

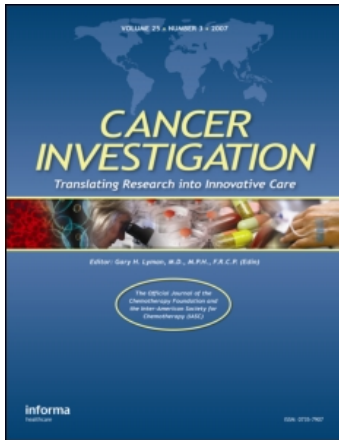
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Publisher Informa Healthcare

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Cancer Investigation

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title-content=t713597231>

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Online Publication Date: 28 December 2004

To cite this Article Stone, Anne, Cooper, Jay, Koenig, Karen L., Golfinos, John G. and Oratz, Ruth(2004)'A Comparison of Survival Rates for Treatment of Melanoma Metastatic to the Brain',Cancer Investigation,22:4,492 — 497

To link to this Article: DOI: 10.1081/CNV-200026387

URL: <http://dx.doi.org/10.1081/CNV-200026387>

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A Comparison of Survival Rates for Treatment of Melanoma Metastatic to the Brain

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ABSTRACT

Introduction: A retrospective review of 91 patients with brain metastases from malignant melanoma treated at New York University Medical Center between 1989–1999. Overall survival was the outcome evaluated. *Methods:* Charts of 91 patients having malignant melanoma with brain metastases were reviewed. Cases were stratified according to therapy: surgical excision, surgical excision plus whole brain radiation therapy, gamma knife stereotactic radiosurgery, gamma knife stereotactic radiosurgery plus whole brain radiation therapy, and whole brain radiation therapy alone. Patients treated with gamma knife stereotactic radiosurgery plus radiation therapy were combined with patients treated with surgical excision plus radiation therapy and compared to those treated with radiation therapy alone. Prognostic characteristics of the two groups were compared and survival curves were generated using the Kaplan-Meier method. The Cox proportional hazards model was used to control for prognostic factors that differed between the groups. *Results:* Patients treated with gamma knife stereotactic radiosurgery or surgical excision plus radiation therapy were younger, less likely to present with symptoms, and presented with fewer metastases to the brain than patients treated with radiation therapy alone. A survival benefit of 7.3 months ($p=0.05$) was found to be associated with gamma knife radiosurgery or surgical excision plus radiation therapy over radiation therapy alone after controlling for differences in age, number of brain lesions, and presence of

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symptoms. *Discussion:* This retrospective study of 91 patients treated for melanoma metastases to the brain attempts to examine the effectiveness of different treatments in prolonging survival. Our results suggest that surgical excision or stereotactic radiosurgery with gamma knife in addition to radiation therapy may be more effective than radiation alone at prolonging survival for patients with a limited number of brain lesions. *Conclusion:* Survival of patients with melanoma metastases to the brain may be prolonged by treatment with gamma knife stereotactic radiosurgery or surgical excision plus whole brain radiation therapy.

Key Words: Brain; Gamma knife radiosurgery; Melanoma; Metastasis; Radiotherapy; Stereotactic radiosurgery.

INTRODUCTION

Despite improvements in the early diagnosis of malignant melanoma, brain metastases are a common complication for patients with advanced disease. A limited array of treatment options for brain metastases results in poor prognoses and a high mortality rate.^[1,2]

Among primary neoplasms, melanoma and lung cancer are most likely to metastasize to the brain.^[2] In clinical series, the occurrence of brain metastases in melanoma patients ranges from 6% to 43%.^[1] The incidence of metastases to the brain in patients with advanced melanoma is 36% to 54% at autopsy.^[2] Brain metastases are a common cause of death among melanoma patients, with different series reporting 20% to 54% of melanoma patients dying from intracranial lesions.^[2] Melanoma patients who develop brain lesions are more likely to die from parenchymal brain involvement rather than from disease at other sites.^[3]

Treatment for brain metastases directed at relieving neurologic symptoms and decreasing tumor burden include whole brain irradiation, surgical excision, and/or gamma knife stereotactic radiosurgery.^[4] Various combinations of these procedures also can be administered. The frequency with which patients acquire brain metastases and the resulting poor prognosis warrants a comparison of the available therapies. This retrospective review of 91 patients treated at New York University (NYU) Medical Center for metastatic melanoma to the brain seeks to provide some insight into the life expectancies that are associated with various treatment options.

METHODS

Patients were grouped according to treatment received. Because of the small number of patients in our study, we combined patients treated with gamma

knife stereotactic radiosurgery plus whole brain radiation therapy (8 patients) with patients treated with surgery plus whole brain radiation therapy (16 patients). All statistical comparisons were made between this combined group and the group treated with radiation therapy alone (59 patients). Prognostic characteristics of the patients treated with surgery or gamma knife were compared with those of patients treated with radiation therapy alone using descriptive statistics along with Chi-squared tests for categorical variables and Chi-squared tests for trend for ordered categorical variables. Survival curves following diagnosis of brain metastases were constructed for each of the treatment groups using the Kaplan-Meier method. Survival times of the different treatment groups were compared using the log-rank test. The Cox proportional hazards model was used to compare survival times while controlling for prognostic factors that differed between the groups. Two-sided p -values < 0.05 were considered statistically significant.

RESULTS

Characteristics of the patients receiving different treatments are shown in Table 1. Patients treated with surgery or gamma knife plus adjuvant radiation therapy had a significant prognostic advantage over patients treated with radiation therapy alone: they were significantly younger than those treated with radiation therapy alone ($p=0.02$), presented with fewer metastatic lesions in the brain ($p=0.001$), and were less likely to present with symptoms ($p=0.06$). Sixty-one percent of the patients treated with radiation therapy alone were older than 60, compared to 32% of the patients treated with surgery or gamma knife plus radiation therapy. In addition, 58% of the patients treated with radiation therapy alone presented with three or more metastases to the brain compared to 17% of the patients treated with surgery or gamma knife

Table 1. Prognostic characteristics of patients treated with surgery or gamma knife plus radiation therapy compared with patients receiving radiation therapy alone.

Prognostic factor	Surgery or gamma knife plus radiation	Radiation alone	P-value
	Number (percent) ^a	Number (percent) ^a	
	Total=24	Total=59	
Age at presentation with brain metastases			
<50	11 (44%)	11 (19%)	.02 ^b
50–59	6 (24%)	12 (20%)	
60–69	4 (16%)	22 (37%)	
70+	4 (16%)	14 (24%)	
Sex			
Male	15 (63%)	43 (73%)	NS
Female	9 (38%)	16 (27%)	
Location of primary melanoma			
Head and neck	5 (25.0%)	17 (30%)	NS
Trunk	9 (45.0%)	28 (50%)	
Extremities	6 (30.0%)	9 (16%)	
Other	0	2 (4%)	
Thickness of primary melanoma (mm)			
<2	5 (31%)	13 (28%)	NS
2–4	5 (31%)	16 (35%)	
>4	6 (38%)	17 (37%)	
Presentation of primary			
Local disease only	15 (75%)	49 (88%)	NS
Nodal metastases	4 (20%)	5 (9%)	
Visceral metastases	1 (5%)	2 (4%)	
Location of metastases			
Brain only	2 (8%)	3 (5%)	NS
Brain and lung	3 (13%)	7 (12%)	
Brain and soft tissue	4 (17%)	14 (24%)	
Brain and other	1 (4%)	1 (2%)	
More than two sites	14 (58%)	34 (57%)	
Number of brain lesions at presentation			
1	11 (48%)	12 (20%)	.001 ^b
2	8 (35%)	13 (22%)	
3 or more	4 (17%)	34 (58%)	
Largest brain metastasis (mm)			
<15	8 (36%)	7 (20%)	NS
15–30	10 (45%)	25 (71%)	
>30	4 (18%)	3 (9%)	
Presentation of brain metastasis			
With symptoms	11 (46%)	40 (68%)	.06 ^c
Asymptomatic	13 (54%)	19 (32%)	

NS signifies that difference between groups was not statistically significant.

^aNumbers do not add to total in columns because of unknown values.

^bP-values are based on the Chi-squared test for trend.

^cP-value is based on the Chi-squared test.

plus radiation therapy. Moreover, 46% of those receiving gamma knife stereotactic radiosurgery or surgical excision plus radiation therapy presented with symptoms compared to 68% of those who received radiation alone. All other patients presented asymp-

tomatically with parenchymal disease detected on screening scans. These three factors may confer a more favorable prognosis for the patient with melanoma metastatic to the brain. For this reason, comparisons of survival times were controlled for

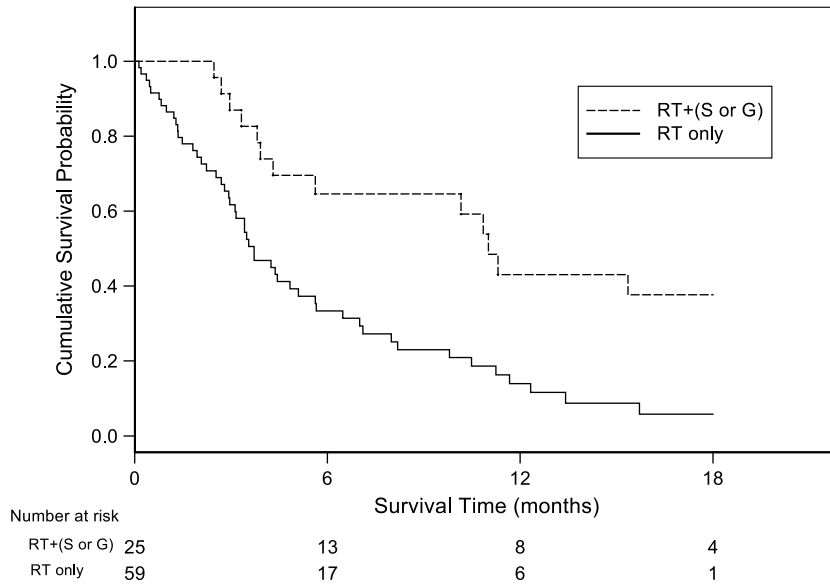


Figure 1. Probability of patients with melanoma metastatic to the brain surviving following treatment with whole-brain radiation therapy (RT) only, or RT plus either gamma knife or surgery [RT+(SorG)].

age, the number of presenting metastatic brain lesions, and the presence of symptoms using the Cox proportional hazards model. Other prognostic characteristics between the two treatment groups did not differ significantly.

Survival curves following the diagnosis of brain metastases are shown in Fig. 1. Patients treated with either surgery or gamma knife in addition to radiation

lived significantly longer than patients treated with radiation therapy alone ($p=0.05$ after controlling for age, number of presenting metastatic brain lesions, and the presence of symptoms). The median survival time of patients treated with surgery or gamma knife was 10.9 months compared with 3.6 months for those receiving radiation therapy alone. The longest survival times were exhibited by the patients treated with gamma knife plus

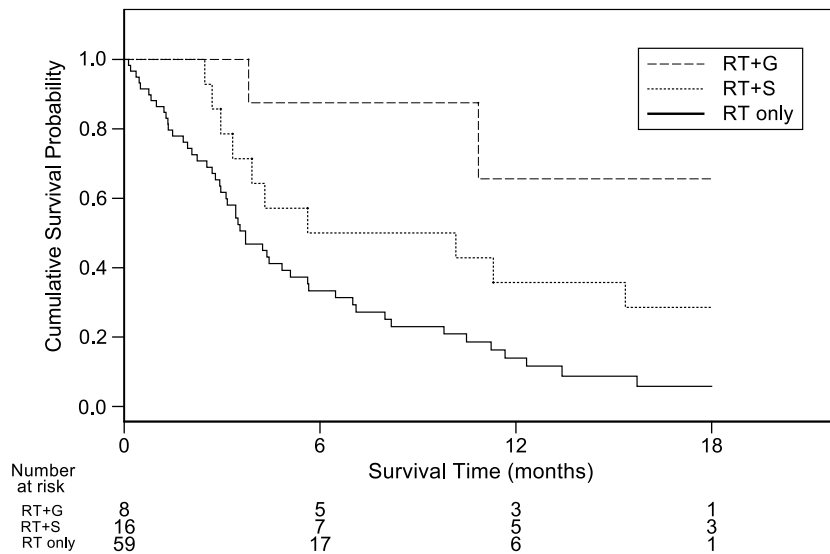


Figure 2. Probability of patients with melanoma metastatic to the brain surviving following treatment with whole-brain radiation therapy (RT) only, or RT plus gamma knife (RT+G), or RT plus surgery (RT+S).

radiation therapy (Fig. 2), but the sample size (eight patients) was too small to estimate accurately the median survival time in this group. The difference between the survival times of the patients treated with gamma knife plus radiation therapy and those treated with surgery plus radiation therapy was not statistically significant, but this comparison had low statistical power due to the small sample sizes. Of the patients treated with gamma knife radiosurgery plus radiation therapy, 70% were alive at 10.8 months compared to 43% of patients treated with surgical excision and radiation therapy who were alive at 10.2 months. Sixty-four percent of patients treated with surgical excision plus radiation therapy were alive at 3.9 months compared to 88% of patients treated with gamma knife plus radiation therapy who were alive at 3.8 months. These survival rates compare to 50% patients treated with radiation therapy alone who survived 3.6 months.

Four patients in our study refused adjuvant radiation therapy and were treated with gamma knife radiosurgery alone. Two of the four patients survived 4 and 8 months, respectively, and were still alive at the time that our study was concluded. The third patient survived 8.3 months after presenting with disease in the brain. The fourth patient survived 2.9 months only, but had presented with more than four brain metastases.

Two other patients presented with two metastases as assessed by triple-dose gadolinium enhanced MRI. Both had one lesion excised and the other lesion treated by gamma knife irradiation (because of location). One of these patients then had adjuvant radiation therapy and lived 11 months, while the other refused such treatment and lived 8.2 months.

DISCUSSION

This retrospective study of 91 patients treated for melanoma metastases to the brain seen at a single institution over a decade attempts to examine the effectiveness of different treatments in prolonging survival. Our results suggest that surgical excision or stereotactic radiosurgery with gamma knife in addition to radiation therapy may be more effective than radiation alone at prolonging survival for patients with a limited number of brain lesions.

The prognosis for patients with melanoma that has metastasized to the brain is poor, with median survival times of 3.6 months for patients treated with radiation therapy alone compared to 10.9 months for those treated with surgery or gamma knife radiosurgery (Fig. 1). Previous studies have suggested that selection biases may be solely responsible for differences in survival

times between surgically treated patients and patients offered radiation therapy.^[1] Our study groups were similar with regard to sex, location of their primary melanoma, thickness of primary melanoma, presentation of their primary lesion, location of metastases, and size of the largest brain lesion. The groups differed in age ($p=0.02$), number of brain lesions ($p=0.001$), and presence of symptoms ($p=0.06$). After controlling for these differences with the Cox proportional hazards model, however, a statistically significant difference in survival rates between the two groups remained ($p=0.05$). As this was not a prospective randomized trial, other possible differences between the two groups may remain obscure and may have produced a selection bias. Patients treated with surgery or gamma knife were selected both by the size and number of brain lesions in addition to the location of their disease. Large, non-resectable metastases were treated with radiation therapy alone, and it is possible that disease at inaccessible locations is associated with a decreased survival or more aggressive course than are resectable lesions, though such an association has not been proven. Another prognostic factor not explored in this study is the extent of metastatic disease at extracranial sites. Previous studies have demonstrated that the presence of metastases to organs other than the brain significantly impacts survival.^[1] There was no significant difference between our treatment groups in terms of presence of visceral metastases at time of presentation with brain lesions; however, possible differences in the size of distant metastases and their effect on overall health were not studied. Despite the possible effects of selection bias in the prolonged survival of patients treated with surgical excision or gamma knife stereotactic radiosurgery in addition to radiation therapy, our study suggests that more aggressive therapy such as surgery or gamma knife irradiation may be capable of prolonging survival for some patients with metastatic melanoma in the brain.

Our study also explored if there was a survival benefit to gamma knife radiosurgery plus radiation therapy in comparison to surgical excision plus radiation therapy (Fig. 2). Patients treated with gamma knife stereotactic surgery plus radiation had a longer median survival; however, the small number of patients prevented analysis of statistical significance. Furthermore, the longer survival time may be partially attributable to the limited number and small size of these cranial lesions amenable to treatment with the gamma knife.

The number of patients involved in our study permitted us to compare survival rates between the 24 patients treated with gamma knife or surgical excision plus adjuvant radiation therapy to the 59 patients treated

with radiation therapy alone. This comparison suggests that survival may be prolonged by treatment with gamma knife or surgery in addition to radiation therapy. Moreover, other studies have indicated that a better quality of life is associated with surgically treated patients compared to patients treated with radiation therapy alone.^[5] Gamma knife radiosurgery offers the added benefit of outpatient treatment and noninvasive therapy by delivering a high single dose of radiation to a relatively small volume.^[6] A prospective randomized trial would best answer the question of what treatment is most efficacious at both prolonging survival and improving quality of life, but none has been done yet. Patients could be randomized into groups that are treated with surgery plus adjuvant radiation therapy vs. gamma knife plus adjuvant radiation therapy vs. radiation therapy alone.

CONCLUSION

This retrospective study of 91 patients followed for melanoma metastases to the brain suggests that patients with accessible lesions will be able to prolong their survival most effectively by treatment with gamma knife radiosurgery or surgical excision in addition to whole brain radiation therapy.

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