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Stereotactic Radiosurgery in Treatment of Cerebral Metastases: Histological Differences in Predictors of Survival

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Abstract

Brain metastases are the most common intracranial neoplasm. The incidence of metastatic disease has increased with improved survival of patients with common malignancies, such as lung, breast and melanoma [1]. Brain metastases generally represent an advanced stage of cancer with survival varying between two to three months [2-3] with only palliative treatment and eight to 13 months [4-6] with stereotactic radiosurgical treatment. Several reports have proposed that survival is adversely affected by increasing number and volume of lesions, old age (>65), low Karnofsky performance scores, presence of extracranial metastases, poor control of extracranial disease, and synchronicity of metastases. Several composite classifications, such as Recursive Partitioning Analysis (RPA) and Graded Prognostic Assessment (GPA), have been proposed based on some of the above variables. Though these classifications have been validated by numerous studies, they alone do not explain the risk of mortality [7-10]. For example, numerous reports have shown that the duration of survival and risk factors for mortality varies widely between histologies and that composite classification system, such as the RPA or GPA, cannot be generalized across all pathologies. We describe our multicenter experience treating 1,318 patients with intracranial disease and describe histological differences in predictors of survival and discuss the application of the composite prognostic criteria's across different histologies.

Categories: Radiation Oncology, Neurosurgery
Keywords: karnofsky performance scores (kps), stereotactic radiosurgery, cerebral metastases, gamma knife, graded prognostic assessment (gpa), recursive partitioning analysis (rpa)

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Introduction

Brain metastases are the most common intracranial neoplasm. The incidence of metastatic disease has increased in recent decades, likely secondary to with improved survival of patients with common malignancies such as lung, breast and melanoma [1]. Brain metastases generally represent an advanced stage of cancer with survival varying between two to three months with only palliative treatment [2-3] and eight to 13 months with aggressive management [4-6], which often includes stereotactic radiosurgery. Several reports have reported that survival is

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adversely affected by increasing number and volume of lesions, old age (>65), low Karnofsky performance scores, presence of extracranial metastases, poor control of extracranial disease, and synchronicity of metastases. Based on these variables, several composite classifications, such as Recursive Partitioning Analysis (RPA) and Graded Prognostic Assessment (GPA), have been proposed to estimate the survival of patients with brain metastases. Though these classifications have been validated by numerous studies [7-10], the duration of survival and risk factors for mortality vary widely between tumors of different histologies, which is not taken into account by these classifications.

Here, we describe our multicenter experience treating 1,318 patients with metastatic intracranial disease. We describe histological differences in predictors of survival and discuss the application of the composite prognostic criteria for metastatic brain lesions that originate from different primary sites.

Materials And Methods

Patient population

Between 1993 and 2009, 1,318 patients with metastatic brain cancer underwent Gamma Knife (GK) radiosurgery at two tertiary care centers: the Miami Neuroscience Center in Miami, Florida (1,070 (81%) patients) and the Johns Hopkins Hospital (JHH-248 (19%) patients) in Baltimore, MD. After obtaining approval from the institutional review boards of both institutions, data regarding primary tumor type, number and volume of lesions, radiosurgery treatment plan, clinical follow-up, and radiological evaluation and mortality was retrospectively collected and analyzed. Histological diagnosis of primary cancer was confirmed by biopsy of local tissue in all patients, and an MRI of the brain was used to confirm presence of brain metastases. Patient selection for radiosurgical treatment was done after consultation with a multidisciplinary team, including a neurosurgeon and a radiation oncologist for all cases. The demographic and clinical characteristics of patients treated at both centers are described in Table *1*. The median patient age was 60 years. Complete follow-up data were known for 1,268 patients, of which 981 (84.64%) patients were treated with GK alone, while 178 (15.36%) received adjuvant WBRT with GK.

	MNC (%)	JHH (%)	Total	p
N	1035 (81.62)	233 (18.38)	1268	
Median age (IQR)	62 (51-70)	56 (47-64)		<0.001
Age >65	638 (61.67)	182 (78.11)	820	<0.001
Age <65	397 (38.36)	51 (21.89)	448	
Gender				
Males	442 (42.71)	123 (52.79)	565	0.006
Female	593 (57.29)	110 (47.21)	703	
Primary				
Breast	255 (24.64)	37 (15.88)	292	0.002
Colorectal	51 (4.93)	15 (6.44)	66	0.216
Melanoma	127 (12.27)	27 (11.59)	154	0.437

Non-small cell lung cancer	383 (37)	84 (36.05)	467	0.437
Renal	51 (4.93)	17 (7.30)	68	0.14
Small cell lung cancer	51 (4.93)	10 (4.29)	61	0.865
Others	117 (11.30)	43 (18.45)	160	0.003
Number of lesions				
1 lesions	353 (34.11)	97 (42.54)	450	<0.001
2-3 lesions	316 (30.53)	83 (36.40)	399	
>3 lesions	366 (35.56)	48 ((21.05)	414	
Lesion volume				
<3.8 ml (p25)	180 (17.39)	139 (60.96)	139	<0.001
3.8 - 8.7 ml (p25-p50)	265 (25.60)	49 (21.49)	314	
8.7- 18.6 ml (p50-p75)	291 (28.12)	23 (10.09)	314	
>18.6m1 (>p75)	299 (28.89)	17 (7.46)	321	
KPS				
Median KPS (IQR)	90 (80-90)	80 (80-90)		0.065
KPS<=70	211 (23.79)	32 (18.93)	243	0.19
KPS>70	676 (76.21)	137 (81.07)	813	
Treatment				
GK	792 (85.53)	189 (81.12)	981	0.06
GK+WBRT	134 (14.47)	44 (18.88)	178	
Median treatment dose (Gy) (IQR)	16 (13-18)	18 (16-20)		<0.001

TABLE 1: Demographics and Clinical Features of Patients

Stereotactic radiosurgical treatment

The Leksell Gamma Knife (Elekta AB, Stockholm Sweden) was used for stereotactic radiosurgical treatment of patients at Johns Hopkins Hospital. At Miami Neuroscience Center, Model U was used during the first eight years of the study, followed by Model C and B over the subsequent seven years, and Model Perfexion over the remaining study duration.

No hospital stay was required for the treatment, with planning and radiosurgery done on an outpatient basis. Head frame was placed using lidocaine as a local anesthetic. The lesions were contoured and treatment planning was done by consultation between a neurosurgeon, radiation oncologist, and radiation physicist. The mean prescription isodose line was 18 Gy for

the first treatment and 21 Gy for the second treatment, prescribed to the 50% isodose line. Patients with brainstem lesions were treated with lower doses, usually <16 Gy. The radiation dose prescription was dependent on the tumor volume, location in the brain and history of prior radiation therapy to the brain. Pre-treatment steroids (Dexamethasone) were routinely given.

Patients underwent follow-up evaluations at approximately four weeks post-radiosurgery, and approximately every three months thereafter. At follow-up, patients were evaluated for neurological and radiological progression of disease.

Statistical analysis

Demographic and clinical features were summarized and compared between two treatment centers with categorical data described as frequencies and compared using Fishers Exact test. All means and medians of continuous data were compared using t-test and Wilcoxon rank sum test, respectively. For the primary analysis, overall survival time was calculated from the time of GK radiosurgery to the time of death from any cause. For surviving patients, survival was censored at the date of last follow-up. The Kaplan Meier time to event analysis was applied to calculate overall median survival and to compare survival times between the two centers, as well as clinical and radiologic features of the study population using log rank test. Multivariate analysis was performed using Cox Proportional Hazards regression analysis using a backward selection of predictors to calculate hazard ratios for mortality. The significance level for retention of variable in the nested model was set at $p<0.05$, based on which parsimonious model was sought. Variables included in the full model were patient's age at time of radiosurgery, gender, Karnofsky performance scores (KPS), number of lesions, volume of lesions, synchronicity of metastatic lesions with diagnosis of lesions, adjuvant whole brain radiotherapy (subgroup analysis for patients whose data was available), and radiation dose. Subgroup analysis was later performed for each of the histological subtypes. All p-values reported are two-sided and corresponding statistical tests were significant when $p<0.05$ with 95% confidence intervals calculated using standard methods. All analysis was done using Stata 9.0 (Stata Corp, College Station, TX).

Results

Complete follow-up data were known for 1,268 patients (96.2%). The median patient age was 60 years with the patient cohort consisting of 44.5% men and 55.5% women. Nine hundred and eighty-one patients (84.64%) were treated with GK alone, while 178 patients (15.36%) received adjuvant WBRT with GK. Descriptive analysis showed significant differences in age, gender, number and volume of lesions, and treatment dose between JHH and MNC (Table *1*). The median time to mortality from procedure at MNC was 6.51 months compared to 8.48 months at JHH (p=0.02). Statistically significant differences in survival were observed between males and females, age, KPS, number of lesions, and volume of lesions (Table *2*).

Variable	Number of Patients	Dead(%)	Median Survival Time (Months)	95% CI Survival Time (Months)	Log Rank p-value
All patients	1268	1105 (87.14)	6.78	6.28 - 7.57	
Center					
M NC	1035	950 (91.78)	6.51	5.99 - 7.2	0.02
JHH	233	115 (49.35)	8.48	6.90 - 10.55	

Gender					
Male	565	492 (87.07)	5.66	5.03 - 6.51	0.0001
Female	703	613 (87.19)	7.76	6.97 - 8.52	
Age					
Age <65	820	690 (84.14)	7.7	6.74 - 8.49	<0.001
Age >65	448	415 (92.63)	5.82	4.77 - 6.55	
Primary type					
Breast	292	251 (85.95)	9.08	7.86 - 10.63	
Colorectal	66	58 (87.87)	4.05	2.4 - 5.36	
Melanoma	154	130 (84.41)	5.03	4.05 - 6.09	
NSCLC	467	416 (89.07)	7.14	6.09 - 7.93	
Renal	68	60 (88.23)	8.26	5.29 - 9.8	
SCLC	61	54 (88.52)	4.57	3.16 - 6.68	
Others	160	136 (85)	7.14	5.36 - 7.89	
KPS					
KPS <70	243	232 (95.47)	3.42	2.96 - 4.34	
KPS >70	813	690 (84.87)	8.41	7.7 - 9.28	
Number of lesions					
1	450	384 (85.33)	7.4	6.32 - 8.72	<0.001
2-3	399	334 (83.70)	8.06	6.68 - 9.31	
>3	414	385 (92.99)	5.53	4.64 - 6.41	
Tumor volume (by quartiles)					
<3.8 (01)	319	260 (81.50)	8.36	6.71 - 9.44	0.004
3.8-8.7 (02)	314	270 (85.98)	7.26	6.16 - 9.21	
8.7-18.6 (03)	314	284 (90.44)	6.41	5.53 - 7.7	
>18.6 (04)	321	291 (90.65)	5.36	4.51 - 6.74	
Concurrent RT (within 90 days of GK)					
No	981	848 (86.44)	6.91	6.22 - 7.66	0.72
Yes	178	162 (91.01)	6.71	5.39 - 8.48	

TABLE 2: Survival

While survival of patients with solitary lesions (7.4 months; 95% CI: 6.32-8.72 months) was comparable to those with two to three lesions (8.06 months; 95%CI: 6.68-9.31 months) (p=0.59), patients with more than three lesions had significantly shorter survival (5.53 months; 95% CI: 4.64-6.41 months) than patients with three or fewer lesions (7.8 months; 95%CI: 6.81-8.59 months) (p<0.001). To compare survival by lesion volume, we compared quartiles of volume and found significant differences between patients who had volume below median volume (8.7 cc) (median survival: 7.92 months; 95%CI: 6.67 - 8.78) as compared to those harboring lesions with more than 8.7 cc (median survival 6.15 months; 95%CI: 5.36 - 6.91, p<0.001).

On multivariate analysis of the overall population (Table *3*), significant independent risk factors included poor KPS (⩽70), multiple lesions (>3), male gender, low prescription dose (<18 Gy), and old age (age >65). Higher total lesion volume (> 8.7 cc) was a significant predictor using survival analysis and on bivariate regression, but it was not found to be significant predictor of mortality on multivariate analysis. We performed multivariate analysis stratified by histological type or primary site and compared the results with overall multivariate analysis to check generalizability of overall results to the various histological subtypes (Table *3*).

The predictors of survival in the overall group were similar to those seen with NSCLC and breast cancer. Metastases from melanoma were similar to breast and NSCLC, except that mortality in melanoma was independent of age at treatment. In patients with lesions from SCLC and colorectal primaries, KPS scores ⩽70 was the only risk factor for mortality. Metastases from renal primaries were unique in that none of the risk factors, except for the interaction term between KPS ⩽70 and age ⩽65 were significant, indicating that any significance seen on bivariate analysis was a result of this interaction. Patients with KPS >70 and age ⩽65 were 50% less likely to die than others with neither or only one of these characteristic (Table *3*). We categorized all histologies with fewer than 30 cases or in patients with unknown histology as "Others." This subgroup was similar to breast and NSCLC, except that outcomes were independent of treatment dose.

Male gender was a significant risk factor for overall analysis but failed to be associated with risk of mortality in any of the histological subtypes. This is could be due to the large number of female patients (23%) with breast cancer, which had the highest survival (9.08 months) when compared to other histological types. Furthermore, in the melanoma subgroup, which was the third most prevalent tumor type (12.27%), male gender tended to be associated with increased risk of mortality (hazard ratio=1.41, p=0.07). We suspected male gender to be an artifact because one-third of patients had breast cancer or melanoma, and we therefore reanalyzed the overall data, excluding male gender. However, we did not find any statistically significant difference in the results when compared to that tabulated in Table *3*.

Histology	KPS<70 (95% CI)	Age>65 (95% CI)	Multiple (>3) Lesions	Dose <18Gy
			(95% CI)	
Overall	2.01	1.44	1.58	1.23
	(1.73 - 2.34)	(1.26 - 1.66)	(1.37 - 1.81)	(1.07 - 1.41)
Breast	3.4	1.41	1.79	1.57
	(2.39 - 4.83)	(0.99 - 2.02)*	(1.36 - 2.37)	(1.11 - 2.21)
Colorectal	3.22	n.s.	n.s.	n.s.
	(1.62 - 6.3)			
Melanoma	2.43	n.s.	2.1	1.58
	(1.51 - 4.0)		(1.38 - 3.20)	(1.04 - 2.39)
NSCLC	1.54	1.48	1.53	1.4
	(1.21 - 1.97)	(1.19 - 1.83)	(1.22 - 1.91)	(1.13 - 1.74)
Renal**	n.s.	n.s.	n.s.	n.s.
SCLC	2.0	n.s.	n.s.	n.s.
	(1.09 - 3.64)			
Others	1.87	1.54	1.59	n.s.
	(1.19 - 2.94)	(1.02 - 2.33)	(1.02 - 2.50)	

TABLE 3: Stratified Multivariate Regression Analysis

*P=0.052 ** Only interaction term of Age <65 and KPS >70 was found to be significant. n.s. = not significant

Discussion

Here, we demonstrate that the risk factors for mortality in patients with intracranial metastases differ depending on the various primary tumor histology. This work suggests that the risk factors used to calculate indices, such as GPA (KPS, age, presence of extracranial metastases, and number of lesions) or RPA (KPS, age and extracranial progression), are not applicable to all intracranial metastases. Our study provides added evidence to studies that highlight these differences, suggesting a revision of the current practice of deriving patient prognosis using the same composite scale for all histologies is warranted.

Our current data is consistent with previous studies that revealed differences in prognostic indicators for intracranial metastases from various primary sites. In a series of 4,259 patients, Sperduto, et al. reported the same prognostic factors for metastases originating from primary melanoma (KPS and number of intracranial metastases) and gastrointestinal (KPS) cancers. Fewer prognostic factors were found to be significant in our cohort in patients with NSCLC and

SCLC as only KPS score was significant, as compared to age, KPS, presence of extracranial metastases, and number of intracranial metastases. Similarly, no significant prognostic variable was found in our cohort of patients with renal cancer primaries, as compared to KPS and number of intracranial metastases. While both studies show some heterogeneity in significant prognostic variables, both argue that universal application of GPA to metastases of different histologies require modification [8].

Heterogeneity of significant prognostic variables was also shown by Golden, et al. in a series of 479 patients with brain metastases treated with Gamma Knife [7]. The authors report primary tumor control as the only prognostic marker for breast cancer brain metastases. Survival of patients with metastases from lung cancer was predicted by age, KPS, and number of metastases. Melanoma brain metastases outcome were independent of age but was determined by number of lesions, KPS, and primary tumor control.

A review of the histology specific literature reveals a wide variation within different histological subtypes, making generalizing any staging criteria difficult [6, 8, 10-24]. To our knowledge, there are five studies (including the current study) reporting outcomes of brain metastasis from breast primaries with a study size of at least 100 patients [6, 8, 21, 25]. KPS was reported as independent prognostic factor on four studies [8, 21, 25], extracranial disease control on two studies [6, 21], lesion number by one study (current study), age on one study (current study), lesion volume on one study [21], intracranial lesion location by one study [26], and estrogen/progesterone status on one study [21]. Outcomes of brain metastases originating from non-small cell lung carcinoma have been reported by five large studies, including this study [8, 10, 27-28]. Three studies reported KPS as a significant prognostic factor on multivariate analysis [8, 10], while extracranial control was reported by two studies [10, 28], presence of extracranial metastasis was reported by two studies (8, 28) and age was reported by two studies (8).

Only the current study shows that increasing number of lesions predict poor prognosis. Synchronicity was reported as significant prognostic factor by three studies, although these groups defined synchronous lesions differently from each other (within two months from diagnosis of primary [27] versus three months from treatment of primary [10]). Our study defined synchronicity as diagnosis of metastasis within two months from diagnosis of primary. This was found to be a predictor of poor outcome only in patients with KPS≤70. Similar variations in prognostic factors were reported in melanoma secondaries in brain in six large studies [7-8, 19-20, 22] with KPS being reported as significant multivariate prognostic factor in five studies [7-8, 19, 22]. The number of lesions was important in four studies [7-8, 19, 22], extracranial control in three studies [7, 19, 22], tumor volume in two studies [20, 22], and hemorrhagic lesions in two studies [19-20]. In addition, Liew, et al. also included in their multivariate analysis that adjuvant immunotherapy or chemotherapy, and both were found to affect prognosis [19].

Although there is a tendency towards worse prognosis for survival with increasing number of metastasis when treatment is given with radiosurgery, this approach still may be an appropriate choice for many patients seeking to avoid the short and potentially long-term toxicities of whole brain radiotherapy [29-32]. Indeed, it is unclear that survival would have been improved as there is decreasing survival with increased number of metastasis when whole brain radiotherapy is utilized [33].

Randomized trials have confirmed similar survival whether or not whole brain radiotherapy is utilized for patients with up to four metastasis [34-36], and the outcomes from uncontrolled reports cited above appear similar with both approaches for those with four or more lesions. Therefore, the choice may still appropriately depend upon individualized patient specific issues

related to available resources, state of systemic spread, quality of life choices, time commitment, and ongoing systemic therapies.

These differences in results observed in our series arise as a result of variability regarding the variables that were collected and queried in the various respective studies. Although analyses account for KPS and extracranial control, variation in results may be caused by failure to account for intracranial lesion location, location of extracranial metastases, and amenability for surgical resection. Other confounding factors with the existing staging systems include the fact that often the preoperative MRI that is used for staging may fail to reveal additional lesions seen during high resolution imaging used for treatment planning. Furthermore, inconsistencies between data collection protocols introduce error and lack of comparability between data. Chernov, et al. suggested that patients with low KPS, although regarded as those with poor prognosis, are more likely to benefit from radiosurgery if the poor function is caused by brain metastases [37-38]. Furthermore, authors suggest that some sites of extracranial metastases, such as liver, kidney, and bone, carry a worse prognosis. While challenging, accounting for these factors while developing histology specific prognostic staging criteria will improve accuracy and lead to greater agreement between studies.

Management decisions in patients with brain metastases are largely based on patient prognosis, and hence staging criteria should be accurate and widely validated. Our results show that most existing composite criteria's cannot be generalized across various histologies, and therefore, diagnosis specific staging should be developed. We suggest that staging should be based upon a set of criteria that takes into account histology and high resolution imaging, in addition to the currently used variables. Inaccurate staging has profound impact on patients with metastatic disease, including over-treating those patients that would have minimal benefit and under-treating those that would have the most to gain [39]. Furthermore, it is important that the risk classification be accurate in order to precisely test new treatment modalities in clinical trials. Moreover, the impact of new systemic therapies targeted at particular histologies or biologic subtypes of tumor may be important in the future and should be tracked, especially as better systemic control may increase the importance of optimal management of the CNS disease not reached by most systemic agents. In view of our results and review of literature, we believe KPS ⩽70 is the most reliable predictor of poor outome as survival in patients with KPS ⩽70 is no more than three to four months, which is comparable to outcomes after palliative treatment [2, 40-43]. Therefore, we recommend that radiosurgical intervention in patients with poor KPS be discouraged, particularly when there are appropriate alternative options for treatment of the brain disease.

Conclusions

In our experience, outcomes after radiosurgery for cerebral metastases are largely dependent upon the histology of the lesion. Prognosis and treatment decisions should therefore take into account the histology, in addition to other intracranial and extracranial factors. Survival using radiosurgery is generally poor for patients with a poor KPS, and should be utilized only for carefully selected patients under this circumstance.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. The institutional review boards of the Miami Neuroscience Center in Miami, Florida and the Johns Hopkins Hospital in Baltimore, MD. issued approval NA_00044584. **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:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **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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