Survival and Intracranial Control of Patients With 5 or More Brain Metastases Treated With Gamma Knife Stereotactic Radiosurgery

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Purpose: Limited data are available to help inform decisions about stereotactic radiosurgery for patients with ≥ 5 brain metastases. We therefore performed a retrospective analysis of patients treated for >5 brain metastases.

Materials/Methods: Patients who underwent treatment for ≥ 5 brain metastases from October 2000 to September 2010 were identified. Overall survival (OS) for each patient was calculated from the date of first treatment of ≥ 5 metastases. Intracranial recurrence-free survival was defined when posttreatment magnetic resonance imaginag showed evidence for disease progression. Cox proportional hazards regression was performed for OS and intracranial recurrence free survival. Variables included sex, age, Karnofsky Performance Status (KPS), histology, prior whole-brain radiation treatment or Gamma Knife treatment, and number of metastases treated.

Results: A total of 103 patients were identified. Median OS was 8.3 months. Median OS was 7.6 months and 8.3 months, for patients with 5 to 9 and ≥ 10 metastases, respectively. KPS was the only significant variable affecting OS ($P < 0.01$). Forty-six patients had post–Gamma Knife surveillance imaging recorded. There was a trend towards a higher hazard for intracranial failure for patients with 10+ versus 5 to 9 metastases, however, the association did not reach statistical significance (univariate $P = 0.09$, multivariate $P = 0.21$).

Conclusions: OS for carefully selected patients with 5 or more brain metastases treated with stereotactic radiosurgery alone is reasonable and compares well with historical controls. KPS is the most important factor predicting OS.

Key Words: gamma knife, brain metastases, stereotactic radiosurgery

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Metastases account for more than one half of all intracranial tumors in adults, and are found at autopsy in 15% to 40% of patients with cancer.[1–4] Treatment approaches include whole brain radiation therapy (WBRT), neurosurgical resection, and stereotactic radiosurgery (SRS). SRS uses multiple convergent beams to distribute high radiation doses to a distinct target volume, while sparing normal surrounding tissues. The rationale for using WBRT in addition to SRS is to reduce recurrence rates by eradicating residual microscopic disease at the original metastatic sites and elsewhere in the brain.[5] Although WBRT is the standard treatment for brain metastases, it is associated with significant cognitive side effects.[6] For patients with 1 to 4 metastases, multiple randomized trials have shown no difference in OS for patients who undergo SRS alone versus those who undergo SRS + WBRT, although the rate of intracranial recurrence is higher with the omission of WBRT.[5–8]

Similar randomized trial evidence does not exist for patients with 5 or more brain metastases. However, at our institution, we have been treating highly selected patients with 5 or more brain metastases with good systemic disease control or good chemotherapeutic options, good functional status, or radioresistant histologies such as melanoma and renal cell carcinoma, with SRS followed by every 6-week surveillance magnetic resonance imaginag (MRI) rather than immediate WBRT. In addition, patients who fit the above criteria, with 5 or more brain metastases and have previously undergone WBRT are also offered SRS alone followed by every 6-week surveillance MRI. Typically, we are able to deliver Gamma Knife (GK) SRS within 1 week of consultation for brain metastases, and therefore patients are treated with SRS alone before they would otherwise finish fractionated WBRT.

The benefit from SRS for treatment of patients with multiple brain metastases may be minimized if patients have a short survival posttreatment. Given the limited OS and intracranial disease-free survival data available to help inform treatment management of patients with 5 or more lesions, we performed a retrospective analysis of patients in the Yale Gamma Knife database treated for 5 or more brain metastases from 2000 to 2010.

METHODS

The Yale Gamma Knife database was queried for patients treated from 2000 through 2010 who underwent treatment for 5 or more metastases. Patients were treated using standard Gamma Knife radiosurgical technique. Treatment doses typically ranged from 16 to 24 Gy prescribed to isodose surfaces ranging from 40% to 85%. If patients underwent treatment more than once for 5 or more metastases, the earliest treatment was used for this survival analysis as the time of treatment. Patients may have undergone previous GK for 1 to 4 lesions, but time of survival was calculated from the first treatment of ≥ 5 metastases. This baseline time point was chosen to help answer the clinical question, "When patients have 5 or more brain metastases, at that moment, is it reasonable to offer SRS based on the patient's expected OS?" Therefore, this analysis was not limited to patients who first presented with 5+ metastases at their first diagnosis of brain metastases. Whether patients underwent WBRT or had a history of intracranial

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surgery was recorded. Intracranial disease progression was defined when the neuroradiologist or neurosurgeon assessment of posttreatment MRI showed progression of disease. Patients for whom there was slight tumor growth but subsequent regression were not recorded as having disease progression.[9]

Cox proportional hazard regressions were performed for OS and intracranial control. Univariate analysis was performed for the following variables: sex, age (as a categorical variable: 30 to 44, 45 to 59, 60 to 74, and 75+), Karnofsky Performance Status (KPS), histology, prior WBRT, number of metastases treated, and time from first GK treatment to first GK treatment for ≥ 5 metastases. Variables significant in univariate analysis with a threshold of $P < 0.10$ were included in the multivariate model.

Kaplan-Meier survival curves were created to estimate OS for patients with 5 to 9 versus ≥ 10 metastases. For patients with prior GK, the time from first GK to the GK for 5 or more metastases was recorded. Finally, Kaplan-Meier curves were also used to compare intracranial disease-free survival for patients. The log-rank test was used to analyze differences between survival curves.

RESULTS

Our study sample consisted of 103 patients, whose characteristics are shown in Table 1. Of these patients, 42 underwent no prior radiation treatment, 12 underwent prior GK alone, 34 underwent prior WBRT, and 15 underwent prior GK and WBRT. The median survival for the entire sample was 8.3 months. Eighty-four patients were treated for 5 to 9 metastases, and 18 patients were treated for ≥ 10 metastases. Median survival was 7.6 months and 8.3 months, for patients with 5 to 9 and ≥ 10 metastases, respectively (Fig. 1).

Patient sex, age, KPS, histology, prior radiation treatment, number of metastases treated, and time from first GK treatment to first GK treatment for ≥ 5 metastases, and total volume of metastatic disease were included in univariate and multivariate analysis (Table 2). Total aggregate volume of metastases treated ranged from 0.33 to 34.6 cm^3. Total aggregate volume of metastasis was not associated with survival [hazard ratio 1.00 (95% confidence interval 0.96-1.04), $P = 0.89$]. KPS was the only variable significantly associated with OS in multivariate analysis.

Intracranial disease-free survival was assessed for the 46 patients with post-GK imaging (Table 3). There were no statistically significant factors associated with more rapid failure on multivariate analysis. However, if patients had 10+ metastases at the time of treatment, there was a trend towards a more rapid intracranial failure rate in univariate Cox proportional hazards analysis ($P = 0.09$) and log-rank testing ($P = 0.053$) (Fig. 2).

TABLE 1. Patient Characteristics (N = 103)

	Number
Sex	
Female	57
Male	46
Race	
White	97
Black	3
Asian	2
Hispanic	1
Year of GK treatment	
2000-2003	2
2004-2007	20
2008	29
2009	29
2010	23
Age	
30-44	11
45-59	38
60-74	42
75 y and above	12
KPS	
90-100	39
70-80	19
50-60	4
<50	1
Unknown or unrecorded	40
Histologies	
Melanoma	34
NSCLC	33
Breast cancer	17
Renal cell carcinoma	6
Small cell lung cancer	5
Bladder cancer	2
Cervical cancer	1
Esophageal cancer	1
Rectal cancer	1
Thymic carcinoma	1
Thyroid cancer	1
Sarcoma	1
Prior radiation treatment	
None	42
Prior GK alone	12
Prior whole-brain radiation	34
Prior whole-brain radiation and GK	15
No. metastases treated	
5-9	84
10+	19
Volume of metastases treated	
>0.33 and <2 cm^3	43
>2.0 and <5 cm^3	19
≥5.0 and <10 cm^3	22
≥10.0 to 34.6 cm^3	16
Volume unavailable	3

GK indicates Gamma Knife; KPS, Karnofsky Performance Status; NSCLC, non small-cell lung cancer.

DISCUSSION

There are 2 major conclusions from our analysis. The first is that the OS of patients treated with GK SRS for 5+ brain metastases is reasonable, and is associated with KPS but not the number of brain metastases (5 to 9 vs. 10+). In our cohort, the median survival was 8.3 months and KPS was the only significant variable affecting OS ($P < 0.01$). This survival compares favorably to the historical survival of patients treated with WBRT. For example, the Radiation Therapy Oncology Group recursive partitioning analysis predicts that patients in the most favorable category (age <65, KPS ≥ 70, and controlled extracranial disease and primary disease) have an average survival of 7.2 months.[10] The finding of a reasonable OS in this population, independent of number of metastases, is consistent with previously published literature.[11] Finally, the hazard for intracranial failure may be higher for patients with 10+ metastases, although this hazard did not reach the threshold for statistical significance.

Multiple other institutions have also published retrospective series including patients treated with SRS for ≥ 4 brain metastases indicating reasonable survival.[12,13] KPS[12,14] and systemic disease control[12,14] have been reported to be more important in predicting survival than the absolute number of metastases. Several retrospective studies,[11,15–18] have also

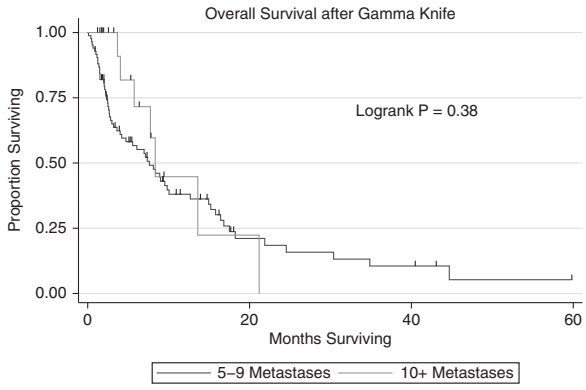

FIGURE 1. Overall survival for patients with 5 to 9 versus 10+ brain metastases.

demonstrated that the number of metastases may not predict OS. In the largest study to date, Karlsson et al[16] analyzed factors influencing survival time in 1885 patients undergoing a total of 2448 SRS treatments, and found that age and primary tumor control were more significant factors than number of brain metastases when predicting OS. Together, these studies support our findings that KPS score, as opposed to the number of metastases, is more significantly associated with OS in patients undergoing SRS.

Our finding of a trend towards worse intracranial disease-free survival is consistent with an analysis of 323 patients with 1 to 5, 6 to 10, 11 to 15, and 16 to 20 brain metastases by Chang et al.[18] Like ours, this study did not demonstrate differences in OS based on number of brain metastases. However, the patients with ≥ 16 metastases in this study had a greater risk of intracranial recurrence ($P = 0.014$) and remote disease progression ($P = 0.014$).

Our study is limited by its retrospective nature and highly selected cohort. Treatment of multiple metastases remains a time intensive process requiring the expertise of multiple physicians and allied health professionals including nursing staff, radiation therapists, and a radiation physicist. Patients selected for treatment were typically those with good performance status and either stable systemic disease, or good systemic treatment options. Unfortunately, we were unable to assess what percentage of all patients seen at Yale New Haven Hospital with brain metastases underwent Gamma Knife radiosurgery, and it is uncertain what factors may have led referring physicians outside the institution to have sought a consultation for any given patient for this procedure. Therefore, it cannot be determined exactly how selective we were in treating patients with brain metastases. Therefore, the general applicability of this study is limited. Unfortunately, we were

TABLE 2. Cox Proportional Hazards Analysis—Overall Survival

	Univariate		Multivariate	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex		0.14		
Female	1*			
Male	1.45 (0.89-2.37)			
Age		0.04		
30-44	1*		1*	
45-59	2.19 (0.61-7.79)		1.18 (0.40-3.51)	0.77
60-74	0.38 (0.08-1.75)		0.97 (0.33-2.89)	0.96
75 y and above	1.00 (0.25-4.04)		0.65 (0.18-2.35)	0.51
KPS*** (only recorded for 63 patients)		<0.01		
90-100	1*		1*	
70-80	2.38 (1.26-4.50)		2.25 (1.14-4.45)	0.02
50-60	27.3 (5.66-131.23)		33.9 (6.56-175)	<0.001
<50	Too few to calculate**		Too few to calculate**	
Histologies		0.61		
Melanoma or renal cell	1*			
Breast cancer	0.87 (0.43-1.74)			
Lung cancer (NSCLC or SCLC)	0.93 (0.53-1.65)			
Other	1.72 (0.70-4.25)			
Prior radiation treatment		0.93		
None	1*			
Prior GK alone	1.26 (0.58-2.73)			
Prior whole-brain radiation	1.00 (0.57-1.75)			
Prior whole-brain radiation and GK	0.92 (0.41-2.03)			
No. metastases treated		0.36		
5-9	1*		1*	
10+	0.70 (0.31-1.55)		0.81 (0.30-2.14)	0.67
Time from first GK treatment to first GK treatment with 5+ metastates		0.42		
0 (first GK treatment was for 5+ metastates)	1*			
>0 and <6 mo	1.58 (0.74-3.35)			
≥6 mo	0.82 (0.40-1.69)			
Volume treated (continuous variable)	1.00 (0.96-1.04)	0.89		

*Reference value.
**Too few to calculate.
***Only recorded for 63 patients.
CI indicates confidence interval; HR, hazard ratio; KPS, Karnofsky Performance Status; NSCLC, non small-cell lung cancer; SCLC, small-cell lung cancer.

TABLE 3. Cox Proportional Hazards Analysis—Intracranial Control, for Those Patients With Record of Follow-up Imaging (N = 46)

	Univariate		Multivariate	
Variable	**HR (95% CI)**	***P***		***P***
Sex		0.88		
Female	1*			
Male	1.07 (0.45-2.56)			
Age		0.04		
30-44	1*		1*	
45-59	2.19 (0.61-7.79)		2.76 (0.74-10.28)	0.13
60-74	0.38 (0.08-1.75)		0.56 (0.11-2.98)	0.50
75+	1.00 (0.25-4.04)		1.39 (0.31-6.32)	0.67
KPS (only known for 37 patients with record of follow-up imaging)		0.52		
90-100	1*			
70-80	1.46 (0.47-4.55)			
Histologies		0.92		
Melanoma or renal cell	1*			
Breast cancer	0.79 (0.28-2.34)			
Lung cancer (NSCLC or SCLC)	0.68 (0.22-2.06)			
Other	0.85 (0.10-6.86)			
Prior radiation treatment		0.49		
None	1*			
Prior GK alone	3.16 (0.78-12.80)			
Prior whole-brain radiation	1.02 (0.37-2.86)			
Prior whole-brain radiation and GK	1.30 (0.34-5.03)			
No. metastases treated		0.09		
5-9	1*		1*	
10+	2.50 (0.94-6.67)		2.04 (0.67-6.20)	0.21
Volume treated (continuous variable)	1.03 (0.97-1.08)	0.32		

*Reference value.
CI indicates confidence interval; HR, hazard ratio; KPS, Karnofsky Performance Status; NSCLC, non small-cell lung cancer.

only able to obtain follow-up imaging for 46 patients. This was because of many patients being referred for Gamma Knife radiosurgery at our center and subsequently receiving follow up at the original referring radiation center. Therefore, although our data regarding survival was robust (through the use of the social security death index), intracranial control was less so.

However, our study does support the hypothesis that the treatment of 5 to 9 and even 10+ brain metastases with focal therapy provides patients with a reasonable survival. Although the inclusion of 103 patients (19 of whom had 10+ metastases) makes it one of the largest studies focusing on patients with 5 or more brain metastases, the numbers of patients are still relatively small and the cohort heterogeneous enough that only 1 independent variable (KPS) was associated with OS. Our findings are tempered by missing KPS information on 40/103 patients. In addition, neurocognitive testing and comprehensive review of side effects from treatment are difficult if not impossible to perform in this retrospective cohort, especially given that most patients have died at the time of this analysis. Further study and follow-up is needed to assess continued differences in survival and intracranial disease control. Ideally, a prospective trial is indicated to compare patients with 5+ metastases who undergo SRS versus SRS+WBRT, with the primary outcomes of survival and neurocognitive function.

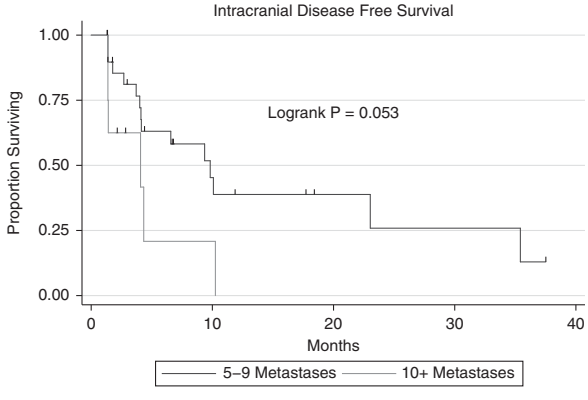

FIGURE 2. Intracranial failure for patients with 5 to 9 vs. 10+ brain metastases.

CONCLUSIONS

Our results suggest that OS for carefully selected patients with 5 or more brain metastases treated with SRS alone is reasonable and that KPS is the most important factor predicting OS. Although our study did not indicate other statistically significant factors, other known prognostic factors such as histology and extent and control of systemic disease may also be important. Number of metastases does not appear to be associated with OS. Randomized controlled trials are necessary to fully answer questions regarding the outcomes after SRS as compared with SRS+WBRT for ≥ 5 brain metastases.

Appropriate patient selection is important to ensure that patients will benefit from radiosurgery for multiple metastases. Further investigation through prospective trials should attempt to identify selection factors that predict for improved survival, and to produce robust guidelines for the evaluation of patients and their appropriateness for this aggressive focal approach. Before these results can be generalized to other institutions,

further consensus as to who will benefit from radiosurgery for 5+ brain metastases should be achieved.

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