Outcomes of Patients with Brain Metastases from Melanoma and Renal Cell Carcinoma after Primary Stereotactic Radiosurgery

Randy L. Jensen, M.D., Ph.D., Annabelle F. Shrieve, M.A., Wolfram Samlowski, M.D., and Dennis C. Shrieve, M.D., Ph.D.

Patients with melanoma or renal cell carcinoma (RCC) frequently have brain metastases.[3,9,15,38,46,47] These patients have traditionally been treated with surgery, palliative whole-brain radiation (WBRT), or both. Surgery, even today, is generally reserved for assessable, symptomatic lesions in patients with a good Karnofsky Performance Score. Recursive partition analysis (RPA), which classifies patients on a scale of I to III based on Karnofsky Performance Score, age, and tumor control, has been used to identify patients that are expected to have the greatest clinical benefit from WBRT.[10,15,40] Although WBRT is the most widely used treatment for these patients, there is a general sense among those treating these patients that melanoma and RCC are considered radioresistant.[6,8,14,18,25,26]

Stereotactic radiosurgery (SRS) performed using either linear accelerator- or gamma knife-based systems can achieve higher radiation doses within the tumor volume and theoretically can increase responses in these radioresistant tumors. Numerous reports have shown effective local control and prolonged patient survival after SRS for these lesions.[1,6,8,16,18,30,33,35,43] Early control of brain metastases is important in these patients, because many of them also have extracranial metastases. We hypothesized that early diagnosis and aggressive treatment of brain metastases with SRS in these patients could spare many patients WBRT. In addition, it seemed likely that this would permit early systemic therapy. The ultimate goal was to achieve improvement in survival rates. We report our experience with using SRS as a primary treatment modality in patients with RCC and melanoma brain metastasis.

CLINICAL MATERIALS AND METHODS

Data Collection

After obtaining approval from the Institutional Review Board, we prospectively (from January 2006) collected patient clinical data on patients undergoing SRS procedures at the Huntsman Cancer Institute at the University of Utah. We also retrospectively reviewed patients treated before January 2006. All patients included in this analysis had a minimum potential follow-up of 1 year after treatment with SRS. The following clinical information was obtained: age and sex; RPA class; date of primary diagnosis (if known); date of radiographic diagnosis of brain metastases and number of brain metastases; date of SRS, surgery, or WBRT; number of SRS treatments; radiation dose administered by SRS; and apparent cause of death (systemic, neurologic, or both). Follow-up imaging studies, when available, were used to assess tumor response. The Internet-based Social Security Death Index (http//ssdi.genealogy.rootsweb.com) was used to obtain survival data when it was not available from our records. Presumed cause of death (when no autopsy data were available) was determined according to imaging information and clinical notes at last follow-up visit.

Clinical Management Strategy

All patients with Stage IIIb or IV melanoma (based on 2001 American Joint Committee on Cancer recommendations[4]) are screened with magnetic resonance (MR) imaging or contrast-enhanced computed tomography scan of the brain at the time of initial evaluation at the Huntsman Cancer Institute. Patients with RCC were screened with brain MR imaging at the time of any neurological symptoms. Follow-up brain imaging was performed annually for 2 years or earlier if symptoms warranted. Patients were treated aggressively when brain metastases were discovered. SRS was used as the primary treatment modality if there were five or less brain metastases. WBRT was usually used if more than five brain metastases were detected, with stereotactic boost to larger lesions. Patients were closely monitored with brain imaging studies (generally gadolinium-enhanced MR imaging) at least every 2 months, and salvage treatment (including SRS boost to one or more growing lesions or WBRT, if not previously used, to five or more new lesions) was used if there was evidence of radiographic disease progression. Palliative sur-

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gery was considered if there was a dominant symptomatic and surgically accessible lesion. Early biochemotherapy was planned after SRS. Biochemotherapy was initiated when the patient demonstrated stable central nervous system disease on brain MR imaging in the absence of clinically significant edema requiring glucocorticosteroids. Biochemotherapy was generally planned to begin within 28 days after SRS.[39]

Stereotactic Radiosurgery Planning and Treatment

Patients were treated with a BrainLAB m3 micromultileaf collimator (BrainLAB AG, Feldkirchen, Germany) attached to a Clinac 21EX (Varian, Salt Lake City, UT) or a Novalis (BrainLAB AG) SRS unit. High-resolution MR (2-mm T1-weighted, postgadolinium enhancement) images were used to define target volumes and risk structures after fusion with computed tomography scans obtained with a stereotactic localizer frame (BrainLAB AG). BrainSCAN (BrainLAB AG) software was used to fuse the images and plan the SRS with dynamic conformal arc techniques. This allowed each lesion to be treated with a single isocenter with total treatment times under 1 hour for up to five metastases. Dose was prescribed to the isodose line, which covered 95% or more of the target volume. Conformity indices were calculated for each lesion (range, 1.00–2.67; median, 1.52; mean, 1.50). The planned radiotherapy dose was based on maximal diameter of the metastasis as follows: less than 2 cm, 22 Gy; 2 to 3 cm, 18 Gy; greater than 3 cm, 15 Gy. Lesions greater than 4 cm were usually not considered for SRS, although rare exceptions were made. After initial therapy, patients were monitored in the multidisciplinary brain tumor clinic approximately every 2 months with brain MR imaging with the intent of providing additional treatment (SRS if less than five new or uncontrolled lesions or WBRT if more than five lesions) to control central nervous system progression.

Assessment of Response and Survival

The primary end points of the analysis were survival and local control of each lesion. Survival was defined as the time (in months) from the date of first SRS treatment of brain metastases until death or last clinical follow-up visit. Local control was based on radiographic analysis of each lesion. Measurements were made on maximal cross-sectional area on two orthogonal measures. Increases of more than 25% were considered failures. Measurements similar to original measurement (<25% change) or less than original measurement were considered stable. Any lesion that required any further treatment including surgery (usually for suspected radiation necrosis), WBRT, or repeat SRS was considered a failure.

Statistical Analysis

Statistical calculations were done using XLSTAT software (Addinsoft, www.xlstat.com). Overall survival and freedom from local and distant failure after SRS were assessed using Kaplan-Meier analyses. Univariate analyses were performed to assess factors such as primary histology, sex, age, WBRT (given as either primary or secondary treatment), number of radiosurgery sessions, and number of lesions treated at a given radiosurgery. Statistical significance was established at probability levels ≤ 0.05.

RESULTS

Patient Population

Between April 20, 1999, and May 23, 2006 (allowing for at least 1 year follow-up), 141 SRS procedures were performed on 101 patients with 339 brain metastases from melanoma (73 patients, 280 lesions) or RCC (28 patients, 59 lesions) (*Table 20.1*). Of these 101 patients, 88 patients with 200 lesions had newly diagnosed metastases that were treated either with radiosurgery alone (71 patients, 143 lesions) or SRS combined with WBRT (17 patients, 57 lesions). Radiosurgery was used as a salvage therapy in an additional 13 patients with 139 lesions after failure of prior WBRT (usually at an outside institution). Patient demographic information is presented in Table 20.1.

The majority of patients in our study were RPA Class II (88%) (89% in melanoma and 86% in RCC). Median tumor volume was 0.35 cm^3, mean 2.42 cm^3, with a range of 0.01 to 36.24 cm^3. Melanoma lesions measured a median of 0.61 cm^3 and mean of 2.45 cm^3 with a range of 0.03 to 16.56 cm^3; RCC tumors measured a median of 0.90 cm^3 and mean of 2.57 cm^3 with a range of 0.01 to 36.24 cm^3.

The mean number of lesions treated at a given SRS session was 2.45 overall and 2.42 for melanoma and 2.57 for RCC. The 101 patients underwent 141 SRS procedures. The 73 patients with melanoma had 109 total SRS treatments for a mean of 1.49 treatment sessions per patient. The 28 patients with RCC underwent 32 total SRS treatments for a mean of 1.14 treatment sessions per patient.

Local control could be assessed for 275 lesions. Most lesions (175) were controlled with only a single SRS treatment. There were 100 local failures, which included 29 lesions that required resection after SRS.

Survival

Overall median survival of the entire group of 101 patients was 7.03 months from the time of SRS (*Fig. 20.1*; *Table 20.2*). Patient age had no effect on survival, because patients aged 55 years or younger (N = 44) had a median survival of 7.67 months compared with a median survival of 6.30 months for the 57 patients older than 55 years (P = 0.172). When age was analyzed using 65 years as a cut point (like RPA classification), this finding was not altered (P = 0.969). Patient sex was not predictive of survival either; median survival for male patients was 6.57 months and for female

TABLE 20.1. Patient information[a]

Patient Characteristics	Melanoma	Renal Cell Carcinoma	All
Number of patients	73	28	101
Total number of lesions treated (mean per patient)	280 (1.89/patient)	59 (2.67/patient)	339 (2.23/patient)
Total number of SRS sessions (mean per patient)	109 (1.49/patient)	32 (1.14/patient)	141 (1.40/patient)
Age (yr)	Median, 54.26 ± 14.83; range, 26–89	Median, 61.61 ± 7.94; range, 47–80	Median 57.57 ± 13.56; range 26–89
Sex	24 F/49 M	4 F/24 M	28 F/73 M
RPA class	3 (4%) Class I	1 (3%) Class I	4 (4%) Class I
	65 (89%) Class II	24 (86%) Class II	89 (88%) Class II
	5 (7%) Class III	3 (11%) Class III	8 (8%) Class III
Number of patients who also received WBRT	22 (30%)	9 (32%)	31 (31%)
Mean tumor volume	2.45 cm^3	2.57 cm^3	2.42 cm^3
Median tumor volume (range)	0.61 cm^3 (0.01–16.24 cm^3)	0.90 cm^3 (0.03–16.56 cm^3)	0.35 cm^3 (0.01–36.24 cm^3)

[a]SRS, stereotactic radiosurgery; RPA, recursive partition analysis; WBRT, whole-brain radiotherapy; F, female; M, male.

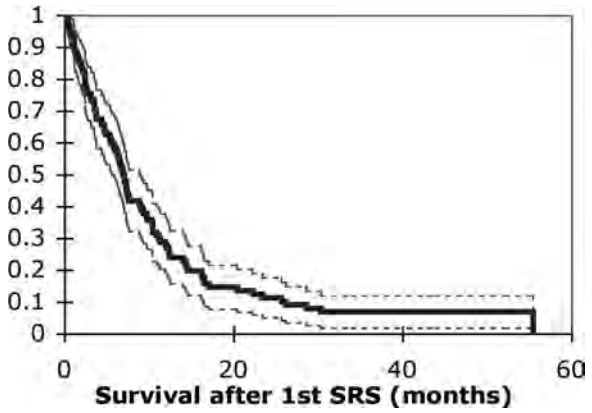

FIGURE 20.1. Kaplan-Meier plot showing overall survival (in months) from the time of initial SRS treatment for the entire patient series (101 patients).

patients, it was 7.63 months ($P = 0.575$). Tumor type (melanoma versus RCC) was also not a predictor of patient survival. The 73 patients with melanoma had a median survival of 7.4 months compared with the 28 patients with RCC who had a median survival time of 6.07 months ($P = 0.368$).

As might be expected, RPA class had a significant effect on overall survival (*Fig. 20.2*); however, there were only four RPA Class I patients. Their overall median survival was 23.5 months. The 91 patients with an RPA Class II had a 7.1-month median survival time and the seven patients with an RPA Class III had a 1.7-month median survival ($P < 0.0001$). There was significantly better survival in the patients with the fewest brain metastases (*Fig. 20.3*). Patients treated for four or more lesions had a median survival of 5.0 months, whereas the patients with a single lesion had a median survival of 7.63 months, those with two lesions 7.67 months, and those with three lesions 2.63 months ($P = 0.006$). The relatively poor median survival of patients treated for three lesions may have been a result of the small number of patients with three lesions. We also examined the total number of SRS treatments a given patient received. Sixty-eight patients had a single SRS treatment with a median survival time of 4.77 months, 28 patients had two sessions of SRS and a median survival time of 11.23 months, and five patients had at least three SRS sessions (four patients with three sessions and one with four SRS treatments) with a median survival of 14.5 months ($P = 0.002$). This paradoxical result is probably the result of the underlying biology of the cancer in these patients providing a selection bias (those who survive longer receive more treatments).

When looking at patients treated with SRS alone or in combination with WBRT as primary treatment of brain metastases (88 patients), overall median survival was 7.03 months. Patients who received SRS as salvage treatment after WBRT failure (N = 12) had a similar median survival of 7.10 months ($P = 0.285$). Like in the larger group of patients, neither patient age ($P = 0.212$) nor sex ($P = 0.797$) had a significant effect on survival in patients treated with SRS as initial treatment. Similarly, tumor histology was also not a predictor of patient survival. The 65 patients with melanoma had a median survival of 7.4 months compared with the 24 patients with RCC with a median survival time of 6.07 months ($P = 0.581$).

RPA class had a significant effect on overall survival in this patient population similar to the previously described analysis for the entire study patient population. Median sur-

TABLE 20.2. Survival statistics for patients treated with SRS[a]

	All Patients			Patients Receiving SRS as Initial Therapy		
	No. Patients	**Survival (mo)**	**Significance (*P* value)**	**No. Patients**	**Survival (mo)**	**Significance (*P* value)**
Overall	101	7.03		88	7.03	
Age (yr)			0.172			0.212
≤55	44	7.67		37	9.03	
>55	57	6.30		51	6.07	
Sex			0.575			0.797
Male	73	6.57		63	8.27	
Female	28	7.63		25	9.33	
Tumor type			0.368			0.581
Melanoma	73	7.4		64	7.4	
RCC	28	6.07		24	6.07	
RPA class			<0.0001			<0.0001
I	4	23.5		4	23.5	
II	90	7.1		78	7.1	
III	7	1.7		6	1.2	
No. of lesions treated			0.006			0.01
1	42	7.63		37	10.5	
2	26	7.67		22	9.83	
3	9	2.63		9	2.63	
4	24	5.0		20	5.47	
No. of treatments			0.002			0.003
1	68	4.77		61	4.77	
2	28	11.23		22	12.37	
3	5	14.5		5	14.07	

[a]SRS, stereotactic radiosurgery; RCC, renal cell carcinoma; RPA, recursive partition analysis.

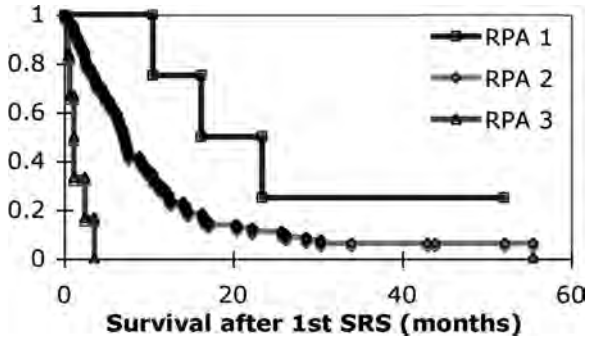

FIGURE 20.2. Kaplan-Meier plot showing overall survival (in months) from the time of first radiosurgery for patients stratified by RPA class. Median survival for RPA Class I was 23.5 months, for RPA Class II 7.1 months, and for RPA Class III 1.7 months ($P < 0.0001$).

vival decreased with increasing RPA class: RPA I (23.5 months), RPA Class II (7.1 months), and RPA Class III (1.2 months) ($P < 0.0001$). In an examination of number of lesions treated during a SRS session, 20 patients treated for

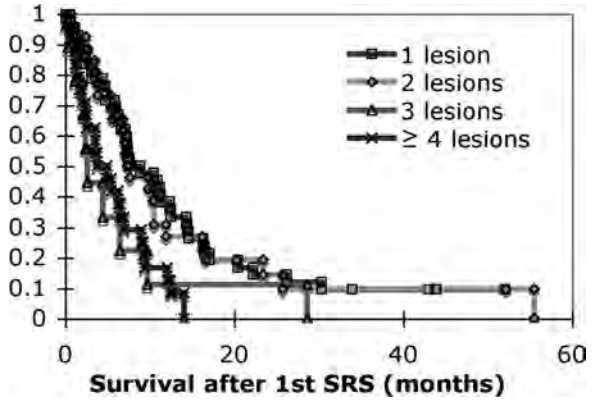

FIGURE 20.3. Kaplan-Meier plot showing overall survival (in months) from the time of first radiosurgery for patients categorized according to the total number of brain metastases treated during the initial SRS session. Median survival for patients treated for four or more lesions was 5 months compared with 7.63 months for patients with a single lesion, 7.67 months for the patients with two lesions, and 2.63 months for patients with three lesions ($P = 0.006$).

four or more lesions had a median survival of 5.47 months compared with 10.5 months for the 37 patients with a single lesion, 9.83 for the 22 patients with two lesions, and 2.63 months for the nine patients treated for three lesions ($P = 0.010$). The total number of SRS treatments given to individual patients as salvage therapy after WBRT failure demonstrated results similar to those for the entire study population: median survival of 4.77 months, 12.37 months, and 14.07 months for patients undergoing one, two, and three or more SRS sessions, respectively ($P = 0.003$).

Local Control

Local control data were available for 275 of 339 lesions treated (*Table 20.3*). A total of 175 lesions were controlled by SRS. One hundred lesions were classified as treatment failures based on growth of more than 25% in cross-sectional

TABLE 20.3. Local control of patients treated with SRS[a]

	Number of Lesions Controlled (control rate)	Median PFS (mo)	Significance
Overall	175/275 (63.6%)	9.23	
Treatment timing			0.002
SRS as primary treatment	133/203 (65.5%)	12.0	
SRS as salvage treatment	42/72 (58.3%)	5.4	
Age (yr)			0.125
<55	81/137 (59.1%)	8.4	
≥55	94/138 (68.1%)	12.03	
Sex			0.020
Male	127/207 (61.3%)	8.16	
Female	48/68 (70.6%)	18.76	
RPA class			0.732
I	7/12 (58.3%)	8.80	
II	157/245 (64.1%)	9.23	
III	11/18 (61.1%)	18.76	
Tumor type			0.89
Melanoma	147/229 (64.2%)	9.23	
RCC	28/46 (60.9%)	10.2	
Number of lesions treated			0.020
1	29/38 (76.3%)	NA	
2	37/60 (61.7%)	9.23	
3	16/33 (48.5%)	5.16	
≥4	93/144 (64.6%)	8.43	
Tumor location			0.08
Frontal	72/107 (67.3%)	12.0	
Temporal	17/33 (51.5%)	8.80	
Parietal/occipital	69/116 (59.5%)	8.13	
Cerebellum	17/19 (89.5%)	NA	
Dose			0.396
12–15 Gy	10/26 (38.9%)	8.17	
15–18 Gy	49/77 (63.6%)	12.0	
18–20 Gy	79/116 (68.1%)	7.07	
>20 Gy	37/56 (66.1%)	10.2	
Tumor volume			0.615
<1 cm^3	111/165 (67.3%)	10.2	
1–2 cm^3	16/26 (61.5%)	7.27	
>2 cm^3	48/84 (57.1%)	8.40	

[a]SRS, stereotactic radiosurgery; PFS, progression-free survival; RPA, recursive partition analysis; RCC, renal cell carcinoma; NA, median progression-free survival was not reached.

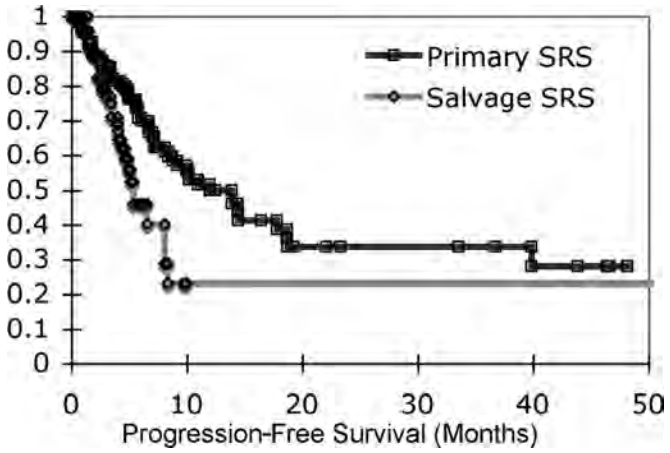

FIGURE 20.4. Kaplan-Meier plot showing central nervous system progression-free survival (in months) from the time of first radiosurgery for patients treated initially with primary SRS and those treated with salvage SRS after progression after prior WBRT. The median time to failure was 12.0 months for lesions treated primarily compared with 5.4 months for those treated after failing previous radiotherapy ($P < 0.002$).

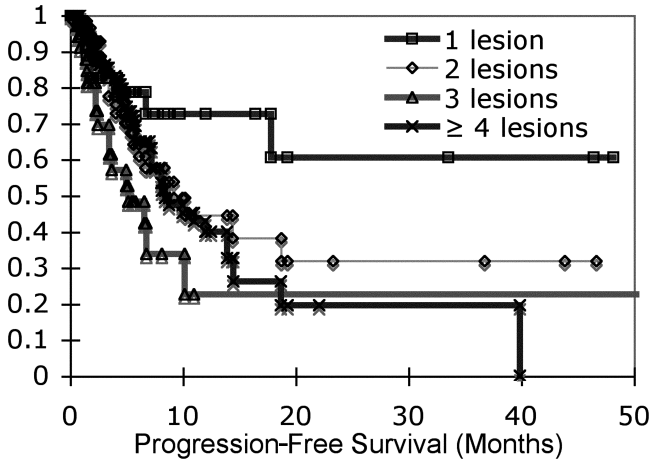

FIGURE 20.5. Kaplan-Meier plot showing central nervous system progression-free survival (in months) from the time of first radiosurgery for patients categorized according to the total number of brain metastases treated during the initial SRS session. SRS sessions in which one lesion was treated in a given SRS session (76.3% control rate, median PFS not reached) resulted in higher survival than sessions treating two lesions (61.7% control rate, median PFS 9.23 mo), three lesions (48.4% control, median PFS 5.17 mo), and four or more lesions (64.6% control, median PFS 8.4 mo) ($P = 0.020$).

measurements. This yielded a 63.6% local control rate with at least 1-year follow-up monitoring. The median progression-free survival (PFS), evaluating all lesions in this study, was 9.23 months. Comparing local control rates for lesions treated with primary SRS (203 lesions, 133 improved on imaging studies for a 65.5% control rate) and those treated for recurrence after initial WBRT failure (72 lesions, 42 improved on imaging for a 58.3% control rate), we see a significant difference in PFS of these group (12.0 months versus 5.4 months, respectively, $P = 0.002$) (*Fig. 20.4*). Age had no effect on local control rates ($P = 0.188$) nor did RPA class ($P = 0.732$).

The number of lesions treated in a given SRS session significantly affected local control rates when one lesion (29 of 38 lesions controlled, 76.3% control rate, median PFS was not reached) was compared with two lesions (37 of 60, 61.7%, median PFS 9.23 months), three lesions (16 of 33 [48.4%], median PFS 5.17 months), and four or more lesions (93 of 144 [64.6%], median PFS 8.4 months) ($P = 0.020$). It is most interesting that treating more than three lesions in a single session of SRS really did not decrease the control rate of those lesions compared with sessions treating only two or three lesions (*Fig. 20.5*).

Tumor histology (melanoma or RCC) was not important in predicting local control of a given lesion. Patients with melanoma were treated for 229 lesions with 82 failures (64.2% control) and a median PFS of 9.23 months. On the other hand, patients with RCC had 46 lesions treated with 18 failures (60.9% control) and median PFS of 10.2 months ($P = 0.89$). Lesions in female patients had a higher local control (48 of 68 [70.6%]) than lesions in male patients (127 of 207 [61.3%]) with PFS of 18.76 months versus 8.16 months, respectively ($P = 0.020$).

An analysis of the effect of SRS dose yielded no difference between patients receiving less than 15 Gy (PFS 8.17 months), 15 to 18 Gy (PFS 12.0 months), 18 to 20 Gy (PFS 7.06 months), or greater than 20 Gy (PFS 10.2 months) ($P = 0.396$). If this is broken down into larger groups such as patients receiving less than 15 versus 15 Gy or more ($P = 0.101$), less than 18 versus 18 Gy or more ($P = 0.815$), or less than 20 versus 20 Gy or more ($P = 0.443$), there is still no difference in local control. An examination of tumor volumes treated shows that lesions less than 1 cm^3 (111 of 165 lesions controlled, 67.3% control, PFS 10.2 months), lesions 1 to 2 cm^3 (16 of 26 [61.5%], PFS 7.27 months), and lesions greater than 2 cm^3 (48 of 84 [57.1%], PFS 8.40 months) were not statistically different from one another in length of PFS ($P = 0.615$). Lesion size can also be divided into those patients with 4 cm^3 or less (approximately 2 cm diameter) total tumor volume and those with greater than 4 cm^3 treatment volume ($P = 0.331$) or into those with less than 2 cm^3 (approximately 1 cm diameter) total tumor volume and those with greater than 2 cm^3 treatment volume ($P = 0.362$), but the factor still does not affect local control.

The effect of anatomic location of brain metastases was also evaluated. Local control for patients with metastases in the frontal lobes (72 of 107 lesions controlled, 67.3% control) did not differ significantly from outcomes of lesions in the temporal lobes (17 of 33, 51.5% control) and parietal/occip-

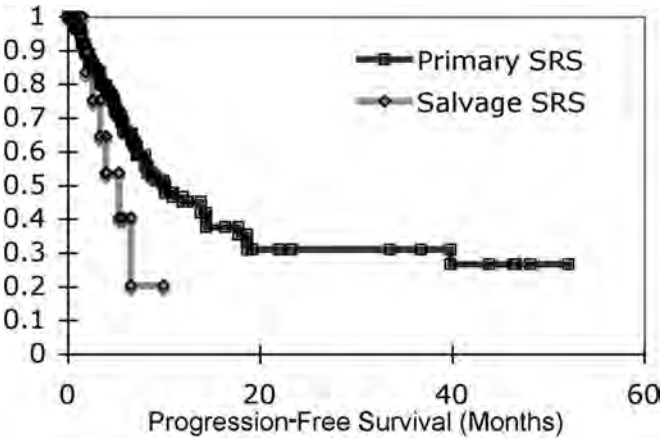

FIGURE 20.6. Kaplan-Meier plot showing overall local lesion progression-free survival (in months) from the time of first radiosurgery for patients treated initially with primary SRS and those treated with SRS after progression after SRS. Local control rates for lesions treated only with one SRS session versus those treated with SRS for recurrence of a tumor previously treated with SRS demonstrate a 10.0-month median PFS versus 5.4-month median PFS ($P = 0.049$).

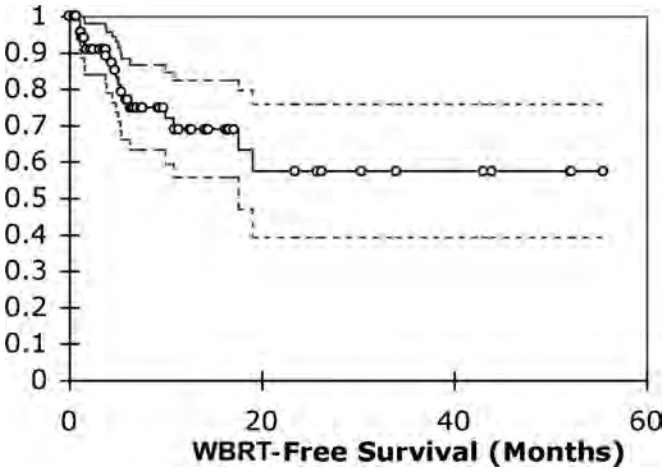

FIGURE 20.7. Kaplan-Meier plot showing overall WBRT progression-free survival (in months) from the time of first radiosurgery. WBRT-free survival was 57% 2 years after treatment with SRS.

ital lobes (69 of 116, 59.5% control). Control of lesions in the posterior fossa (infratentorial) appeared to be somewhat better (17 of 19, 89.5% control) ($P = 0.08$), although this difference was not significant. This was paralleled by a PFS of 8.8 months for the supratentorial lesions, whereas the infratentorial lesions never reached median PFS ($P = 0.038$); this difference in PFS was significant.

Twenty-eight tumors treated after resection in which the "tumor bed" was treated with SRS in lieu of WBRT had a control rate of 67.8% (nine failed lesions) and a median PFS of 14.5 months. This was similar to the 311 lesions treated only with SRS alone, of which 220 were controlled (70.7% control rate), yielding a median PFS of 9.23 months ($P = 0.689$).

Local control for lesions treated with only one SRS session (169 of 262 lesions improved on imaging studies, 64.5% control rate; PFS 10.0 months) was longer than for those treated with SRS for recurrence of a lesion previously treated with SRS (six of 13, 46.2% control rate, PFS 5.4 months) ($P = 0.049$) (*Fig. 20.6*).

Effect of Whole-brain Radiotherapy

Fifty-three of 71 (74.6%) patients initially treated without WBRT had never received WBRT by last follow-up. WBRT-free survival was 57% at 2 years after treatment with SRS (*Fig. 20.7*). These differences between patients that required WBRT and those that did not was not influenced by histological type ($P = 0.387$), sex ($P = 0.549$), or age ($P = 0.906$).

DISCUSSION

Management of Melanoma and Renal Cell Carcinoma Brain Metastasis

Brain metastases present symptomatically in as many as 18 to 46% of patients with melanoma with a prevalence of 55 to 75% at the time of autopsy, and at least 10% of patients with RCC have brain metastasis.[38,44] Thirty percent of patients referred to our center with high-risk melanoma already have brain metastases from melanoma and an additional 34% of these patients develop them during the course of their treatment or follow-up care.[24] As newer therapies for RCC and melanoma emerge and older treatments such as biochemotherapy are further refined, patient survival will increase and patients will be more likely to develop brain metastases sometime during their treatment course. Because untreated brain involvement of melanoma and RCC is a significant source of morbidity and mortality to patients with these cancers,[9,34] our overall treatment strategy for patients with melanoma and RCC has been an aggressive approach for detection and treatment of brain metastases.

In a large series of patients with brain metastases from melanoma, the median survival of those treated with supportive care was 2.1 months and those treated with WBRT was 3.4 months, whereas median survival of 8.7 to 8.9 months was found for those treated with surgery with or without radiotherapy.[9] Many patients with melanoma and RCC, however, have multiple deep-seated lesions[41] and would not be considered to be surgical candidates. Unfortunately, WBRT as a standalone treatment has generally not been particularly effective against the relatively radioresistant lesions examined in this study.[6,8,14,18,25,26] We have used systematic

screening of patients with advanced melanoma and RCC for brain metastases in conjunction with methodical use of SRS in patients found to have five or fewer brain metastases. Additional treatments, including WBRT, retreatment with SRS, and resection, were used, whenever necessary, in conjunction with systemic chemo- or immunotherapy treatment.

Stereotactic Radiosurgery and Survival

SRS for RCC and melanoma metastatic lesions has been suggested to prolong survival in patients when compared with historical controls.[1,6,16,30,35,49] Our median survival time of 7 months is similar to those reported in prior studies for RCC and melanoma. Specifically in other SRS series, patients with melanoma metastases had survival rates (generally calculated from the date of SRS as in our study) in the range of 4.8 to 10.6 months.[6,8,11–13,21,25,27,30,41,42,49] For RCC metastases, survival rates (again generally calculated from the date of SRS) range from 6.8 to 16.2 months.[1,6,33,48] Our survival rate is in the middle of this range. We have previously reported higher median survival rates,[24] but with our increased confidence in SRS as a primary treatment for both metastatic melanoma and RCC, we are treating patients regardless of extracranial disease status or large number of total lesions. We found no significant correlation between survival and age or radiosurgical dose to the tumor margin like in some other previous studies,[27,44] although such correlations have been reported by others.[43] Similar to other studies, tumor histology did not predict greater survival in our study, although RCC has been shown by a few reports to be associated with a higher survival rate than melanoma in patients receiving SRS.[6,16,19]

RPA class has been used to predict which patients are expected to have the greatest clinical benefit from WBRT. To be classified as RPA Class I, a patient must have a Karnofsky Performance Score greater than 70% with a controlled primary site, be younger than 65 years of age, and have no evidence of extracranial metastases.[10,15,40] Most patients in our series fell into RPA Class II because of the presence of active extracranial disease or advanced age. Our study, however, confirms findings from previous papers evaluating SRS that indicate that patients with lower RPA class have increased survival.[5,15,19,35,40,44,50] In our study, the number of treated lesions at first SRS treatment was a significant predictor of overall survival; others have reported similar findings.[27,44] In fact, patients with a solitary metastasis can have a significant increase in median survival compared with patients with multiple metastases.[35] However, recent reports of using SRS for metastatic melanoma indicate that survival is not affected if up to six lesions are treated at the time of initial radiosurgery.[27]

Local Control

Recent publications have suggested high local control rates for RCC or melanoma brain metastases with SRS using either linear accelerator- or gamma knife-based approaches.[6,8,11,13,18,21,22,25,29,33,35,41,43,48] In these studies, SRS has generally been limited to patients with one to three metastases, but more contemporary series seem to be accepting patients with larger numbers of lesions.[11,20,27] Our local control rate of 64% is within the range of previously reported 47 to 86.3% local control rate.[8,11,21,27,33,35,41,42] Median time to progression of 9.2 months also is similar to the reported 2.9 to 9.3 months.[6,12,27,30] Tumor histology did not affect local control in our study, although RCC has been found to have higher local control rates in other reports.[8] Radiation dose did not predict local control in our series or in prior studies,[27] although a dose of 20 Gy or more is associated with improved local control after SRS in some series.[17] In fact, marginal doses of 18 to 20 Gy or more have been recommended to achieve higher local control of RCC metastatic lesion.[33,44] Tumor volume did not predict local tumor control after SRS in our study, but larger tumor volume as a local prognostic factor has been reported.[12,27,41]

Lesions in female patients had a higher local control and longer median time to progression than lesions in male patients. It is unclear why this is true because the other factors examined seem to be split evenly between male and female patients. This warrants further study. Infratentorial location correlated with better local control, but the small numbers of these lesions compared with the supratentorial lesions make the significance of this result questionable, especially given that further, more in-depth analysis on local control was not significant. The number of legions at initial SRS was found to correlate with local control. This finding is also difficult to explain given that local control of each lesion should be independent of the local control of another given lesion. Because of the unexpected nature of this result, it also bears further study in the future.

Need for Whole-brain Radiotherapy

There have been significant concerns that treatment with SRS alone may increase the risk of brain tumor recurrence.[36] Development of new metastases after SRS is common.[27,44] Distant metastasis to the brain occurs in roughly one-third of patients treated with radiosurgery.[43] The role of WBRT as a preventive measure for development of distant RCC and melanoma metastases is unclear.[30] This is in part related to the reported objective response rates of symptomatic brain metastases from melanoma to WBRT alone which range from 11 to 14%.[7,23,31,37] The recent American Society for Therapeutic Radiology and Oncology review indicated that SRS in addition to WBRT improves local control rates and survival compared with WBRT alone for patients with a solitary metastasis.[28] At least one randomized trial has shown

that WBRT followed by SRS for selected histologies results in a survival and local control advantage for unresectable metastases.[2]

For radioresistant metastases, WBRT has been shown to increase local control rates and decrease distant brain failure, but its impact on overall survival remains unclear.[6,49] Others have noted no difference in survival or local lesion control for patients managed with radiosurgery alone compared with patients receiving both WBRT and radiosurgery.[6,27,41] Distant development of metastases is, however, decreased by WBRT.[6] We have usually repeated SRS for patients with less than five new or uncontrolled lesions after they have been treated only with radiosurgery, and others have similar treatment strategies.[1,32,33,44] Patients in our series with more than five brain metastases were treated with WBRT, and SRS was used as salvage therapy for any lesions that persisted or when new lesions arose after WBRT.

Some authors have suggested that for well-selected patients with one or two cerebral metastases, WBRT should not be part of the initial treatment because they have not found a survival benefit with WBRT.[16,45] We found that the addition of WBRT did not provide a survival benefit. Our results taken with others support the withholding of WBRT for treatment of cerebral radioresistant metastases, because patients with up to five brain metastases who were treated with SRS alone in our series demonstrate a comparable survival rate to those who received additional WBRT.

CONCLUSION

We have found that aggressive screening for brain metastases in patients with high-risk melanoma or RCC followed by SRS alone for patients found to have five or less brain metastases is well tolerated, allows patients to proceed to systemic therapy in a rapid fashion, leads to good local control while sparing a majority of patients WBRT, and results in excellent overall survival compared with other series. This is especially true in patients with RPA Class I and II.

Acknowledgments

We thank Kristin Kraus for her excellent editorial guidance.

Disclosure

The authors did not receive financial support in conjunction with the generation of this article. The authors have no personal or institutional financial interest in drugs, materials, or devices described in this article.

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