

LINEAR ACCELERATOR STEREOTACTIC RADIOSURGERY FOR METASTATIC BRAIN TUMORS: 17 YEARS OF EXPERIENCE AT THE UNIVERSITY OF FLORIDA

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OBJECTIVE: To review one of the largest single-institution experiences treating metastatic brain disease with stereotactic radiosurgery.

METHODS: We performed a retrospective analysis of 619 patients who underwent linear accelerator-based stereotactic radiosurgery for 1569 brain metastases between May 1989 and February 2006. Patient characteristics and treatment parameters were obtained prospectively. Patients were followed up at regular intervals clinically and with imaging studies to document local control, regional control, and survival. Cox proportional hazards analysis was performed using SAS version 9.1 software (SAS Institute, Cary, NC).

RESULTS: Median actuarial survival was 7.9 months. 1- and 2-year actuarial survival probabilities were 0.36 and 0.14, respectively. Radiation Therapy Oncology Group Recursive Partitioning Analysis Class I or II was associated with improved survival, but the difference between the two was insignificant. Female sex, younger age, higher Karnofsky performance status, controlled primary tumor, absence of systemic metastases, asynchronous presentation of brain metastasis, fewer brain metastases, smaller total volume of brain metastases, surgery prior to radiosurgery, and multiple radiosurgical treatments were also associated with improved survival. Melanoma metastasis was associated with impaired survival. Local control was achieved in 84.3% of all lesions treated. 1- and 2-year actuarial local control probabilities were 0.82 and 0.72, respectively. Whole brain radiation therapy prior to radiosurgery was associated with improved regional control.

CONCLUSIONS: Linear accelerator-based stereotactic radiosurgery is a safe and effective treatment for patients with metastatic brain tumors. Selection of patients who are likely to benefit most from radiosurgery is complex and treatment decisions should be based on the entire clinical picture.

KEY WORDS: Metastases, Radiosurgery

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Conservative estimates indicate that there are approximately 170,000 new cases of metastatic brain disease each year in the United States (41), and it has been suggested that there may be as many as 500,000 cases (74). This means that brain metastases are the most common intracranial tumors, outnumbering primary brain tumors more than ten to one (62). Twenty to 40% of patients with systemic cancer will develop metastatic brain disease; 30 to 40% of these patients will present with a single brain metastasis and the remaining 60 to 70% will present with multiple brain metastases (2). It has also been suggested that the incidence of brain metastasis is increasing, due in part to earlier diagnosis and more effective treatment of primary neoplastic disease—often with chemotherapeutic agents that do not effectively cross the blood-brain barrier—and the rising incidence of lung cancer, the most common primary source of brain metastases (85).

The primary goal in the management of metastatic brain disease is palliation of debilitating neurological symptoms, in order to attain an optimal combination of duration and quality of life. The median survival of patients with metastatic brain disease is a dismal 1 month without intervention. Corticosteroid therapy generally produces rapid palliation of symptoms, which are usually primarily attributable to peritumoral vasogenic edema, but extends median survival to only 2 months (65). Whole-brain fractionated external-beam radiotherapy (WBRT), generally administered to a total dose of 30 Gy in 10 3-Gy fractions (10), further extends median survival to 4 to 6 months (37, 63, 67), but at least half of all patients treated with this modality ultimately die from progression of their metastatic brain disease (72). Two landmark studies in the early 1990s proved that, for patients with a single resectable brain metastasis and good neurological performance status, the addition of microsurgical resection to

WBRT significantly extends survival (58, 61), and a recent prospective randomized trial demonstrated comparable outcome with the addition of stereotactic radiosurgery (SRS) to WBRT (2). Both modern surgical series and large radiosurgical series generally report median survivals of 7 to 13.5 months, with a majority of deaths attributable to systemic disease progression (1, 5, 7, 8, 11, 14, 19, 22, 28, 29, 33, 38, 54, 55, 58–62, 70, 71, 73, 75, 77, 86, 87, 89, 90). However, to date no prospective randomized trial has directly compared SRS and surgery.

Much debate exists concerning the optimum treatment for metastatic brain disease, and it has been suggested that aggressive treatment is probably underused in current practice (6). Treatment paradigms vary from center to center, and care is generally individualized based on known prognostic factors. Numerous studies have found younger age (usually <65 yr) (1, 7, 20), higher Karnofsky Performance Scale (KPS) score (usually ≥ 70) (17, 20, 31, 34, 38, 55, 62, 70, 75, 77), controlled primary tumor (11, 17, 33, 36, 88), absence of systemic metastatic disease (1, 11, 17, 31, 36, 38, 49, 50, 62, 70, 75, 77, 88), and asynchronous presentation of brain metastases (21, 75) to be significantly associated with improved survival. Many have also found Radiation Therapy Oncology Group Recursive Partitioning Analysis (RPA) Class (27), a composite of age, KPS score, primary tumor status, and status of systemic metastatic disease, to be highly correlated with survival (7, 12, 33, 54–56). As larger experiences are accumulated and analyzed, the significance of such prognostic indicators is backed by greater statistical power, allowing future treatment decisions to be made with greater confidence, even as we await more abundant Class I data. We report, to the best of our knowledge, the third-largest single-institution experience treating metastatic brain disease with SRS (28, 38, 74), and the largest such experience using a linear accelerator-based SRS system.

PATIENTS AND METHODS

Study Design

Between May 1989 and February 2006, 619 patients underwent linear accelerator-based SRS at the University of Florida, Gainesville, for metastatic brain tumors. We have conducted a retrospective review of all patient characteristics, treatment parameters, and follow-up data, in order to evaluate the impact of patient and treatment variables available at the time of treatment on survival, local control, and regional control following treatment. No patients were excluded from this analysis.

Diagnosis of metastatic brain disease was based on a history of an appropriate primary tumor and characteristic appearance of the brain lesion(s) on magnetic resonance imaging (MRI). Patient characteristics were entered prospectively into a computerized database at the time of treatment. These included age, sex, KPS, site and histology of the primary tumor, whether the primary tumor was well controlled, whether the patient had systemic metastatic disease, whether the presentation of brain metastasis occurred within 3 months of diagnosis of the primary tumor (synchronous presentation of brain metastasis) or more than three months after diagnosis of the primary tumor (asynchronous presentation of brain metastasis), number of brain metastases, location of brain metastases, history of WBRT, and history of surgical resection of a metastatic brain lesion. Primary tumor control was operationally

defined as no body imaging demonstrating progression of primary disease at the time of evaluation for and delivery of SRS. Lesions determined radiographically to be located in motor, sensory, visual, or language areas of the cerebrum or in the brainstem were considered lesions to eloquent brain. The use of WBRT and/or surgical resection in the initial management of metastatic brain disease was solely at the discretion of the referring physician.

All patients were treated using the University of Florida linear accelerator-based SRS system. The system and its use have been described in detail in multiple previous publications (23–25). Treatment parameters, including radiation dose, total dose volume (equal to total tumor volume), and number of isocenters used, were entered prospectively into a computerized database at the time of treatment.

Follow-up of each patient consisted of frequent clinical evaluation and serial MRI scans obtained every 3 months, either at the University of Florida or at a location closer to the patient's home. All scans were reviewed by the senior author (WAF) as soon as they were available and were compared with the stereotactic treatment scans. His findings were entered into a computerized database at the time of review. Local control was evaluated on a per-lesion basis. If a follow-up scan demonstrated any perceivable enlargement of a previously treated lesion, local control of that lesion was considered to be lost on the date of that scan. Additionally, if a previously treated lesion was resected for any reason, local control of that lesion was considered to be lost on the date of surgery, regardless of prior radiographic evidence of local control or the results of surgical pathology. For the purpose of this analysis, duration of local control is calculated as the interval between the date of treatment and the date on which local control was proven to be lost. If a follow-up scan demonstrated metastatic brain disease not evident on the treatment scan, it was counted as a loss of a regional control. No data on duration of regional control was collected. Recurrent and/or new brain metastases were managed with palliative care, WBRT, surgery, or repeat SRS, at the discretion of the treating physician and depending on the wishes of the patient and his or her family.

In order to obtain the most accurate, up-to-date data possible on the vital status of each patient, a search of the Social Security Death Index (SSDI) was conducted using two publicly available online search engines (80, 81) and the search algorithm described by Hauser and Ho (30). This algorithm, which involves manually searching for one patient at a time, first by social security number alone, then by last name, first name, birth year, birth month, and birth date, and finally by last name, first name, birth year, and birth month, has been shown to be 86% sensitive and 100% specific (30). If a patient who was not listed as deceased in the SSDI was discovered to be overdue for a follow-up clinical evaluation or MRI scan, phone calls were placed to the patient and/or referring physician in order to determine the vital status of that patient.

Statistical Methods

The Cox proportional hazards model was used to explore the relationship between sex, age, KPS score, primary tumor type (non-small cell lung cancer reference), status of the primary tumor (controlled versus uncontrolled), presence or absence of systemic metastases, timing of presentation of brain metastasis (synchronous versus asynchronous), number of brain metastases, total volume of brain metastases, location of brain metastases (eloquent versus non-eloquent), history of WBRT, history of surgery, SRS dose, and number of SRS treatments, and survival and local control. Added-in-last with fixed order was used to select the significant variables; variables were added in the order listed here. Final model analysis of variables that were significant on model selection analysis was performed using the Type I (sequential) method, and Type I *P* values, Type I hazard ratios, and 95% confidence intervals

are reported. These analyses were conducted using the PROC PHREG and PROC LIFETEST procedures in SAS (Version 9.1; SAS Institute, Cary, NC).

Logistic regression was used to explore the relationship between these same variables and regional control. Added-in-last with fixed order was used to select the significant variables; variables were added in the order listed here. Final model analysis of variables that were significant on model selection analysis was performed using the Type I (sequential) method, and Type I *P* values, Type I odds ratios, and 95% confidence intervals are reported. These analyses were conducted using the PROC LOGISTIC procedure in SAS (Version 9.1).

Because RPA class is a composite variable composed of age, KPS score, presence or absence of systemic metastases, and status of the primary tumor (controlled versus uncontrolled), each analysis was conducted twice: once including these four variables but excluding RPA class, and once excluding these four variables and including RPA class. The results of both analyses are reported. Parameters were deemed to be statistically significant at a *P* value of 0.05 or less.

RESULTS

Patient and Treatment Characteristics

Between May 1989 and February 2006, a total of 619 patients underwent 745 treatments for 1569 metastatic brain tumors. Median age at the time of first treatment was 60 years (mean, 59 yr; range, 4–86 yr). Median KPS score was 80 (mean, 81.5; range, 40–100) and 579 patients (93.5%) had a KPS score of 70 or greater. The remainder of the pertinent patient data is summarized in *Table 1*. Three hundred forty-eight patients (56.2%) were initially treated for single brain metastasis and 271 patients (43.8%) were initially treated for multiple metastases (868 lesions total). The locations of all 348 single metastases are summarized in *Table 2*. Ninety patients (14.5%) underwent additional radiosurgery: 10 for lesions recurrent after radiosurgical treatment, 65 for new lesions, and 15 for both recurrent and new lesions. Twenty-nine metastases in 25 patients were treated with radiosurgery twice; no lesion was treated with radiosurgery more than twice. Median dose to the target periphery was 1750 cGy (mean, 1736 cGy; range, 1000–2250 cGy). Almost all lesions were treated to the 70 or 80% isodose line. In general, larger lesions were treated with lower doses, and doses used early in our experience were lower than those presently used. Currently, we recommend a dose of 2000 cGy to the periphery of lesions smaller than 2.5 cm in diameter. Median total dose volume (equal to total tumor volume) was 4.6 cm³ (mean, 8.0 cm³; range, <0.1–49.4 cm³). The median number of isocenters used was two (mean, 3.3; range, 1–22). The number of metastases treated during each SRS procedure is summarized in *Table 3*.

Survival

Survival data were available for 597 of 619 patients (96.4%) treated during the study interval. At the time of analysis, 46 patients (7.4%) were alive, with a median follow-up of 12.8 months (mean, 29.5 mo; range, 5.6–117.6 mo) and 551 patients (89.0%) had died. No data on cause of death was collected. Twenty-six patients (4.2%) died within 30 days of their first treatment. Twenty-two patients (3.6%) were lost to follow-up a

TABLE 1. Patient characteristics^a

	Patients (n = 619)	
	No.	%
Sex		
Male	331	53.5
Female	288	46.5
RPA class (25)		
I	127	20.5
II	453	73.2
III	39	6.3
Primary tumor type		
NSCLC	290	46.8
Breast	81	13.1
Melanoma	66	10.7
Other	49	7.9
SCLC	39	6.3
Renal	37	6.0
Gastrointestinal	37	6.0
Unknown	20	3.2
Status of primary tumor		
Controlled	399	64.5
Uncontrolled	220	35.5
Systemic metastatic disease		
Absent	356	57.5
Present	263	42.5
Presentation of brain metastasis		
Asynchronous	409	66.1
Synchronous	210	33.9
Lesion(s) to eloquent brain		
None	346	55.9
One or more	273	44.1
Prior WBRT		
Yes	366	59.1
No	253	40.9
Prior surgery		
Yes	167	27.0
No	452	73.0
No. of SRS treatments		
1	529	85.5
2	70	11.3
3	11	1.8
4	6	1.0
5	2	<1.0
9	1	<1.0

^a RPA, recursive partitioning analysis; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery.

TABLE 2. Single brain metastases

	Metastases (n = 348)	
	No.	%
Laterality		
Right	166	47.7
Left	172	49.4
Midline	10	2.9
Location		
Frontal lobe	98	28.2
Parietal lobe	74	21.3
Cerebellum	58	16.7
Temporal lobe	36	10.3
Occipital lobe	30	8.6
Other	19	5.5
Thalamus	12	3.4
Pons	10	2.9
Midbrain	7	2.0
Basal ganglia	4	1.1

TABLE 3. Radiosurgical treatments

	Treatments (n = 745)	
	No.	%
Metastases treated, no.		
1	404	54.2
2	160	21.5
3	75	10.1
4	40	5.4
5	25	3.4
6	17	2.3
7	9	1.2
8	2	<1.0
9	5	<1.0
11	2	<1.0
12	1	<1.0
13	2	<1.0
14	1	<1.0
15	1	<1.0
20	1	<1.0

median of 8.4 months after treatment (mean, 25.9 mo; range, 0–124.0 mo), and although 12 of them were considered very likely to be alive at the time of manuscript preparation, based on available pre-treatment and follow-up data, all were excluded from the statistical analysis. The median actuarial survival was 7.9 months (95% confidence interval, 7.0–8.8 mo) from the time of first SRS treatment. The 1- and 2-year actuar-

ial survival estimates were 0.36 (95% confidence interval, 0.34–0.38) and 0.14 (95% confidence interval, 0.12–0.16), respectively (Fig. 1). RPA class was found to be significantly associated with survival, as discussed below. Median actuarial survival was 9.4 (range, 8.0–12.7), 7.8 (range, 6.7–8.7), and 3.9 (range, 2.0–6.0) months for RPA Classes I, II, and III, respectively. The 1- and 2-year actuarial survival estimates were 0.42 ± 0.05 and 0.21 ± 0.04 , 0.35 ± 0.02 and 0.13 ± 0.02 , and 0.25 ± 0.07 and 0.03 ± 0.03 , respectively (Fig. 2).

Model selection hazard analysis identified female sex, younger age, higher KPS score, tumor type, controlled primary tumor, absence of systemic metastases, better RPA class, asynchronous presentation of brain metastasis, fewer metastases, smaller total tumor volume, prior surgery, and more SRS treatments to be significantly associated with improved survival when adjusting for their respective previous variables in the model. Eloquent tumor location, prior WBRT, and SRS dose were not significantly associated with survival probability.

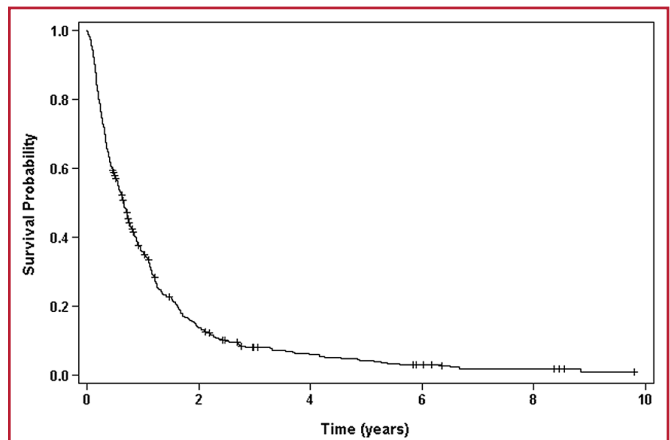


FIGURE 1. Kaplan-Meier plot demonstrating actuarial survival.

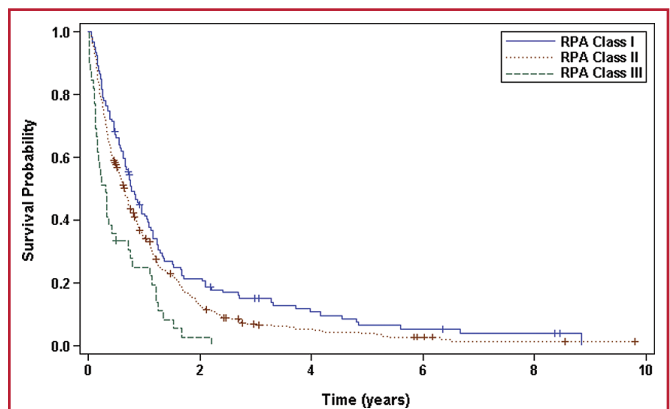


FIGURE 2. Kaplan-Meier plot demonstrating actuarial survival, stratified by Recursive Partitioning Analysis (RPA) class. Survival did not differ significantly between RPA Classes I and II, but RPA Class III was associated with impaired survival.

Type I final model hazard analysis identified the following: female sex was associated with improved survival, with male sex exhibiting a 33.3% higher hazard rate ($P = 0.001$). Younger age was associated with improved survival, with each increasing year exhibiting a 0.9% higher hazard rate ($P = 0.016$). Higher KPS score was associated with improved survival, with each additional 10 points exhibiting a 1.3% lower hazard rate ($P = 0.004$). Using non-small cell lung cancer as the reference category, melanoma metastasis was associated with impaired survival, exhibiting a 64.5% higher hazard rate in the analysis excluding RPA class ($P = 0.001$) and a 51.5% higher hazard rate in the analysis including RPA class ($P = 0.004$). There was a trend toward improved survival with small-cell lung cancer metastasis, which exhibited a 27.2% lower hazard rate in the analysis excluding RPA class ($P = 0.072$) and a 28.6% lower hazard rate in the analysis including RPA class ($P = 0.054$), as well as with metastasis from an unknown primary, which exhibited a 36.5% lower hazard rate in the analysis excluding RPA class ($P = 0.053$) and a 33.9% lower hazard rate in the analysis including RPA class ($P = 0.079$). Primary control was associated with improved survival, exhibiting a 19.9% lower hazard rate than uncontrolled primary tumor ($P = 0.024$). Absence of systemic metastases was associated with improved survival, with systemic metastases exhibiting a 24.7% higher hazard rate ($P = 0.026$). RPA Class III was associated with impaired survival, exhibiting a 128.2% higher hazard rate than RPA Class I ($P = 0.000$). Notably, although model selection analysis identified a significant survival advantage for RPA Class I relative to RPA Class II, this significance was lost on Type I final model analysis, in which RPA Class II exhibited only a 4.9% higher hazard rate than RPA Class I ($P = 0.625$). Asynchronous presentation of brain metastasis was associated with improved survival, with synchronous presentation exhibiting a 24.9% higher hazard rate in the analysis including RPA class ($P = 0.044$). Synchronicity of presentation was not evaluated in the final model analysis excluding RPA class because it was not significant in the model selection analysis excluding RPA class, although it did approach significance in that model ($P = 0.068$). Fewer metastases was associated with improved survival, with each additional lesion exhibiting a 6.2% higher hazard rate in the analysis excluding RPA class ($P = 0.014$) and a 7.7% higher hazard rate in the analysis including RPA class ($P = 0.002$). Smaller total tumor volume was associated with improved survival, with each additional cm^3 exhibiting a 1.2% higher hazard rate in the analysis excluding RPA class ($P = 0.041$). Total tumor volume was not evaluated in the final model analysis including RPA class because it was not significant in the model selection analysis excluding RPA class, although it did approach significance in that model ($P = 0.059$). Prior surgery was associated with improved survival, exhibiting a 28.0% lower hazard rate in the analysis excluding RPA class ($P = 0.001$) and a 26.9% lower hazard rate in the analysis including RPA class ($P = 0.002$). Finally, multiple SRS treatments was associated with improved survival, with each additional treatment exhibiting a 37.8% lower hazard rate in the analysis excluding RPA class ($P = 0.000$) and a 37.2% lower hazard rate in the analysis including RPA class ($P = 0.000$) (Table 4).

Local Control

Local control data were available for 878 (56.0%) of 1569 brain metastases in 366 (59.1%) of 619 patients treated during the study interval. At the time of analysis, 740 metastases were well controlled (84.3%) and control of the remaining 138 metastases (15.7%) had been lost. The median actuarial local control was 7.67 years (95% confidence interval, 7.67 yr—greater than current length of follow-up) from the time of SRS treatment. The 1- and 2-year actuarial local control estimates were 0.82 (95% confidence interval, 0.80–0.84) and 0.72 (95% confidence interval, 0.69–0.75), respectively (Fig. 3).

Model selection hazard analysis identified female sex, uncontrolled primary tumor, asynchronous presentation of brain metastasis, more metastases, and more SRS treatments to be significantly associated with longer duration of local control when adjusting for their respective previous variables in the model. Age, KPS score, tumor type, presence or absence of systemic metastases, RPA class, prior WBRT, and SRS dose were not significantly associated with local control probability. Tumor volume, eloquent location, and prior surgery were not evaluated in this analysis because these variables were not, for the purposes of this study, readily available on a per-lesion basis in cases of multiple brain metastases. However, a separate model selection hazard analysis performed on data from a subset of 167 single metastases, including all of the previously mentioned variables, found tumor volume ($P = 0.591$), eloquent location ($P = 0.296$), and prior surgery ($P = 0.668$) to be insignificant.

Type I final model hazard analysis identified the following: female sex was associated with longer duration of local control, with male sex exhibiting a 74.5% higher hazard rate ($P = 0.001$). Uncontrolled primary tumor was associated with longer duration of local control, with controlled primary exhibiting a 74.6% higher hazard rate ($P = 0.004$). Multiple metastases was associated with longer duration of local control, with each additional lesion exhibiting a 31.7% lower hazard rate in the analysis excluding RPA class ($P = 0.000$) and a 32.1% lower hazard rate in the analysis including RPA class ($P = 0.000$). Finally, multiple SRS treatments was associated with longer duration of local control, with each additional treatment exhibiting a 17.4% lower hazard rate in the analysis excluding RPA class ($P = 0.005$) and a 17.9% lower hazard rate in the analysis including RPA class ($P = 0.002$) (Table 5).

Regional Control

Regional control data were available for 366 (59.1%) of 619 patients treated during the study interval. Two hundred nineteen (59.8%) of these 366 patients received WBRT prior to radiosurgery, and 147 (40.2%) did not. At the time of analysis, regional control had been maintained in 243 patients (66.4%) and lost in the remaining 123 patients (33.6%).

Model selection logistic analysis identified asynchronous presentation of brain metastasis, fewer brain metastases, eloquent tumor location, and prior WBRT to be significantly associated with improved regional control when adjusting for their respective previous variables in the model. Prior surgery, higher SRS dose, and multiple SRS treatments were associated with impaired

TABLE 4. Hazard analysis of factors contributing to survival^a

Factor	Model selection analysis				Final model analysis			
	Excluding RPA class		Including RPA class		Excluding RPA class		Including RPA class	
	Hazard ratio (CI)	P value ^b	Hazard ratio (CI)	P value ^b	Hazard ratio (CI)	P value ^b	Hazard ratio (CI)	P value ^b
Male sex	1.333 (1.126–1.579)	0.001	1.333 (1.126–1.579)	0.001	1.333 (1.126–1.579)	0.001	1.333 (1.126–1.579)	0.001
Age	1.009 (1.002–1.017)	0.016	Excluded		1.009 (1.002–1.017)	0.016	Excluded	
KPS	0.987 (0.979–0.996)	0.004	Excluded		0.987 (0.979–0.996)	0.004	Excluded	
Tumor type		0.006		0.027				
Breast	0.990 (0.737–1.330)		0.937 (0.700–1.254)		1.027 (0.773–1.364)	0.856	0.969 (0.732–1.283)	0.826
GI	0.932 (0.638–1.361)		1.000 (0.688–1.453)		0.968 (0.669–1.400)	0.860	1.029 (0.714–1.482)	0.880
Melanoma	1.505 (1.140–1.987)		1.400 (1.064–1.842)		1.645 (1.256–2.153)	0.001	1.515 (1.162–1.977)	0.004
Other	0.801 (0.574–1.119)		0.843 (0.604–1.175)		0.859 (0.618–1.195)	0.359	0.899 (0.648–1.249)	0.521
Renal	0.913 (0.629–1.324)		0.957 (0.660–1.386)		0.986 (0.682–1.425)	0.940	1.032 (0.715–1.491)	0.865
SCLC	0.704 (0.491–1.010)		0.692 (0.483–0.992)		0.728 (0.508–1.043)	0.072	0.714 (0.498–1.021)	0.054
Unknown	0.635 (0.388–1.038)		0.661 (0.405–1.081)		0.635 (0.388–1.038)	0.053	0.661 (0.405–1.081)	0.079
Primary control	0.801 (0.662–0.969)	0.024	0.801 (0.662–0.969)	0.024	Excluded			
Systemic mets	1.247 (1.028–1.513)	0.026	Excluded		1.247 (1.028–1.513)	0.026	Excluded	
RPA class								
II	Excluded		1.240 (0.998–1.542)	0.000	Excluded		1.049 (0.865–1.273)	0.625
III	Excluded		2.282 (1.555–3.348)	0.000	Excluded		2.282 (1.555–3.348)	0.000
Synchronous	1.294 (0.982–1.707)	0.068	1.249 (1.007–1.549)	0.044	1.249 (1.007–1.549)	0.044		
Metastases, no.	1.062 (1.014–1.112)	0.014	1.077 (1.030–1.125)	0.002	1.062 (1.015–1.113)	0.014	1.077 (1.030–1.125)	0.002
Tumor volume	1.011 (1.000–1.022)	0.050	1.011 (1.000–1.022)	0.059	1.012 (1.001–1.023)	0.041		
Eloquent location	0.965 (0.813–1.146)	0.687	0.962 (0.812–1.140)	0.653				
Prior WBRT	0.954 (0.793–1.147)	0.614	0.938 (0.782–1.125)	0.490				
Prior surgery	0.695 (0.566–0.854)	0.000	0.689 (0.561–0.846)	0.000	0.720 (0.588–0.881)	0.001	0.731 (0.598–0.893)	0.002
SRS dose	0.995 (0.958–1.033)	0.802	1.000 (0.964–1.038)	0.996				
SRS Tx, no.	0.615 (0.519–0.729)	0.000	0.623 (0.525–0.739)	0.000	0.622 (0.526–0.736)	0.000	0.628 (0.531–0.741)	0.000

^a RPA, recursive partitioning analysis; CI, confidence interval; KPS, Karnofsky Performance Scale; GI, gastrointestinal cancer; SCLC, small cell lung cancer; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; Tx, treatments.

^b P ≤ 0.05 indicates statistical significance.

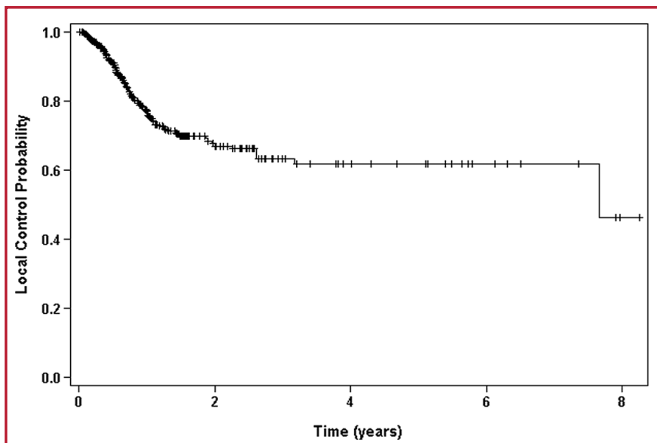


FIGURE 3. Kaplan-Meier plot demonstrating actuarial local control.

regional control. Sex, age, KPS score, tumor type, status of primary tumor (controlled versus uncontrolled), presence or absence of systemic metastases, RPA class, and total tumor volume were not significantly associated with local control probability.

Type I final model logistic analysis identified the following: fewer metastases was associated with improved regional control, with each additional lesion exhibiting a 13.8% lower odds ratio ($P = 0.031$). Eloquent tumor location was associated with improved regional control, exhibiting a 75.9% higher odds ratio than non-eloquent tumor location ($P = 0.014$). Prior WBRT was associated with improved regional control, exhibiting a 68.5% higher odds ratio in the analysis including RPA class ($P = 0.025$). Prior WBRT was not evaluated in the final model analysis excluding RPA class because it was not significant in the model selection analysis excluding RPA class, although it did approach significance in that model ($P = 0.056$). Prior surgery was associated with impaired regional control, exhibiting a 66.0% lower odds ratio in the analysis

TABLE 5. Hazard analysis of factors contributing to local control^a

Factor	Model selection analysis				Final model analysis			
	Excluding RPA class		Including RPA class		Excluding RPA class		Including RPA class	
	Hazard ratio (CI)	P value ^b	Hazard ratio (CI)	P value ^b	Hazard ratio (CI)	P value ^b	Hazard ratio (CI)	P value ^b
Male sex	1.745 (1.246–2.444)	0.001	1.745 (1.246–2.444)	0.001	1.745 (1.246–2.444)	0.001	1.745 (1.246–2.444)	0.001
Age	1.002 (0.987–1.017)	0.811	Excluded					
KPS	0.998 (0.985–1.012)	0.826	Excluded					
Tumor type	0.174		0.276					
Breast	1.209 (0.665–2.198)		1.207 (0.665–2.192)					
GI	0.827 (0.377–1.813)		1.005 (0.528–1.916)					
Melanoma	2.161 (1.311–3.563)		1.939 (1.210–3.107)					
Other	0.981 (0.419–2.299)		1.047 (0.450–2.434)					
Renal	0.794 (0.371–1.699)		0.778 (0.365–1.659)					
SCLC	0.922 (0.459–1.851)		0.869 (0.437–1.725)					
Unknown	0.820 (0.253–2.664)		0.901 (0.280–2.899)					
Primary control	2.294 (1.458–3.608)	0.000	Excluded		1.746 (1.173–2.599)	0.004	Excluded	
Systemic mets	0.871 (0.581–1.306)	0.503	Excluded					
RPA class								
II	Excluded		0.701 (0.472–1.041)	0.080				
III	Excluded		1.551 (0.635–3.788)	0.080				
Synchronous	2.181 (1.277–3.723)	0.005	(0.723–1.870)	1.163	0.535	1.389 (0.868–2.221)	0.177	
Metastases, no.	0.655 (0.575–0.745)	0.000	0.643 (0.561–0.739)	0.000	0.683 (0.595–0.785)	0.000	0.679 (0.592–0.778)	0.000
Prior WBRT	0.775 (0.533–1.127)	0.184	0.797 (0.551–1.155)	0.233				
SRS dose	0.960 (0.901–1.024)	0.215	0.953 (0.895–1.014)	0.134				
SRS Tx, no.	0.822 (0.705–0.957)	0.008	0.772 (0.674–0.883)	0.000	0.826 (0.712–0.957)	0.005	0.821 (0.712–0.946)	0.002

^a RPA, recursive partitioning analysis; CI, confidence interval; KPS, Karnofsky Performance Scale; GI, gastrointestinal cancer; SCLC, small cell lung cancer; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; Tx, treatments.

^b P ≤ 0.05 indicates statistical significance.

excluding RPA class ($P = 0.000$) and a 66.6% lower odds ratio in the analysis including RPA class ($P = 0.000$). Higher SRS dose was associated with impaired regional control, with each 1 Gy increase in dose exhibiting a 18.6% lower odds ratio in the analysis excluding RPA class ($P = 0.000$) and a 18.2% lower odds ratio in the analysis including RPA class ($P = 0.000$). Finally, multiple SRS treatments was associated with impaired regional control, with each additional treatment exhibiting a 96.8% lower odds ratio ($P = 0.000$). This is because most retreatments were to treat new metastases outside the original radiosurgical field (Table 6).

Complications

Fourteen (2.3%) of 619 patients developed radiation necrosis a median of 8.7 months after treatment (mean, 8.8 mo; range, 3.1–17.3 mo). No patient developed more than one necrotic focus, and no lesion that ultimately became necrotic was treated with radiosurgery more than once. Twelve patients underwent resection of the necrotic focus and were definitively diagnosed based on surgical pathology; one of these patients subsequently underwent a second operation for the same necrotic focus. Two patients were diagnosed based on charac-

teristic symptoms and MRI findings and responded well to corticosteroid therapy.

Forty-four (7.1%) of 619 patients underwent surgical resection for symptomatic tumor recurrence a median of 6.3 months after treatment (mean, 7.8 mo; range, 0.9–38.0 mo). One patient underwent a single operation for resection of two recurrent lesions, one patient underwent two operations for resection of two separate recurrent lesions, and one patient underwent three operations for the repeated resection of the same recurrent lesion. Ten resected recurrent tumors in as many patients were found to have features of radiation necrosis. One of these patients later underwent a second resection of the same recurrent lesion, at which time surgical pathology revealed only radiation necrosis. This patient was also included among the 14 patients with radiation necrosis, reported above. Three resected tumors in two patients—one non-small cell lung metastasis and two melanoma metastases—were hemorrhagic.

Two additional patients each underwent surgical resection of a lesion previously treated with radiosurgery, 20.4 and 20.8 months after treatment, respectively. However, because these operations were performed at outside medical centers, the surgical pathology reports were not available for review.

TABLE 6. Logistic analysis of factors contributing to regional control^a

Factor	Model selection analysis				Final model analysis			
	Excluding RPA class		Including RPA class		Excluding RPA class		Including RPA class	
	Odds ratio (CI)	P value ^b	Odds ratio (CI)	P value ^b	Odds ratio (CI)	P value ^b	Odds ratio (CI)	P value ^b
Male sex	1.113 (0.721–1.718)	0.628	1.113 (0.721–1.718)	0.628				
Age	1.006 (0.987–1.025)	0.564	Excluded					
KPS	0.989 (0.966–1.012)	0.340	Excluded					
Tumor type		0.215		0.190				
Breast	0.634 (0.306–1.314)		0.633 (0.309–1.295)					
GI	1.124 (0.414–3.051)		1.175 (0.436–3.169)					
Melanoma	0.488 (0.230–1.036)		0.494 (0.235–1.037)					
Other	0.714 (0.316–1.616)		0.726 (0.322–1.640)					
Renal	0.749 (0.306–1.834)		0.778 (0.320–1.895)					
SCLC	0.328 (0.132–0.815)		0.329 (0.133–0.815)					
Unknown	1.275 (0.334–4.868)		1.328 (0.349–5.049)					
Primary control	1.471 (0.858–2.522)	0.162	Excluded					
Systemic mets	0.882 (0.531–1.468)	0.630	Excluded					
RPA class								
II	Excluded		0.774 (0.456–1.313)	0.625				
III	Excluded		0.752 (0.224–2.524)	0.625				
Synchronous	0.356 (0.158–0.802)	0.012	0.459 (0.252–0.836)	0.010	0.679 (0.426–1.084)	0.106	0.679 (0.426–1.084)	0.106
Metastases, no.	0.839 (0.725–0.970)	0.017	0.851 (0.740–0.979)	0.023	0.862 (0.751–0.990)	0.031	0.862 (0.751–0.990)	0.031
Tumor volume	1.030 (0.995–1.066)	0.082	1.030 (0.995–1.066)	0.081				
Eloquent location	1.701 (1.062–2.725)	0.026	1.672 (1.048–2.670)	0.030	1.759 (1.118–2.768)	0.014	1.759 (1.118–2.768)	0.014
Prior WBRT	1.616 (0.988–2.643)	0.056	1.696 (1.045–2.754)	0.032	1.685 (1.069–2.655)	0.025		
Prior surgery	0.273 (0.161–0.465)	0.000	0.269 (0.157–0.459)	0.000	0.340 (0.212–0.547)	0.000	0.334 (0.207–0.538)	0.000
SRS dose	0.850 (0.759–0.952)	0.004	0.845 (0.755–0.946)	0.003	0.814 (0.744–0.890)	0.000	0.818 (0.741–0.904)	0.000
SRS Tx, no.	0.021 (0.009–0.052)	0.000	0.024 (0.010–0.056)	0.000	0.032 (0.015–0.070)	0.000	0.032 (0.014–0.069)	0.000

^a RPA, recursive partitioning analysis; CI, confidence interval; KPS, Karnofsky Performance Scale; GI, gastrointestinal cancer; SCLC, small cell lung cancer; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; Tx, treatments.

^b P ≤ 0.05 indicates statistical significance.

No data on acute or minor complications associated with radiosurgical treatment were collected.

DISCUSSION

SRS was first described by Leksell (44) in 1951 as a method of using multiple, convergent radiation beams to deliver a high dose of radiation to a discrete intracranial target with the precision necessary to safely and effectively perform minimally-invasive functional neurosurgery. Use of SRS in a clinical setting began in 1967 (43), but the first report of SRS for metastatic brain disease was not published until 20 years later (46, 84). Since that time, tens of thousands of patients with metastatic brain tumors have been treated with both linear accelerator-based and gamma knife SRS, and the two platforms have proven equally safe and effective (2, 79).

SRS is well suited for the treatment of brain metastases. It is minimally invasive and does not require general anesthesia, making it a viable option for patients who cannot tolerate surgery, and

is generally performed as an outpatient procedure. Metastatic lesions are typically spherical and clearly defined on neuroimaging due to contrast uptake, facilitating treatment planning. They are also small and histologically well defined, justifying the rapid fall-off of radiation dose at the periphery of the target volume generated by SRS (47). SRS is readily applicable to lesions located nearly anywhere in the brain, including eloquent locations and deep brain locations that would be difficult or impossible to access surgically with acceptable morbidity, and can be used to treat multiple lesions in a single treatment session (7, 26, 28, 32, 33, 54, 70, 71). It has proven to be an effective treatment even for melanoma, sarcoma, and renal cell carcinoma metastases—lesions traditionally considered to be radioresistant (12, 15, 28, 42, 49, 50, 51, 57). SRS may also be used in combination with WBRT and/or surgery, and may be repeated when necessary to treat recurrent disease (16, 28, 56, 70, 73). Additionally, SRS has been shown to be more cost-effective than surgery (48, 66).

Like all treatment modalities, SRS has disadvantages as well. It is incapable of rapidly resolving symptoms due to tumor

mass effect, and surgical resection is generally a more appropriate treatment for patients with symptomatic mass effect, provided that they are surgical candidates. SRS also has limited applicability for large metastatic lesions (≥ 3 cm in diameter) due to increasing radiation exposure to normal brain with increasing target volume (73) and for lesions located within close proximity of structures with low radiation tolerance, such as the optic nerves and chiasm (83).

Currently, the optimal role of SRS in the management of metastatic brain disease is not well defined. Results of the first prospective randomized trials of WBRT with or without SRS have only recently been reported (2, 40), and although they have shown that SRS offers a significant survival benefit for patients with a single brain metastasis, they have not corroborated a large body of retrospective literature suggesting that SRS similarly improves survival for patients with multiple brain metastases (7, 33, 54, 70, 71). Although large SRS series consistently report survival durations comparable to those reported in surgical series, no randomized prospective comparison of these two treatment modalities has been conducted (1, 5, 7, 8, 11, 14, 19, 22, 28, 29, 33, 38, 54, 55, 58–62, 70, 71, 76, 77, 86, 87, 89, 90).

Survival and Local Control after SRS

We report a median actuarial survival of 7.9 months following SRS and 1- and 2-year actuarial survival probabilities of 36 and 14%, respectively. These values are consistent with those reported in other large radiosurgical series, in which median survival typically ranges from about 7 to 13.5 months (1, 5, 7, 11, 14, 19, 22, 28, 29, 33, 38, 54, 55, 62, 70, 71, 75, 76, 77, 86, 87, 90), and 1- and 2-year survival probabilities typically range from 31 to 53% and 13 to 30%, respectively (5, 14, 54, 55, 62, 76, 90), but fall at the low end of these ranges. However, many of these other series were limited to solitary brain metastasis (5, 22, 77, 87), excluded patients with large tumor volumes (14, 28, 76), or excluded patients with unfavorable characteristics (1, 5, 28, 29). The wider range of patient and tumor characteristics encompassed in the present study may account for the lower than expected median survival. The use of the SSDI to determine survival status may also contribute, because many patients who would otherwise have been considered lost to follow-up and excluded from the survival analysis were identified as deceased in the SSDI and were considered deceased for the purposes of this analysis due to the 100% specificity of the SSDI (30).

We also report a median local control time of 7.67 years, a crude local control rate of 84.3%, and 1- and 2-year actuarial local control probabilities of 82 and 72%, respectively. These values are consistent with those reported in other large radiosurgical series, in which crude local control rates typically range from 82 to 96% (5, 9, 19, 22, 28, 29, 33, 35, 54, 55, 69, 75, 77, 87), and 1- and 2-year local control probabilities typically range from 64 to 91% and 46 to 77%, respectively (1, 5, 7, 14, 29, 54, 55, 62, 68, 71, 82).

Andrews et al. (2) recently reported the Phase III results of Radiation Therapy Oncology Group protocol 9508, the first prospective, randomized trial of WBRT with or without SRS for

the treatment of metastatic brain disease to reach full accrual. Three hundred thirty-three patients with one to three newly diagnosed brain metastases, KPS score of 70 or greater, and no history of WBRT were randomly allocated either WBRT alone (167 patients) or WBRT followed by an SRS boost (164 patients). Analysis revealed a significant survival advantage for patients with a single brain metastasis treated with WBRT plus SRS rather than WBRT alone (median survival, 6.5 versus 4.9 mo), but failed to reveal a similar advantage for patients with two to three brain metastases. However, all patients in the WBRT plus SRS group were significantly more likely to have a stable or improved KPS score 6 months post-treatment, and were less likely to be dependent on corticosteroids, than those treated with WBRT alone. Multivariate analysis revealed RPA Class I and non-small cell lung primary to be significantly associated with improved survival. Analysis also revealed significantly better 1-year local control of lesions treated with WBRT plus SRS, compared to those treated with WBRT alone (82 versus 71%). The authors concluded that the addition of SRS to WBRT should be standard treatment for patients with a single brain metastasis and considered for patients with two to three brain metastases (2). Kondziolka et al. (40) had previously conducted a similar randomized prospective study, in which patients with two to four brain metastases and KPS score of 70 or greater were randomly allocated either WBRT alone or WBRT plus SRS, however, this study was stopped at an interim evaluation (60% accrual: 14 patients in the WBRT alone group and 13 in the WBRT plus SRS group) due to detection of significantly better local control following WBRT plus SRS compared to WBRT alone. Median time to local failure was 6 months following WBRT alone versus 36 months following WBRT plus SRS; 1 year after treatment, no patient in the WBRT group had maintained local control, compared with 92% of patients in the WBRT plus SRS group. Although interim analysis revealed a trend toward improved survival following WBRT plus SRS compared to WBRT alone (median survival durations of 11 mo and 7.5 mo, respectively), no conclusions could be made due to the small number of patients in the study (43).

Many groups have conducted retrospective analyses in order to determine patient characteristics and treatment variables associated with improved local control and survival following SRS for metastatic brain disease. In this study, many patient and treatment variables—in fact nearly every patient and treatment variable assessed—were significantly associated with survival after SRS. Many other large retrospective analyses, involving hundreds of patients and/or metastatic brain tumors, most of which are based on gamma knife series, have found higher KPS score (usually ≥ 70) (17, 20, 31, 34, 38, 55, 62, 70, 75, 77), controlled primary tumor (11, 17, 33, 36, 88), absence of systemic metastatic disease (1, 11, 17, 31, 36, 38, 49, 50, 62, 70, 75, 77, 88), better RPA Class (7, 12, 33, 54–56), and asynchronous presentation of brain metastases (21, 75) to be significantly associated with better survival (Table 7). Our results are consistent with these findings. However, even the largest reviews sometimes produce discordant results, and the prognostic value of age and number of metastases, in particular, remains unclear. Although numerous

TABLE 7. Large retrospective reviews of stereotactic radiosurgery for metastatic brain disease^a

Series (ref. no.)	Pts	Mets	SRS	Survival			Local control			
				Median (mo)	1- and 2-yr	Improved with	Crude	Median (mo)	1- and 2-yr	Improved with
Alexander et al., 1995 (1)	248	421	LA	9.4	—	Age < 60 No systemic disease ≤ 2 brain metastases Female sex	89%	8.4	—	Smaller total tumor volume Newly-diagnosed metastasis Supratentorial location
Bhatnagar et al., 2006 (7)	205	≥ 4/pt	GK	8	—	Younger age Lower RPA Class Smaller total tumor volume Higher SRS dose	—	23	71%, 49%	Smaller total tumor volume
Gerosa et al., 2002 (28)	804	1307	GK	13.5	—	—	93%	—	—	—
Nam et al., 2005 (54)	130	719	GK	8.1	40.6% 1 yr.	Lower RPA Class	89.5%	—	63.9% 1 yr.	—
Petrovich et al., 2002 (62)	458	1305	GK	9	33%, 16%	KPS ≥ 70 No systemic disease Smaller total tumor volume Breast cancer Renal cell carcinoma	—	—	87% 1 yr.	Smaller total tumor volume
Sheehan et al., 2002 (75)	273	627	GK	7	—	Higher KPS No systemic disease Asynchronous presentation Adenocarcinoma Female sex	86%	12	—	Smaller total tumor volume Higher SRS dose
Simonova et al., 2000 (77)	237	237	GK	9.5 ^b	38.8% 1 yr.	KPS ≥ 70 NFC I No systemic disease Breast cancer Renal cell carcinoma SRS dose ≥ 20 Gy	91%	—	—	—

^a Pts, patients; mets, metastases; SRS, stereotactic radiosurgery; LA, linear accelerator-based SRS; GK, gamma knife; RPA, recursive partitioning analysis; SRS, stereotactic radiosurgery; KPS, Karnofsky performance status; NFC, neurological functional class.

^b Approximate value, extrapolated from Kaplan-Meier curve.

studies, including this one, have found younger age (usually <65) to be significantly associated with improved survival (1, 7, 20), Noel et al. (55) recently reviewed 117 patients aged 65 years or older treated with linear accelerator-based SRS for 227 brain metastases and found a median survival of 8 months and 1- and 2-year survival rates of 31 and 13%, respectively. These results are comparable to those of numerous studies including patients of all ages. Similarly, although numerous studies, including this one, have found fewer brain metastases to be significantly associated with improved survival (1–3), Bhatnagar et al. (7) recently reviewed 205 patients treated with gamma knife SRS for four or more brain metastases each and found a median survival of 8 months. These results are comparable to median survivals reported for series of patients with solitary brain metastasis or oligometastatic disease. Nam et al. (54) found no significant survival difference in a retrospective comparison of SRS for four or more brain metastases versus one to three metastases. Interestingly, several retrospective reviews have determined that smaller total tumor volume is significantly associated with

improved survival, independent of the number of metastases (7, 33, 62). Smaller total tumor volume is often also significantly associated with improved local control (1, 7, 15, 33, 62, 75, 76, 88), although these are not independent variables, because smaller lesions can be safely treated with higher doses (73). Interestingly, neither smaller tumor volume nor higher SRS dose was associated with improved local control in the present study.

SRS with or without WBRT

In the present study, WBRT prior to SRS was associated with improved regional control, but not improved local control or survival. Patients treated with SRS for metastatic brain disease often also receive WBRT. The rationale behind this treatment strategy is the assumption that WBRT will effectively treat micrometastatic foci outside the radiosurgical field, hopefully preventing them from progressing to become detectable, symptomatic brain lesions that may threaten duration and quality of life. However, there is evidence that the addition of WBRT to SRS is associated with an increased incidence of mild to moderate

treatment-related morbidity and there is concern that WBRT may also cause serious neurological deficit in some long-term survivors. Kondziolka et al. (39) reported the results of 104 surveys completed by patients treated with SRS with or without WBRT and/or their families. They found that patients treated with SRS plus WBRT were significantly more likely to report fatigue, concentration problems, short- and long-term memory problems, and disorders of mood, compared with patients treated with SRS alone (39). DeAngelis et al. (18) reported 12 patients cured of brain metastases who developed progressive dementia, ataxia, and urinary incontinence a median of 14 months (range, 5–36 mo) after treatment with WBRT (total dose, 25–39 Gy delivered in 3–6 Gy fractions) with or without surgery. They found a 1.9 to 5.1% incidence of WBRT-induced dementia in their study population and estimated that the true incidence is probably higher (18). As primary treatment of metastatic brain disease continues to become more and more effective, the same patients who will benefit most from freedom from new brain metastases will be at the greatest risk of developing long-term treatment-related morbidities. Accordingly, many studies have sought to better define the effect of WBRT on survival, local control, and regional control following SRS.

Aoyama et al. (3) recently reported results of the first prospective, multi-institutional, randomized trial of SRS with or without WBRT for the treatment of metastatic brain disease. One hundred thirty-two patients with one to four brain metastases 3 cm or more in diameter and KPS scores of 70 or greater were randomly allocated either SRS plus WBRT (65 patients) or SRS alone (67 patients). Adjuvant WBRT did not affect survival; patients who received both SRS and WBRT had a median survival of 7.5

months and a 1-year actuarial survival rate of 38.5%, compared to 8.0 months and 28.4% for those treated with SRS alone. However, patients who did not initially receive WBRT underwent significantly more salvage procedures. Multivariate analysis revealed age younger than 65 years, controlled primary tumor, stable systemic disease, and KPS score of 90 or greater to be significantly associated with improved survival. Analysis revealed significantly better local, regional, and total brain control following treatment with SRS plus WBRT rather than SRS alone. Patients treated with SRS plus WBRT had 1-year actuarial local control, regional control, and total brain control rates of 88.7, 58.5, and 53.2%, respectively, compared with 72.5, 36.3, and 23.6%, respectively, for patients treated with SRS alone. Multivariate analysis also revealed stable systemic disease and KPS score of 80 or greater to be significantly associated with improved regional control, and a single brain metastasis approached significance ($P = 0.06$). Analysis revealed no difference in post-treatment neurological performance; patients treated with SRS plus WBRT had a 1-year actuarial neurological preservation rate of 72.1%, compared with 70.3% for patients treated with SRS alone (3). These findings are consistent with the only prospective, randomized trial to date of the role of postoperative WBRT in the management of metastatic brain disease; in their trial, Patchell et al. (60) randomized 95 patients with a single resectable brain metastasis and KPS score of 70 or greater to surgery plus WBRT or surgery alone and determined that patients who received postoperative WBRT did not have a survival advantage but did have significantly better local, regional, and total brain control.

Two similar randomized, prospective trials of SRS with or without WBRT for the treatment of metastatic brain disease are

TABLE 8. Stereotactic radiosurgery with or without whole brain radiation therapy: Class II and III data^a

Series (ref. no.) and data class	Patients		Survival			Local control			Regional control		
	SRS only	SRS + WBRT	SRS only	SRS + WBRT	Diff	SRS only	SRS + WBRT	Diff	SRS only	SRS + WBRT	Diff
Li et al., 2000 (45) Class II data	23	18	Median survival			Median LC duration			Median RC duration		
			9.3 mo.	10.6 mo.	NS	6.9 mo.	8.6 mo.	NS	6.7 mo.	8.6 mo.	Significant
Pirzkall et al., 1998 (64) Class III data	158	78	1- and 2-year survival rates			1- and 2-year LC rates			—	—	—
			19.2%, 8.3%	30.4%, 13.9%	NS	89%, 72%	92%, 86%	NS	—	—	—
Sneed et al., 1999 (78) Class III data	62	43	Median and 1-year survival			1-year LC rate			1-year RC rate		
			11.3 mo. 48%	11.1 mo. 46%	NS	71%	79%	NS	37%	80%	Significant
Sneed et al., 2002 (79) Class III data	268	301	Median and 1-year survival			—	—	—	—	—	—
			8.2 mo. 38%	8.6 mo. 35%	NS	—	—	—	—	—	—

^a SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy; Diff, difference; LC, local control; RC, regional control; NS, not significant; —, not reported. Class II data come from non-randomized, prospective trials. Class III data come from retrospective series.

currently underway. North Central Cancer Treatment Group protocol N0574 will randomize 528 patients with one to three newly diagnosed brain metastases to treatment with SRS plus WBRT or SRS alone. Primary outcome will be duration of survival; secondary outcomes will be time to CNS failure, quality of life, duration of functional independence, long-term neurocognitive status, and post-treatment toxicity (13). This trial is a continuation of American College of Surgeons Oncology Group protocol Z0300, which was inactive following suspension of enrollment in December 2004 (4). European Organization for Research and Treatment of Cancer protocol 22952 to 26001 will accumulate 340 patients with one to three newly diagnosed brain metastases. One hundred seventy of these patients will have undergone complete surgical resection and will then be randomized to postoperative WBRT or no postoperative WBRT. The other 170 patients will be randomized to SRS plus WBRT or SRS alone. Primary outcome will be duration of survival with a World Health Organization performance status of 2 or less, secondary outcomes will be duration of survival, duration of progression-free survival, time to neurological progression, acute toxicity, late toxicity, and quality of life (53).

Due to the current paucity of Class I data, several groups have conducted matched nonrandomized prospective and retrospective studies of SRS with or without WBRT for metastatic brain disease (Table 8). They have consistently determined that the addition of WBRT to SRS does not affect survival, but may affect local and regional control (45, 64, 78, 79). Results of this nature have led some authors to conclude that it may be best to initially employ SRS as a monotherapy and reserve WBRT for possible salvage treatment (19, 35, 38, 39, 52). Many centers, including the University of Florida, often use repeat SRS in lieu of WBRT for salvage treatment (16).

Study Limitations

This analysis is limited in that it is based on the experience of a single institution. As with any retrospective analysis, selection bias may be present. It is further limited by the lack of data on post-SRS quality of life and cause of death. Such data are very difficult to obtain reliably for large retrospective analyses such as this one, but must be an important component of any prospective analysis of SRS, and in particular, any prospective trial comparing SRS to surgery. Additionally, only 56% of all treated lesions could be included in the local control analysis and 59.1% of patients in the regional control analysis, due to lack of availability of follow-up imaging as a result of the large distances many patients traveled to reach the University of Florida for treatment.

CONCLUSIONS

Linear accelerator-based SRS is a safe and effective treatment for patients with metastatic brain tumors. Female sex, younger age, higher KPS score, controlled primary tumor, absence of systemic metastases, RPA Class I or II, asynchronous presentation of brain metastasis, fewer brain metastases, smaller total volume of brain metastases, surgery prior to radiosurgery, and

multiple radiosurgical treatments were associated with improved survival. Melanoma histology was associated with impaired survival. This underscores the complexity of selecting patients most likely to benefit from radiosurgical management of metastatic brain disease.

In this single-institution, nonrandomized, retrospective study, the use of WBRT in combination with SRS improved regional control, but did not improve local control or survival.

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COMMENTS

Swinson and Friedman present the large University of Florida experience using stereotactic radiosurgery (SRS) for the treatment of brain metastases over 17 years. Their results are similar to those of other retrospective reports and randomized trials. Younger patients with controlled systemic disease and good performance status do the best with this technique. Variations of their other results from historical norms are probably due to selection bias and statistical variability inherent in retrospective reports. Regardless, the patients treated with SRS at the University of Florida did as well as would be expected at a quality SRS center. Also, the authors achieved a high percentage of patients with survival data owing to their methodology.

Large, prospective, randomized trials have and are addressing many of the issues surrounding SRS and its role in the management of brain metastases. Such Class I evidence lessens the importance of reports such as this one, even though it is one of the largest single institution experiences to date.

The authors correctly highlight one of the key issues facing the radiosurgical community: it is not only important how long one lives, but how well. Although most agree with this point, there remains a lack of consensus on where whole-brain radiotherapy (WBRT) fits into the

management scheme of patients receiving SRS for brain metastases. Does local or regional control of combination therapy trump equivalence in survival, or does the perceived threat of cognitive impairment from WBRT (along with the ability to augment initial treatment with further SRS or delayed WBRT) make more sense? The data implicating severe cognitive decline after WBRT using contemporary dosing is murky and sparse. Clearly, however, some patients are devastated by it, whereas others are devastated by lack of tumor control (perhaps from withholding WBRT). Ongoing trials to assess the impact of SRS with or without WBRT that include mental status and quality of life measures may help with our understanding of what to do with these patients. Accurate, widely accepted predictors of who will or will not suffer cognitive decline from WBRT could be a “game changer.” Similarly, efforts to medically treat radiation-induced cognitive impairment or prevent it could also alter the management landscape. But, as with virtually all medical conditions, few real-world patients match the neat, narrow inclusion and exclusion criteria of randomized studies. For now and for the foreseeable future, the authors’ observation that the management of patients considered for SRS of brain metastases is “complex and treatment decision should be based on the entire clinical picture” is what we should strive for.

Gene H. Barnett
Cleveland, Ohio

SRS treatment has become a well-accepted part of the treatment armamentarium for brain metastases. The advantages of SRS lie primarily with the ease of treating multiple and deep-seated lesions within the brain. This, in concert with the minimal morbidity and mortality of this procedure, makes it an excellent choice for patients who often are frail and have limited overall life expectancy.

This article from the University of Florida concerns their particular experience with linear accelerator radiosurgery for brain metastases. The analysis of data presented in this article represents an immense effort. The results are similar to those reported for other radiosurgery technologies including gamma unit radiosurgery. Virtually any question one might have about SRS for brain metastases is likely to be answered by the data contained within this article. The conclusions of this article, although not necessarily novel, do warrant repeating in the context of the methods used by the authors. In addition, the discussion contains a well-written and concise review of current issues and controversies regarding the radiosurgery management of brain metastases.

Joseph C.T. Chen
Los Angeles, California

The authors describe an extensive retrospective series devoted to linear accelerator-based treatment of brain metastases. Although in neurosurgery we are moving more and more toward Level 1 data to establish guidelines for treatment, these extensive data are nonetheless useful. If nothing else, they corroborate what Level 1 data we have for

treatment of brain metastases. They also validate known prognostic indicators and demonstrate that linear accelerator-based radiosurgery is an effective treatment with outcomes comparable to those of the other radiosurgery units in widespread use today.

David W. Andrews
Philadelphia, Pennsylvania

Any study involving 619 patients with 1569 lesions treated over the course of 17 years requires a Herculean effort to complete. If only for this reason, the analysis by Swinson and Friedman of the sizable radiosurgical experience at the University of Florida in managing brain metastases is useful. Although no new ground has been broken, this article does serve to reinforce the extensive, but often confusing, prior medical literature on this subject.

John R. Adler, Jr.
Stanford, California

In this review of brain metastasis radiosurgery from the University of Florida, the authors identified many factors that correlated with extended survival. Not all patients with these brain tumors die within a few months, and even those with multiple metastases can do well. They found a number of predictive factors that I and others have noted previously. Obviously, better survival is related to less extracranial cancer burden. Better neurological status, a longer interval from the primary diagnosis to the onset of the brain tumor, and fewer brain tumors are important. Perhaps more important than the number of tumors is their total volume. For example, six very small tumors may be better than three larger ones. Female sex appears to be better as well, and this may not just be related to the better prognosis of breast cancer. This was true even in lung cancer.

Concepts for brain metastasis management are changing rapidly, including radiosurgery for multiple tumors and radiosurgery to the tumor bed after a resection (2). I have performed radiosurgery in selected patients more than eight times over many years, usually for small asymptomatic tumors identified early before symptoms arise. Successful cancer management includes radiosurgery and is optimal when tumors are identified early and managed aggressively. However, in a recent evaluation of long-term survivors, only about 7% were still living after 4 years (1). We have much work to do.

Douglas Kondziolka
Pittsburgh, Pennsylvania

1. Kondziolka D, Martin JJ, Flickinger JC, Friedland D, Brufsky A, Agarwala S, Kirkwood J, Baar J, Lunsford LD: Long-term survivors after gamma knife radiosurgery for brain metastases. *Cancer* 104:2784-2791, 2005.
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CONGRESS OF NEUROLOGICAL SURGEONS' MISSION STATEMENT

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