

Gamma Knife Radiosurgery for Melanoma Brain Metastases

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Abstract

Purpose: The objective of this study is to report the combined experience at Johns Hopkins University (JHU) and the Miami Neuroscience Center (MNC) in treating brain metastases from melanoma with stereotactic radiosurgery (SRS).

Methods and Materials: Prospectively collected clinical and demographic data on patients with melanoma treated with Gamma Knife (GK) at JHU between 2003 and 2007 and the MNC between 1993 and 2009 were reviewed. Cox proportional hazards regression and Kaplan Meyer analyses were used to compare survival by clinical and demographic characteristics and treatment.

Results: One hundred and fifty-four patients with melanoma received GK at JHU and MNC and were followed over a mean of 7.29+11.42 months (median reverse Kaplan Meier: 26.02 months). The median survival from the time of treatment was 5.03 months. Survival analysis revealed number of lesions, Karnofsky Performance Score (KPS), and dose as significant variables. Treatment center, age, and volume of metastases were not significant. Multivariate pooled analysis identified KPS <70 (HR 2.4, p<0.001), multiple (>3) lesions (HR 2.1, p<0.01), and dose<17Gy (HR 1.58, p=0.029) as significant predictors of time to mortality from GK treatment.

Conclusions: Radiosurgery seems to be better than conservative treatment only in patients with melanoma brain metastasis with favorable KPS (>70) and less than three lesions. Treatment with higher radiation dose improves the efficacy of radiosurgery.

Published 06/05/2012

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Categories: Radiation Oncology, Neurosurgery

Keywords: brain metastasis, melanoma, stereotactic radiosurgery, survival, predictors

Introduction

Management of brain metastases is a difficult challenge that faces over 170,000 patients and their physicians each year. Treatment options include supportive care, surgical resection, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). As in the palliation of any

How to cite this article

Wolf A L, Stall B, Batra S, et al. (June 05, 2012) Gamma Knife Radiosurgery for Melanoma Brain Metastases . Cureus 4(5): e45. DOI 10.7759/cureus.45

disease, a balance must be struck between the benefit and the cost of treatment, duration of treatment relative to expected survival and potential toxicities. SRS has emerged as a favorable choice for patients who prefer to avoid the risks of surgery and whole brain radiation, while minimizing time committed to treatment and recovery. It is a safe and tolerable procedure with proven local control benefits, particularly for breast and non-small cell lung cancer. Its role in histologies classically thought to be less radiosensitive is not as well-defined.

These histologies are of particular interest, both epidemiologically and radiobiologically. Melanoma brain metastasis account for about 7% of the total brain metastases prevalence [1-2]. Additionally, the incidence of this diseases is rising [3]. Also, while the overall death due to cancer in the US decreased from 1990 to 2005, the death rate from cutaneous melanoma has risen 5.3% [4]. Overall, greater than one-third of melanoma patients have brain metastases during the course of their disease [5]. Historical reports of survival after WBRT alone for melanoma are disappointing at best. In 2004, research showed the median survival rate was 3.6 months [6]. Several smaller series have suggested that the relative radio-resistance to fractionated treatment may be overcome by using larger single fractions as is employed in SRS [6-7]. We present here our experience with SRS in an attempt to elucidate the factors that predict survival for patients with melanoma brain metastases treated with radiosurgery and to validate the efficacy of the treatment.

Materials And Methods

We reviewed all consecutive patients with melanoma brain metastases treated with SRS at the MNC (Miami, FL) between 1993 and 2009 and JHU (Baltimore, MD) between 2003 and 2007. Of the 163 patients treated at two centers during this period, 154 patients were available for analysis after excluding nine patients who lacked follow-up. IRB approval was obtained prior to evaluating prospectively collected data on these patients. Patients were seen in consultation after confirming pathologic diagnosis of malignancy and the presence of brain metastases on MRI. Each patient was evaluated by a radiation oncologist and neurosurgeon who jointly determined the eligibility for Gamma Knife (GK) treatment.

All patients were treated with the Leksell Gamma Knife (Elekta AB, Stockholm, Sweden) on an outpatient basis. Patients were prescribed keppra and dexamethasone to be taken for four days preceding the procedure and were given ativan on the morning of the procedure as well as pain medication when indicated. The stereotactic head frame was attached by the neurosurgeon in standard fashion; the pin sites were prepped and then anesthetized using lidocaine, appropriate pin lengths were selected based on knowledge of the lesion location. After taking bubble measurements, patients underwent a MRI for planning purposes. Treatment plans were formulated by the GK team consisting of a neurosurgeon, radiation oncologist, and radiation physicist. Both the size and location of each lesion was considered in determining the prescription dose. Following treatment, patients were instructed to begin a dexamethasone taper. Patients were seen in follow-up clinic four weeks following the procedure and then every three months thereafter. A neurologic examination was performed and a MRI was obtained at each visit.

Statistical analysis

Demographic and clinical features were summarized and compared between the two treatment centers with categorical data described as frequencies and compared using Fisher's exact test. All means and medians of continuous data were compared using t-test and Wilcoxon rank sum test. Median time to recurrence and death were compared between the two centers, histology, and clinical and radiologic features of the study population using Kaplan Meier analysis. The Cox Proportional Hazards was used to calculate the predicting value of the clinical variables available. All variables with significant association ($p < 0.1$) on univariate proportional hazard

analysis were entered into multivariate analysis and the final model was determined using backward selection of predictors. Risk ratios for variables found to be significant in the final model were determined.

Cumulative incidence of brain metastases-related (BMR) mortality was derived using non-brain metastases-related (non-BMR) mortality as a competing risk factor and compared between covariates using Grays test.

All p-values reported are two-sided and significance was set at $p < 0.05$ and 95% Confidence intervals calculated using standard methods. All analysis was done using Stata 12 (Stata Corp, College Station, TX) and R version 2.13.0 (2011-04-13).

Results

Patient population

Table 1 summarizes the demographic data of the patient population. One hundred and twenty-seven patients at the MNC and 27 patients at JHU received GK treatment for melanoma brain metastases during 1993 - 2009 and 2003-2009, respectively. The mean age in years at the time of the procedure was 58.3 overall but was significantly higher in the Miami (59.2+16.1) than at Johns Hopkins (51.7+12.3), ($p = 0.01$). The mean follow-up was 7.3+11.4 (median reverse Kaplan Meier: 26.0 months). Patients treated at Johns Hopkins (JHH) had a smaller tumor burden than those treated at MNC ($p = 0.004$). There was otherwise no statistical difference between the two institutions. Overall, 70.4% of the patients were male and 29.9% were female. Eighty-three percent had a KPS greater than 70. The cohort was evenly divided into thirds by number of lesions with approximately one-third each having one lesion, two to three, and more than three. Of the 138 patients on whom the data was available, only 16 (13.1%) patients received WBRT in addition to SRS.

Variable	Overall (Percentage)	Miami (N=127)	Hopkins (N=27)	P value
Age at procedure				
Age at procedure <=65	100 (64.94)	76 (59.84)	24 (88.89)	0.004
Age at procedure >65	54 (35.06)	51 (40.16)	3 (11.11)	0.004
Gender				
Male	108 (70.13)	89 (70.08)	19 (70.31)	1.00
Female	46 (29.87)	38 (29.92)	8 (29.63)	1.00
KPS				
<70	27 (22.13)	23 (23.33)	4 (17.39)	0.78
>70	95 (77.87)	76 (76.77)	19 (82.61)	0.78
Number of lesions				
1	52 (33.77)	41 (32.28)	11 (40.74)	0.075
2-3	45 (29.22)	34 (26.77)	11 (40.74)	0.075
>3	57 (37.01)	52 (40.94)	5 (18.52)	0.075
Tumor volume				
<4.6 (p25)	39 (25.49)	25 (19.69)	14 (53.85)	0.004
4.6-9.3 (p25-p50)	36 (23.53)	30 (23.62)	6 (23.08)	0.004
9.33-25 (p50-p75)	40 (26.74)	37 (29.13)	3 (11.54)	0.004
>25 (p75-p100)	38 (24.84)	35 (27.56)	3 (11.54)	0.004
Dose				
<17Gy	58 (37.66)	50 (39.37)	8 (29.63)	0.38
>17 Gy	96 (62.34)	77 (60.63)	19 (70.37)	0.38
Adjuvant WBRT				
GK	122	101 (90.99)	21 (77.78)	0.08
GK+WBRT	16	10 (9.01)	6 (22.22)	0.08

TABLE 1: Cerebral Metastasis - Melanoma

Patient Demographics

Overall survival from time of treatment

The median overall survival from the time of treatment was 5.0 months [95% CI, 4.6-9.4 months]. The survival was independent of gender, age or total volume of lesions. Patients with KPS>70 had significantly higher survival of 5.5 months in patients vs. 3.7 months with a KPS \leq 70 ($p < 0.001$) (Table 2). However, in the subgroup of patients treated at JHH, differences in survival were not statistically significant, probably because only four (17.4%) of 23 patients had KPS<70 making the comparison underpowered. Overall, the number of lesions was also a significant factor affecting the survival with patients with one, two to three, or greater than three lesions having a median survival of 6.2, 6.8 and 3.7 months, respectively ($p<0.001$) (Table 2). However, this univariate association was only observed in cohort of patients at MNC and not at JHH where majority of patients (81.5%) had fewer than four lesions. Since the multivariate analysis yielded a >3 lesions to be an independent predictor of survival, we compared the survival between patients harboring three or fewer than lesions with those having more than three lesions which was 6.3 months and 3.7 months, respectively ($p<0.001$).

Predictor	N	Dead (%)	Overall Median Survival time (95% CI)	P
All patients	154		5.03 (4.6 - 9.4)	0.13
Center				
MNC	127	112 (88.18)	4.7 (3.91 - 5.53)	0.13
JHH	27	18 (66.7)	6.9 (4.60 - 9.44)	0.13
Gender				
Male	108	92 (85.18)	5.03 (3.95 - 5.53)	0.07
Female	46	38 (82.60)	6.09 (3.88 - 8.98)	0.07
KPS				
KPS ≤70	27	22 (92.59)	3.65 (2.24 - 4.6)	<0.001
KPS >70	95	74 (77.89)	5.59 (4.77 - 8.13)	<0.002
Number of lesions				
1	52	42 (80.76)	6.15 (5.03 - 8.98)	<0.001
2-3	45	35 (77.77)	6.78 (4.41 - 8.65)	<0.002
>3	57	53 (92.98)	3.72 (2.8 - 3.95)	<0.003
Age				
Age ≤65	100	84 (84.0)	5.1 (4.05 - 6.09)	0.97
Age >65	54	46 (85.15)	5.03 (3.72 - 7.11)	0.97
Concurrent whole brain RT (within 90 days of GK)				
No	122	102 (83.6)	5.43 (4.6 - 6.9)	0.03
Yes	16	12 (75.0)	3.32 (2.24 - 6.41)	0.03
Tumor volume				
≤4.6 (<25th percentile)	39	32 (82.05)	5.49 (3.72 - 8.65)	0.13
4.6-9.3 (25th – 50th percentile)	36		5.53 (4.41 - 7.11)	0.13
9.3-25 (50th – 75th percentile)	40		5.33 (3.72 - 6.38)	0.13
>25 (>75th percentile)	38	36 (94.73)	3.78 (2.5 - 6.15)	0.13

TABLE 2: Overall survival from diagnosis of metastasis and from radiosurgery

Overall survival from the time of diagnosis

At the time of analysis, 88.2% and 66.7% of the patients from MNC and JHU had died. The median survival from the time of diagnosis was 7.8 months. No difference was seen in median survival based on age, gender, histology, treatment center, or volumes of lesions. Patients with multiple (>3) lesions had a significantly lower median survival (6.5 months) than those with fewer lesions (9.6 months), $p=0.03$. Survival from diagnosis of metastasis tended to differ by performance status with median survival of 8.1 months in patients with KPS>70 vs. 5.8 months with a KPS ≤ 70 ($p < 0.09$).

Cumulative incidence of mortality caused by brain metastases and other causes

Cumulative incidence of BMR and non-BMR mortality using competing risk analysis at 12 months was 18.6% (95%CI: 11.97-26.36%) and 68.8% (95%CI 59.15 - 76.64 %), respectively. While at 36 months cumulative incidence of BMR and non-BMR mortality was 21.8 % (95%CI: 14.43 – 30.07 %) and 73.3% (95%CI 63.64–83.81%), respectively. Multivariate competing risk regression after adjusting for age>65, KPS>70, dose<16Gy, lesions (2-3 and >3) revealed patients lesions >19cc in volume were 3.4 times more likely to die of BMR cause than those treated higher dose (SHR: 3.41, 95%CI 1.49-7.81). None of the other variables were adjusted for, such as KPS>70, 2-3 lesions, >3 lesions, dose<16Gy, and age >65 predicted brain metastases-related mortality with standardized hazard ratios (SHR) of 0.93 (95% CI: 0.30 – 2.89), 1.2 (95% CI: 0.31-4.25), 1.08 (95% CI: 0.30 - 3.86), 1.08 (0.45 – 2.58), and 1.6 (95%CI: 0.60– 4.01), respectively.

Univariate and multivariate predictors for survival from time of procedure

On univariate analysis significant association with survival were found with KPS, number of lesions, adjuvant radiotherapy, and dose ($p<0.1$) (Table 3). These variables were then entered into multivariate analysis which showed that KPS>70, lesions >3 and dose>17Gy were significant predictors of survival (Table 4). Patients with KPS>70 were 0.6 times less likely to die than patients who had a lower KPS. Presence of more than three lesions was a poor predictor of survival with these patients 2.1 times more likely to die than those with fewer lesions. Higher treatment dose was protective, with the patients who received at least 17 Gy of radiation being 0.4 times less likely to die.

Pooled Model	Hazard Ratio	p
KPS		
KPS ≤70	Reference	
KPS >70	0.37 (0.23 - 0.61)	<0.001
Age		
Age <65	Reference	
Age ≥65	1.005 (.69 - 1.4)	0.97
Center		
MNC	Reference	
JHH	0.68 (0.41 - 1.12)	0.13
Lesions		
Solitary lesion	Reference	
2-3 lesions	1.04 (.66 - 1.63)	0.86
>3 lesions	2.4 (1.59 - 3.69)	<0.001
Volume		
≤4.6 (≤25th percentile)	Reference	
4.6-9.3 (25th - 50th percentile)	.84 (.50 - 1.41)	0.53
9.3-25 (50th - 75th percentile)	0.90 (0.55 - 1.47)	0.69
>25 (>75th percentile)	1.4 (.90 - 2.35)	0.12
Dose		
Dose<17 Gy	Reference	
Dose≥17 Gy	0.69 (0.48 - 0.99)	0.045
Treatment		
GK	Reference	
GK+WBRT	1.77 (1.02 - 3.06)	0.04

TABLE 3: Univariate Risk ratios

Pooled Model	Hazard Ratio	p
Lesions > 3	2.1 (1.38 - 3.20)	0.001
KPS > 70	0.41 (0.25 - .66)	<0.001
Dose > 17 Gy	2.1 (1.38 - 3.20)	0.029

TABLE 4: Final Model (Multivariate) Risk Ratio

Discussion

In our series, patients with intracranial disease from melanoma treated with Gamma Knife survived a median of 5.0 months, which is similar to other series [6, 8-10].

First principles of medicine dictate that treatment selection should result as a careful evaluation of the potential benefit and toxicity of an intervention. In the cases of brain metastases, one of the most commonly employed tools is the RTOG RPA. However, the application of this metric to our patient cohort is problematic because the database used to formulate the RPA was mostly comprised of other histologies (Gaspar IJROBP 1997) [11]. Furthermore, the RPA has not been validated in melanoma patients treated with SRS. In our study, KPS and the number of lesions were highly significant predictors of overall survival, however, only one of these is included in the RPA.

Multivariate analysis identified the presence of greater than three lesions highly predictive for poor survival with a HR of 2.1 ($p < 0.001$). Interestingly, in the study by Gaspar, et al., the number of lesions was significant on univariate analysis but was not significant in the recursive partitioning analysis [11]. In RTOG 9508, which randomized patients with one to three lesions to WBRT vs WBRT + SRS boost, patients with one lesion had improved survival on univariate analysis but this did not retain significance on multivariate analysis [12]. Direct comparison of the RTOG 9508 results is problematic, as only 16 pts in the study had melanoma. In a multi-institutional review of SRS alone vs WBRT + SRS, which included 93 patients with melanoma (16% of study population), univariate analysis found decreasing probability of survival with increasing number of metastases [13]. Liew, et al., in 333 patients with melanoma brain metastases, showed higher survival in patients with a solitary lesion (8.2 months (95% CI 6–10.41 months) when compared to those with multiple metastases (211 patients) to 4.1 months (95% CI 3.3–5 months). Also, patients with fewer than eight lesions and in RPA class I had a median survival of 54 month [8]. Similarly, Golden, et al., in their series of 137 melanoma patients, found poor survival in patients with more than three lesions [14]. Our findings suggest that the burden of disease as indicated by number of lesions may be a more significant predictor of survival for patients with melanoma than other histologies.

RPA has not been validated in melanoma patients treated with SRS. Buchsbaum, et al. analyzed the effect of RPA class on survival of melanoma patients treated with various modalities [15]. Although, univariate analysis revealed RPA class to be a significant predictor of survival, multivariate analysis concluded only KPS scores, primary control and treatment modality (radiosurgery/surgery + WBRT) to be significant independent predictors of patient survival. These results contrast with other studies that have indicated RPA to be significant predictor of survival [11, 16-17]. Buschbaum, et al. attributed these deviations from existing evidence on selection bias causing aggressive treatment of patients with favorable RPA class and to

heterogeneity in extracranial control within RPA II and III [15]. Furthermore, most series reported thus far have heterogeneous histologies, with metastatic melanoma constituting a minority of patients [11, 18]. Therefore, the prognostic value of RPA in patients with melanoma may be limited by inadequate power in these studies.

While RPA class I is very restrictive, and represents a minority of patients, class II and III are very heterogeneous. Neider and colleagues, reported a median survival of 10.5, 3.5, and two months for RPA I, II & III, respectively. Patients with KPS<70 had a median survival of 2.0 months, while those with KPS>70 survived a median duration of 3.6 months. Median time to non-CNS mortality of 12.9 months in RPA I as against 4.1 months and 3.9 months in RPA II and III, respectively ($p<0.05$) after treatment with radiotherapy. However, within RPA II the median survival ranged between 6.6 -13.3 months for patients with solitary lesions or absence of extracranial control, suggesting that RPA is useful for estimating prognosis but should not be exclusively used to select treatment. While RPA can help stratify patients, it does not strictly account for each variable. In another series by Neider, they did not demonstrate a role for RPA classification in determining prognosis and management for patients with four or more metastasis treated with radiosurgery [19]. Similarly, like most studies above and as confirmed by our study, RPA III or KPS <70 is associated with poor prognosis [8, 10, 14]. While most studies have failed to find any prognostic features for subclass of RPA III, Lutterbach, et al., in a subgroup analysis of 408 patients with RPA III in a series of 916 patients, revealed age<65, solitary intracranial lesions and control of primary disease as independent predictors of survival [20]. Furthermore, Chernov, et al. emphasized identification of causes of poor KPS, while prognosticating and determining the best treatment for these patients. Chernov and colleagues, in a series of 40 patients with KPS< 50 treated with stereotactic radiosurgery compared survival between patients who had poor KPS caused by intracranial metastasis as compared to those with low KPS caused by extracranial lesions [21]. Median survival of six months was observed in patients with low KPS secondary to intracranial lesions versus a median survival of 3.3 months month in patients with both intracranial and extracranial lesions causing poor KPS. Poor KPS caused by only extracranial disease had a median survival of one month.

Role of WBRT

In our series, administration of adjuvant WBRT was a significant predictor of mortality on univariate analysis with these patients 0.8 times more likely to die as compared to patients treated with Gamma Knife only, indicating aggressive disease requiring salvage therapy. This association did not hold upon multivariate analysis. The principle that WBRT decreases brain failures and local control without impacting overall survival has been well-established in the literature in studies that include a spectrum of histologies [22]. This tenet has also been observed in patients with melanoma treated with SRS and WBRT [6]. However, in the current study, melanoma patients treated with both modalities fared worse. This is likely due to selection bias as the institutional preferences are to treat with SRS alone and reserve WBRT for salvage.

Conclusions

Radiosurgery seems to be better than conservative treatment in patients with melanoma brain metastasis with favorable KPS (>70) and three or fewer lesions. Treatment with higher radiation dose improves the efficacy of radiosurgery.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. IRB approval was

obtained prior to evaluating prospectively collected data on these patients. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** We declare(s) a grant from Elekta. Educational unrestricted grant support. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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