging follow-up.

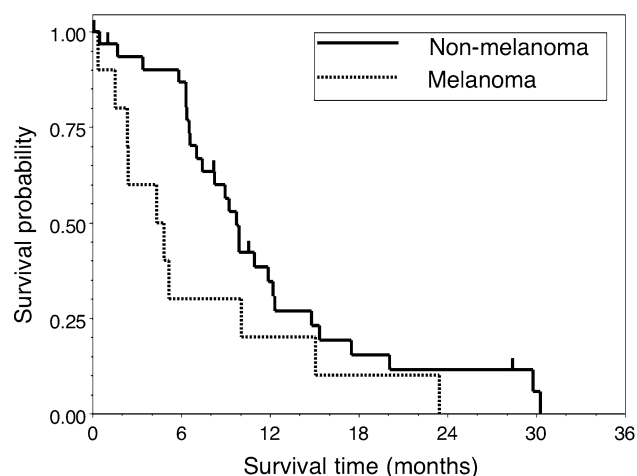


Fig. 3 Actuarial survival. There was a trend toward shorter survival time with melanoma vs. other primary sites (median survival time was 4.9 vs. 9.7 months; log-rank $P = 0.071$)

Using the aforementioned definitions of treatment response, six lesions had NR to SRS, 10 lesions had a PR, and six had a CR to SRS at last imaging follow-up. Two lesions had definite tumor progression (Patient 28 and Patient 6). One lesion enlarged secondary to hemorrhage (Patient 27). Another lesion had enlargement in which there was diagnostic uncertainty as to whether the growth was due to necrosis vs. tumor progression (Patient 3). Each of these four lesions is discussed in detail below.

In our conservative analysis, one hemorrhage of a 0.3 cm, 0.03 ml melanoma metastasis which occurred 1.6 months after SRS with 18.5 Gy (Patient 27) and one case of possible necrosis of a 1.3 cm, 1.2 ml melanoma metastasis which occurred 4.8 months after SRS with 18.5 Gy (Patient 3) were scored as failures along with the two cases of definite tumor progression (Patient 28 and Patient 6) which occurred 10.3 months and 17.2 months after SRS for a 1.6 cm, 1.6 ml renal cell metastasis treated with 12.0 Gy and a 0.8 cm, 0.25 ml melanoma metastasis treated with 19.0 Gy. Accordingly, in the conservative analysis, 22 of the 26 total lesions remained controlled, yielding a crude local control rate of 85% with brainstem lesion FFP probabilities of 90% at 6 months (95% confidence interval, 66–98%) and 77% at 1 year (95% confidence interval, 39–93%), with a median FFP not reached. Univariate analysis demonstrated a significant relationship between tumor progression and melanoma vs. other primary sites (log-rank $P = .0035$). No relationship was found between FFP and prescribed dose (<16 Gy vs. ≥ 16 Gy), tumor volume (less than vs. greater than or equal to the median tumor volume [0.26 ml]), newly-diagnosed vs. recurrent brain metastasis, SRS alone vs. WBRT +SRS for newly-diagnosed brain metastasis, adjuvant WBRT (yes or no; WBRT with SRS boost vs. SRS alone for newly-diagnosed or recurrent brain metastases), or renal cell vs. non-renal cell primary. There was a trend toward improved FFP and brainstem lesion volume <1 ml ($P = 0.086$). Multivariate analyses including melanoma vs. non-melanoma as well as either dose or tumor volume confirmed the significance of melanoma and the lack of significance of dose and volume in this small series (Table 2).

In the other analysis for which hemorrhage was not considered to represent tumor progression and for which questionable imaging lesion growth was defined as radiation-induced necrosis rather than tumor progression, only two of the 26 lesions were scored as having had tumor progression, yielding a crude local control rate of 92%. In this analysis, brainstem lesion FFP was 100% at 6 months and 88% at 1 year (95% confidence interval, 39–98%), with a median FFP not reached. On univariate testing, a dose of at least 16 Gy was associated with a significantly lower risk of tumor progression (log-rank $P = 0.0082$). No significant relationship was found between FFP and tumor

Table 2 Summary of favorable prognostic factors for survival, local control, and complications

Endpoint/Parameter	Univariate log-rank <i>P</i> -value	Multivariate cox <i>P</i> -value
<i>Survival</i>		
Single brain metastasis	0.002	0.003
Controlled extracranial disease	0.029	0.058
Non-melanoma histology	0.071	0.003
Age (<65 vs. ≥65 years)	0.71	0.53
KPS (<70 vs. ≥ 70)	0.33	0.69
<i>FFP (conservative analysis; 4 failures)</i>		
Non-melanoma histology	0.0035	0.025
Brainstem lesion volume <1 ml	0.086	0.12
<i>FFP (non-conservative analysis; 2 failures)</i>		
Prescribed SRS dose ≥16 Gy	0.0082	(Not done)
<i>Brainstem complications (4 events)</i>		
Non-RCC histology	0.013	–
Non-melanoma histology	0.35	–
Non-melanoma and non-RCC histology	0.0090	0.05
Brainstem lesion volume <0.26 ml	0.027	NS
<i>Poor brainstem outcomes (6 events)</i>		
Non-RCC histology	0.039	–
Non-melanoma histology	0.012	–
Non-melanoma and non-RCC histology	0.0005	0.026
Brainstem lesion volume < 1 ml	<0.0005	0.014

Abbreviations:

KPS = Karnofsky performance status; FFP = freedom from progression; SRS = stereotactic radiosurgery; RCC = Renal cell carcinoma

volume, adjuvant WBRT, melanoma vs. non-melanoma primary, or renal cell vs. non-renal cell primary (Table 2). There were too few failures to perform meaningful multivariate analysis.

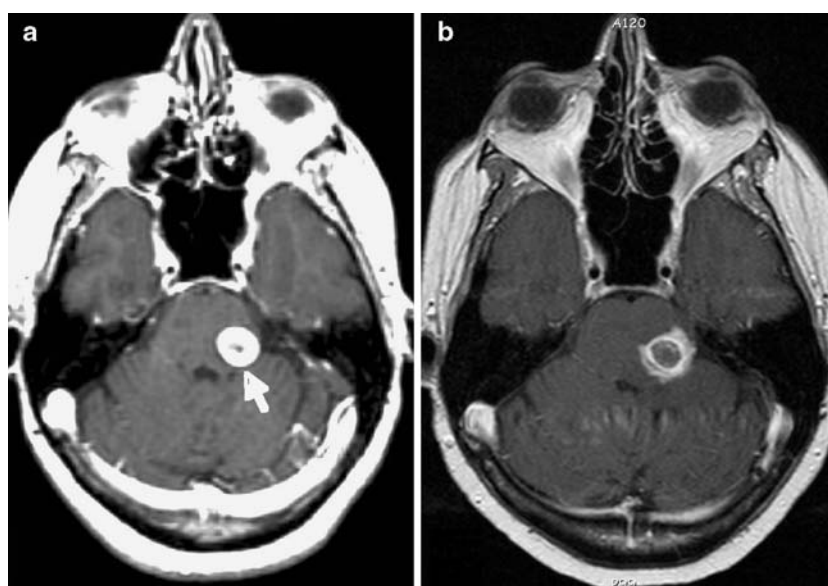
Clinical response and complications

Only 10 patients had known pre-SRS brainstem signs and symptoms. One patient demonstrated an improvement of his symptoms at initial follow-up; he eventually developed neurological symptoms from another intracranial lesion 5 months after SRS. Five patients remained stable at initial follow-up: one of these patients developed mental status and visual changes from new brain metastases 28 months after SRS with her brainstem lesion still in complete response; one patient developed progressive right arm, face, and leg numbness from another intracranial lesion 7.5 months after SRS with his brainstem lesion still in partial response; another patient eventually developed a progressive right hemiparesis approximately 9 months after SRS (imaging was not performed and thus the source of these symptoms was not known); another patient remained asymptomatic from her brainstem lesion until she expired from systemic disease; finally, one patient did not have additional clinical follow-up after his initial follow-up 1 month after SRS in which his symptoms were stable. Two patients demonstrated a worsening of their symptoms

on initial follow-up: one of these patients (Patient 28) is discussed below; the other patient had disseminated leptomeningeal disease at the time of SRS and was scheduled to undergo WBRT but died 1.5 months after SRS from his disseminated leptomeningeal disease. Two patients did not have symptom follow-up. Of note, two patients developed leptomeningeal disease after SRS: one patient (Patient 25) developed leptomeningeal disease 5 months after SRS and the other one (Patient 24) also developed leptomeningeal disease 5 months after SRS. This second patient had undergone right parietal craniotomy for resection of a recurrent non-brainstem lesion 20 days prior to undergoing SRS for her brainstem lesion. This patient was still alive at the time of this analysis, 28.4 months after SRS and 27.4 after WBRT.

There were no acute complications after SRS. One patient (Patient 28) developed symptomatic radiation necrosis of her brainstem lesion 3.7 months after SRS, presenting with ataxia, dysequilibrium, and left facial numbness (Fig. 4). On the subsequent MRI 2 months later, the lesion had decreased in size and appeared to be improving. However, her next MRI showed progression of her brainstem lesion 10.3 months after SRS. Thus, this patient was categorized as having both a brainstem complication as well as having definite tumor progression (as noted above). Another patient (Patient 3) also developed dysequilibrium 4.8 months after SRS. On 3-month imaging

Fig. 4 Axial gadolinium-enhanced T1-weighted magnetic resonance (MR) image of a patient with renal cell metastasis on the day of radiosurgery (Patient 28) (a). At 3.7 month follow-up, MR scan shows radiation necrosis of her brainstem lesion (b). The patient presented with ataxia, dysequilibrium, and left facial numbness when the follow-up MR scan was obtained. The lesion later went on to have a partial response, but ultimately developed tumor progression 10.3 months after SRS



follow-up, this patient's lesion was stable in size with new central necrosis compared with his pre-SRS scan. The patient subsequently became symptomatic at the time noted above and an MRI was obtained that showed the lesion had increased in size. Magnetic resonance spectroscopy could not differentiate between necrosis and tumor progression; PET, however, did show FDG uptake in the brainstem lesion. Two months later, MRI showed the lesion had increased in size with PET continuing to show FDG uptake. Magnetic resonance spectroscopy, however, was negative for tumor. Thus, this patient was categorized as having necrosis vs. progression (analyzed two ways as noted above) as well as having a brainstem complication.

One patient (Patient 19) developed a right hemiparesis secondary to increased internal hemorrhage of a treated renal cell pontine metastasis 1 month after SRS. Importantly, this patient was not analyzed as having had a treatment failure because his lesion did not demonstrate an increase in size as did the other case of hemorrhage (Patient 27). Although the hemorrhage may have been unrelated to SRS, it was scored as a brainstem complication to err on the side of over-scoring rather than under-scoring complications. Another patient (Patient 1) developed right facial numbness and a mild right hemiparesis 7.2 months after SRS, however imaging was not performed and thus her treated brainstem lesion was not assessed radiographically. This patient had a very large left pontine metastasis that was the largest lesion treated in this series. The size of the lesion as well as correlation of her symptoms with the anatomic location of the lesion made it fairly clear that her brainstem metastasis was the source of her symptoms.

In the complications analysis, two categories of patients were assessed: the first, designated "brainstem complications," included the two cases of symptomatic radiographic

necrosis (Patient 3 and Patient 28) as well as the patient with symptoms from his hemorrhagic lesion (Patient 19) and the patient with right facial numbness and a mild right hemiparesis with no imaging of her lesion (Patient 1); the second, designated as "poor brainstem outcomes," included the four patients (Patients 3, 28, 19, and 1) in the "brainstem complications" analysis as well as one patient with asymptomatic tumor progression (Patient 6) and one patient with asymptomatic hemorrhage vs. tumor progression (Patient 27). This second category was created and analyzed because it was thought to be useful from a clinical perspective. Univariate analysis showed a significant association between "brainstem complications" and renal cell carcinoma vs. other primary sites (log-rank $P = 0.013$) as well as melanoma or renal cell carcinoma vs. other primary sites (log-rank $P = 0.009$). A significantly higher risk of brainstem complications was also found with larger tumor volume (<0.26 ml [median value] vs. ≥ 0.26 ml, log-rank $P = 0.027$). Since all four lesions that were associated with complications were over 1 ml, we also analyzed risk of complications comparing tumor volume <1 ml vs. ≥ 1 ml. The freedom from complication probability was 100% for tumor volume <1 ml vs. 40% for tumor volume ≥ 1 ml at 6 months and 100% vs. 0% at 1 year ($P < 0.001$). There was no relationship between brainstem complications and prescribed dose (Table 2). Multivariate analysis including melanoma or renal histology with tumor volume (<0.26 ml vs. ≥ 0.26 ml) confirmed significantly lower risk of complications with non-melanoma, non-renal cell histology ($P = 0.050$).

In the second analysis, univariate testing showed a significant association between "poor brainstem outcomes" (defined above; brainstem lesion complication or failure) and renal cell carcinoma vs. other primary sites (log-rank

$P = 0.039$), melanoma vs. other primary sites (log-rank $P = 0.012$), and melanoma or renal cell carcinoma vs. other primary sites (log-rank $P = 0.0005$). Tumor volume of at least 1 ml was also significantly associated with poor brainstem outcome ($P < 0.0005$), but tumor volume < 0.26 vs. ≥ 0.26 ml was not prognostic ($P = 0.12$). The freedom from poor outcome probability was 96% for tumor volume < 1 ml vs. 40% for tumor volume ≥ 1 ml at 6 months and 96% vs. 0% at 1 year ($P < 0.001$). There was no relationship between poor brainstem outcomes and prescribed dose. Multivariate analysis including tumor volume < 1 ml vs. ≥ 1 ml and melanoma or renal cell carcinoma vs. other primary sites yielded a P -value of 0.014 for tumor volume with a hazard ratio of 27.6 and a P -value of 0.026 with a hazard ratio of 16.6 for melanoma or renal cell histology vs. other primary sites (Table 2). All of the patients who were assigned to the “poor brainstem outcomes” category had pontine lesions with the exception of one patient (Patient 6).

Discussion

Brainstem metastases occur relatively infrequently compared to metastasis elsewhere in the brain. Surgery is generally not considered for brainstem metastases. In contrast to the well-established roles of WBRT and SRS in the treatment of brain metastasis [7–13], the management of brainstem metastases with these treatment techniques has not been clearly delineated. To date, five prior studies have assessed the outcomes of patients with brainstem metastases treated with SRS [14–18] (Table 3). In the earliest of these studies, Huang et al. found that SRS could achieve a crude local control rate of 95%, a median survival time of 9 months, and either improve (50%) or stabilize (40%) the symptoms of 26 patients with brainstem metastases using a median prescribed dose of 16 Gy [15]. This group reported a median treatment volume of 1.1 ml. Furthermore, none of their patients experienced chronic radiation-induced morbidity. All patients with newly-diagnosed brain metastases received WBRT in their study and all but two of the entire patient cohort received WBRT. In their multivariate analyses, the only significant predictor of survival was the absence of active extracranial disease [15]. No factors predictive of local control were reported in this study. In 2003, Shuto and colleagues reported a crude local control rate of 77% and a median survival time of 4.9 months after SRS for brainstem metastases in 25 patients [17]. The “mean calculated volume of tumours” reported by this group was 2.1 ml. These authors also used a relatively lower prescription dose (mean, 13 Gy). Although complications were not clearly delineated, the authors did state that 8% of patients

Table 3 Summary of published reports of stereotactic radiosurgery for brainstem metastasis

Authors	No. of Patients	No. of lesions	Chronic SRS-related morbidity (%)	Median tumor margin dose (Gy)	Crude local control (%)	Median survival after SRS (mos)	Factors predictive of longer survival after multivariate analysis	Factors predictive of improved local control
Huang et al. [15]	26	27	0	16	95	9	Absence of active extracranial systemic disease	Not discussed
Shuto et al. [17]	25	31	8 (“radiation-induced injury”)	13 (mean)	77	4.9	Not discussed	Marginal dose
Fuentes et al. [14]	28	28	0	19.6	92	12	Not discussed	Not discussed
Yen et al. [18]	53	53	0	17.6 (mean)	87	11	Absence of active extracranial systemic disease	None
Hussain et al. [16]	22	25	5	16	100	8.5	Not discussed	Not discussed
Present study	42	44	10–14	16	85–92	9.0	Non-melanoma primary site and single brain metastasis	Non-melanoma or dose ≥ 16 Gy, depending on analysis

Abbreviations: SRS = stereotactic radiosurgery

suffered “radiation-induced injury.” Like Huang et al., this group recommended limiting margin doses to 15 Gy or less. The authors found a significant correlation between the marginal dose delivered and tumor response. No factors predictive of survival were reported in this study.

In 2006, Fuentes et al. reported a crude local control of 92%, a median survival time of 12 months after SRS, and improvement or stabilization of pre-SRS symptoms in 67 and 25% of their cohort of 28 patients, respectively. Their group observed no SRS-related morbidity [14]. The “mean volume” in their study was 2.1 ml. The authors utilized a mean marginal dose of 19.6 Gy, higher than any of the other previous studies. Of note, 79% of their patients underwent SRS without WBRT. Also, 72% of their patients had the brainstem lesion as the only site of metastasis. Although these authors did not report on factors predictive of survival or local control, our analyses found a significant association between survival time and single metastasis at the time of SRS for brainstem metastasis (discussed further below), perhaps accounting for the relatively high survival in the Marseille study. In the same year, Yen et al. found a local control rate of 87%, a median survival time of 11 months after SRS, and also had no SRS-related toxicity among 53 patients [18]. The “mean tumor volume” was 2.8 ml while the mean prescribed dose was 17.6 Gy. With regard to radiosurgical dosing of brainstem tumors, the report stated that “a peripheral dose of 18–25 Gy seems to be safe and effective.” The authors noted the dose may need to be reduced for patients with previous WBRT. Controlled extracranial disease was found to be the only favorable prognostic factor for survival. The authors did not find any factors predictive for local control.

In the most recent study addressing the issue, Hussain et al. reported a 100% local control rate and a median survival time of 8.5 months in 22 patients undergoing SRS for brainstem metastasis. In contrast to the previous two studies, only 9% of their patients demonstrated symptom improvement; 5% of their patients had SRS-related morbidity. Median tumor volume in this study was 0.9 ml and median prescribed dose was 16 Gy. The authors did not report on any prognostic factors for survival or local control.

Thus, for the five previously published reports, crude local control ranged from 77 to 100% and mean or median prescribed dose ranged from 13 to 19.6 Gy. Median survival times ranged from 4.9 months to 12 months. Chronic SRS-related complications ranged from 0 to 8%. The studies had conflicting conclusions regarding the optimal radiosurgical dosing of brainstem metastasis. Of the five studies, only two [15, 18] report prognostic factors for survival, with both of those studies concluding that the absence of active extracranial systemic disease was the only favorable prognostic factor. None of the five studies reported on actuarial freedom from tumor progression.

In the current study, median survival time (9 months) and crude local control (85–92%, depending on the analysis) were consistent with that achieved by the other authors. The freedom from tumor progression in our study was 90–100% at 6 months and 77–88% at 1 year, depending on the analysis, with median FFP not reached. The morbidity (4/42 [10%] or 6/42 [14%], depending on the analysis) in the present study was greater than that of the other studies despite the conservative median SRS dose of 16 Gy. In patients with brainstem AVMs, Flickinger and colleagues have noted higher rates of symptomatic adverse radiation effects compared with lesions elsewhere in the brain [21].

Of note, five of six cases of tumor progression, hemorrhage, or symptomatic necrosis occurred in patients with melanoma or renal cell carcinoma, and the sixth case was in a patient with an unknown primary. Indeed, a significant relationship was found between tumor progression and melanoma vs. other primary sites. Also, a dose of less than 16 Gy was associated with a significantly higher risk of tumor progression. In terms of adverse outcomes, a significant association was found between “brainstem complications” (defined above) and renal cell carcinoma vs. other primary sites as well as melanoma or renal cell carcinoma vs. other primary sites. A significantly higher risk of brainstem complications was also found with larger tumor volume. We also found a significant association between “poor brainstem outcomes” (brainstem lesion complications or failure) and renal cell carcinoma vs. other primary sites, melanoma vs. other primary sites, melanoma or renal cell carcinoma vs. other primary sites, and larger tumor volume.

Assessments of prognostic factors for survival also yielded interesting results. There was a significant association between survival time and single metastasis at the time of SRS for brainstem metastasis as well as was a trend toward shorter survival time with melanoma vs. other primary sites. We also found that absence of active extracranial disease was significantly associated with longer survival times on univariate analysis, with a trend toward longer survival time on multivariate analysis.

Conclusions

In this series, SRS provided excellent local control with relatively low morbidity in patients with brainstem metastases using a median dose of 16 Gy; doses less than this amount were associated with a significantly higher risk of tumor progression. Large tumor volume (>1 ml) as well as melanoma and renal cell histologies were associated with significantly higher risk of adverse outcomes. A significant association was found between survival time and single metastasis at the time of SRS for brainstem metastasis as well as a trend toward shorter survival time with

melanoma vs. other primary sites. We conclude that brainstem location in and of itself is not a reason to exclude patients from consideration of SRS and that safe and effective treatment can be offered to non-melanoma, non-renal cell lesions less than 1 ml.

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