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Gamma Knife Radiosurgery for Breast Cancer Metastases to the Brain: Outcomes and Prognostic Factors from a Large Prospectively Collected Database

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Disclosures can be found in Additional Information at the end of the article

Abstract

Background: To examine outcomes and prognostic factors in a large prospectively collected database of patients treated with Gamma Knife (GK) radiosurgery for breast cancer metastases to the brain.

Methods: All patients were treated with GK radiosurgery for brain metastases from breast cancer between 1993 and 2009. Overall survival time was calculated from the time of GK radiosurgery to the time of death from any cause. Kaplan-Meier analysis was applied to calculate overall median time to failure and clinical and radiologic features of the study population. Multivariate analysis was performed using Cox Proportional Hazards regression analysis to calculate relative risk for mortality.

Results: Two hundred and ninety-two patients with were analyzed over a median follow-up of 8.53 months (reverse Kaplan-Meier follow-up of 66.81 months). The median overall survival for the entire cohort from the time of GK radiosurgery was 9.08 months (95% CI, 7.86-10.63 months). There was a significantly greater median overall survival in patients that had KPS > 70, age < 65, or ≤ 3 brain metastases. Multivariate analysis revealed that poor KPS (KPS < 70), older age (age > 65) and multiple lesions (> 3 lesions) were independent predictors of poor prognosis. The risk of mortality in patients with low KPS, multiple lesions, and older age (as defined above) was 300%, 80%, 50% greater than their counterparts, respectively.

Conclusion: Patients with poor performance status and multiple brain metastases from breast cancer have worse outcomes and may be candidates for conservative management.

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Keywords: brain metastasis, breast cancer, stereotactic radiosurgery, survival, predicators

Introduction

Breast cancer is the most common malignancy diagnosed in women in the United States.

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Approximately 10-20% of patients with breast cancer develop clinical or radiographic evidence of brain metastases during their clinical course [1], and an autopsy series suggest this rate may be as high as 30% [2]. Breast cancer is second only to lung cancer in its propensity to develop central nervous system (CNS) metastasis [1, 3]. Risk factors for the development of brain metastases from breast cancer include young age, greater than three involved axillary lymph nodes, high grade tumor, primary tumor size greater than 2 cm, and negative hormone receptor status [4-7]. The rate of CNS metastases from breast cancer appears to be increasing [8-10], in part because improved systemic therapies are allowing patients to survive long enough to develop distant metastases, including to the brain. Many of these new targeted agents are large molecules which do not cross the blood-brain barrier and are, therefore, likely to be ineffective at controlling CNS disease. In addition, improvements in imaging are allowing earlier detection of otherwise subclinical CNS disease.

Historically, the standard of care for patients with limited CNS metastases has been surgical resection followed by whole brain radiation therapy. Three randomized controlled trials have compared surgical resection plus whole-brain radiation therapy (WBRT) with WBRT [11-13], and two have demonstrated a significant improvement in overall survival with surgery plus WBRT versus WBRT alone. Mintz, et al. found no improvement in overall survival with combination therapy; however, 73% of these patients had extracranial metastases or uncontrolled primary disease [11].

More recently, Gamma Knife (GK) radiosurgery has been established as a minimally invasive treatment alternative for appropriately selected patients. Stereotactic radiosurgery has been shown to improve overall survival in patients with brain metastases compared with observation or steroids [9, 14-16].

A few studies have compared radiosurgery plus WBRT with WBRT alone in patients with oligometastatic disease [14-15, 17]. They found improved control of CNS disease with combined modality therapy but no difference in overall survival. However, Andrews, et al. suggested that patients with RPA Class 2 and favorable histology did demonstrate a survival benefit with combination therapy [14].

To date, there have been no randomized controlled trials comparing stereotactic radiosurgery (SRS) versus surgical resection followed by WBRT. Several retrospective studies suggest that SRS, plus or minus WBRT, is associated with similar overall survival as surgical resection plus WBRT [14-15, 17-18]. Although one retrospective study reports the opposite [13], many believe that the SRS doses were inadequate and may, therefore, be confounding the results.

Although numerous studies have reported outcomes for patients treated with GK for brain metastases, few studies to date have included only patients with breast cancer, and these studies included only a limited number of patients. A breast cancer-specific analysis is valuable because tumor histology is an important factor in predicting survival. Outcomes depend on multiple factors, including the disease burden at the time diagnosis of brain metastasis, and the efficacy of treatment options for the extracranial disease. These factors vary dramatically between histologies and may explain, at least in part, the differential survival between diseases, such as metastatic breast carcinoma and metastatic melanoma.

This study represents the second largest study to date to examine prognostic factors and outcomes in a prospectively collected database of patients treated with GK radiosurgery for breast cancer brain metastases.

Materials And Methods

Patient population

Between 1993 and 2009, 292 patients with breast cancer underwent Gamma Knife radiosurgery at two tertiary care centers: the Miami Neuroscience Center (MNC) in Miami, Florida and the Johns Hopkins Hospital (JHH) in Baltimore, MD. These patients had at least one follow-up visit or their vital status was known during the study period. Thirty-seven (9.9%) patients were treated at JHH and 255 (87.33%) of patients were treated at the Miami Neuroscience Center. After obtaining approval from the institutional review board, an analysis was performed of the prospectively collected data. Histological diagnosis of primary breast cancer was confirmed by a biopsy of breast tissue in all patients, and an MRI of the brain was used to confirm brain metastases. Patient selection for radiosurgical treatment was done after consultation with a multi-disciplinary team including a neurosurgeon and a radiation oncologist for all cases.

Stereotactic radiosurgical treatment

The Leksell GK (Elekta AB, Stockholm Sweden) was used for the 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.

Patients were treated on an outpatient basis. Lidocaine was used as a local anesthetic for head frame placement. The treatment plan was developed by a neurosurgeon, radiation oncologist, and a 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.

Follow-up evaluations were performed approximately four weeks after GK radiosurgery, and approximately every three months thereafter. Follow-up evaluation consisted of a clinical history and physical examination, as well as a brain MRI.

Statistical analysis

Demographic and clinical features were summarized and compared between the 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. For the primary analysis, overall survival time was calculated from the time of GK radiosurgery to the time of death from any cause. Secondary analyses included overall survival from the time of diagnosis of brain metastases. For surviving patients, survival was censored at the date of last follow-up. The Kaplan-Meier test was applied to calculate overall median time to failure and to compare survival times between the two centers, as well as clinical and radiologic features of the study population. Multivariate analysis was performed using Cox Proportional Hazards Regression Analysis using a backward selection of predictors to calculate relative risk for mortality. All p-values reported are two-sided, and significance was set at $p < 0.05$ and 95% confidence intervals were calculated using standard methods. All analysis was done using Stata 9.0 (Stata Corp, College Station, TX).

Results

All patients were treated with GK radiosurgery for breast cancer brain metastases. The demographic and clinical characteristics of patients treated at both centers are described in Table *1*. The mean patient age was 54.4 years. Follow-up data and details of the administered radiotherapy was known for 257 patients, of which 210 (81.72%) patients were treated with GK alone while 47 (18.28%) received WBRT plus GK. Thirty-seven patients were treated at JHH, and 255 patients were treated at the MNC over a median follow-up of 8.53 months (reverse Kaplan-Meier follow-up of 66.81 months). When the patient population at two centers was compared, there was no significant difference in patient age, gender, or KPS between patients treated at the two institutions (Table 1), except that patient population at MNC had a significantly greater number of lesions (p=0.041) as well significantly larger tumor volumes (p=0.006) than those at JHH. Overall, the median age at the time of the procedure was 52.5 years, the median number of lesions was three, and the median tumor volume was 9.1 cc.

Variable	Overall (Percentage)	Miami	Hopkins	P value
Age at procedure				
Age at procedure <=65	233 (79.79)	201 (78.82)	32 (86.49)	0.38
Age at procedure >65	59 (20.21)	54 (21.18)	5 (13.51)	
Gender				
Male	3 (1.03)	3 (1.18)	0	1
Female	289 (98.97)	252 (98.82)	37 (100)	
KPS				
<70	51 (20.56)	47 (21.27)	4 (14.81)	0.61
>70	197 (79.44)	174 (78.73)	23 (85.19)	
Number of lesions				
1	85 (29.21)	73 (28.63)	12 (33.33)	0.133
3 - Feb	83 (28.52)	69 (27.06)	14 (38.89)	
>3	123 (42.27)	113 (44.31)	10 (27.78)	
Tumor volume (in cc)				
<3	73 (25.18)	52 (20.39)	21 (60)	<0.001
3 - 9.1	72 (24.83)	66 (25.88)	6 (17.14)	
9.1 - 19	73 (25.17)	68 (26.67)	5 (14.29)	
>19	72 (24.83)	69 (27.06)	3 (8.57)	
Concurrent radiotherapy				
GK+ radiotherapy	210 (81.71)	180 (81.82)	30 (81.08)	1
GK only	47 (18.29)	40 (18.18)	7 (18.92)	

TABLE 1: Patient characteristics

The median overall survival for the entire cohort from the time of GK radiosurgery was 9.08 months (95% CI, 7.86-10.63 months). The patients were stratified by gender, treatment center, KPS, number of lesions, age, tumor volume, concurrent radiotherapy, and median overall survivals (Tables 2, 3).

Strata	Number of Patients	Dead(%)	Median Survival time from treatment (months)	95% CI Survival time (months)	Log-Rank p-value	Median Survival time from diagnosis of metastasis (months)	95% CI Survival time (months)	Log Rank P Value
All patients	292	251 (85.96)	9.08	7.86 - 10.63		15.59	12.5 - 18.68	
Gender								
Male	3	3 (100)	10.43	8.72 - .	0.73	11. 31	9.21 - .	0.77
Female	289	248 (84.9)	9.08	7.7 - 10.63		15.29	12.50 - 18.42	
Center								
Hopkins	37	21 (56.75)	12.07	8.25 - 30.46	0.082	29.93	17.92 - 37.23	0.008
Miami	255	230 (90.19)	8.72	7.4-10		13.81	10.92 - 16.48	
KPS								
<70	51	50 (98.01)	4.38	2.66 - 6.38	<0.001	8.02	4.57 - 12.66	<0.001
>70	197	162 (82.23)	13.16	10.13 - 15.89		17.02	13.81 - 18.42	
Number of lesions								
1	85	71 (83.52)	9.8	6.94 - 15.86	0.0009	18.68	11.15 - 22.20	0.0002
3 - Feb	83	65 (78.31)	14.24	9.21 - 18.75		24.67	16.41 - 28.48	
>3	123	115 (93.49)	7.17	5.89 - 8.95		10.92	7.99 - 13.18	
Age								
<65	233	197 (84.54)	9.21	7.86 - 11.71	0.012	17.2	13.25 - 20.03	0.0029
>65	59	54 (91.5)	8.72	5.79 - 11.35		10.46	6.54 - 15.82	

Tumor volume (by quartiles)								
<3 (p25)	73	57 (90.4)	11.84	6.97 - 14.24	0.33 (p for trend 0.054)	20	13.32 - 26.67	
3.0-9.1 (p25-p50)	72	64 (88.88)	10.23	8.72 - 14.64		16.94	11.31 - 21.84	
9.1-19.0 (p50-p75)	73	66 (90.41)	9.08	6.74 - 13.65		13.75	8.78 - 16.11	0.29
>19.0 (p75-p100)	72	63 (87.5)	6.74	4.51 - 8.75		12.1	8.02 - 20.03	(p for trend 0.082)
Concurrent radiotherapy								
GK only	210	177 (84.28)	9.08	7.7 - 11.35	0.48	11.84	8.02 - 17.69	0.34
GK+ radiotherapy	47	42 (89.36)	7.96	5.39 - 11.51		15.82	10.92 - 19.24	

TABLE 2: Overall survival from the time of the diagnosis of brain metastasis and GK radiosurgery

Strata	Number of Patients	Progression (%)	Median time to progression or death from treatment (months)	95% CI Survival time (months)	Log- Rank p-value
All patients	292	271 (92.80)	4.9	4.38 - 5.89	-
Gender					
Male	3	3 (100)	10.43	8.72 - .	0.54
Female	289	268 (92.73)	4.87	4.38 - 5.79	
Center					
Hopkins	37	27 (98.03)	8.26	4.8 - 14.21	0.11
Miami	255	244 (95.68)	4.84	4.14 - 5.59	
KPS					
< 70	51	50 (98.03)	2.99	2.24 - 4.38	0.0003
> 70	197	180 (91.37)	5.99	4.84 - 7.37	
Number of lesions					

1	85	77 (90.58)	6.68	5.33 - 8.72	
3 - Feb	83	74 (89.15)	5.72	4.44 - 8.72	<0.001
> 3	123	120 (97.56)	3.85	2.86 - 4.38	
Age					
< 65	233	217 (93.13)	4.84	4.31 - 5.69	0.88
> 65	59	54 (91.52)	5.89	3.91 - 7.43	
Tumor volume (by quartiles)					
< 3 (p25)	73	64 (87.64)	6.15	4.87 - 7.7	0.046
3.0-9.1 (p25 - p50)	72	68 (94.44)	5.79	4.74 - 8.75	
9.1-19.0 (p50 - p75)	73	68 (93.15)	3.85	2.7 - 5.99	
>19.0 (p75 - p100)	72	70 (97.22)	4.01	3.4 - 4.74	
Concurrent radiotherapy					
GK only	210	194 (92.38)	4.84	4.11 - 5.72	0.97
GK+ radiotherapy	47	44 (93.61)	5.39	3.85 - 6.94	

TABLE 3: Progression-free survival

There was a significantly greater median overall survival in patients that had KPS > 70, age < 65, or ⩽ 3 brain metastases. Multivariate analysis revealed that poor KPS (KPS < 70), older age (age > 65), and multiple lesions (> 3 lesions) were independent predictors of poor prognosis (Tables 4-6). The risk of mortality in patients with low KPS, multiple lesions, and older age (as defined above) was 300%, 80%, 50% greater than their counterparts, respectively.

Strata	Hazard Ratio (95% Confidence Interval)	p
Center		
Hopkins	Reference	
Miami	1.48 (0 .94 - 2.32)	0.084
KPS		
<70	Reference	
>70	0.33 (0.24 - 0.46)	<0.001
Number of Lesions		
1	Reference	
3 - Feb	0.85 (0.61 - 1.19)	0.367
>3	1.47 (1.09 - 1.98)	0.011
Age		
<65	Reference	0.013
>65	1.47 (1.08 - 1.99)	
Tumor Volume (by quartiles)		
<3 (p25)	Reference	
3.0 - 9.1 (p25 - p50)	1.14 (0.80 - 1.64)	0.448
9.1 - 19.0 (p50 - p75)	1.26 (0.88 - 1.81)	0.192
>19.0 (p75 - p100)	1.37 (0.96 - 1.96)	0.081
Concurrent radiotherapy		
GK only	Reference	
GK+ radiotherapy	1.128 (0.80 - 1.58)	0.7

TABLE 4: Bivariate predictors of mortality (Cox Regress analysis)

Covariate	Hazard Ratio	95% Confidence interval	P value
KPS <70	3.02	2.16 - 4.42	<0.001
lesions >3	1.83	1.38 - 2.42	<0.001
Age >65	1.53	1.08 - 2.17	0.015

TABLE 5: Independent predictors of mortality (Multivariate Cox Regression analysis)

Covariate	Hazard Ratio	95% Confidence interval	P value
KPS < 70	1.8	1.31 - 2.49	<0.001
lesions > 3	1.87	1.43 - 2.44	<0.001

TABLE 6: Independent predictors of progression-free survival (Multivariate Cox Regression analysis)

The median overall survival for the entire cohort from the time of diagnosis of brain metastases was 15.59 months (95% CI 12.5-18.68 months). The patients were stratified by gender, treatment center, KPS, number of lesions, age, and tumor volume, and median overall survivals (Figure *1a*). There was significantly greater median overall survival from the time of diagnosis of brain metastases for patients with KPS > 70 (Figure *1a*), age < 65 (Figure *1b*), ⩽ 3 metastatic lesions (Figure *1c*), or patients treated at JHH.

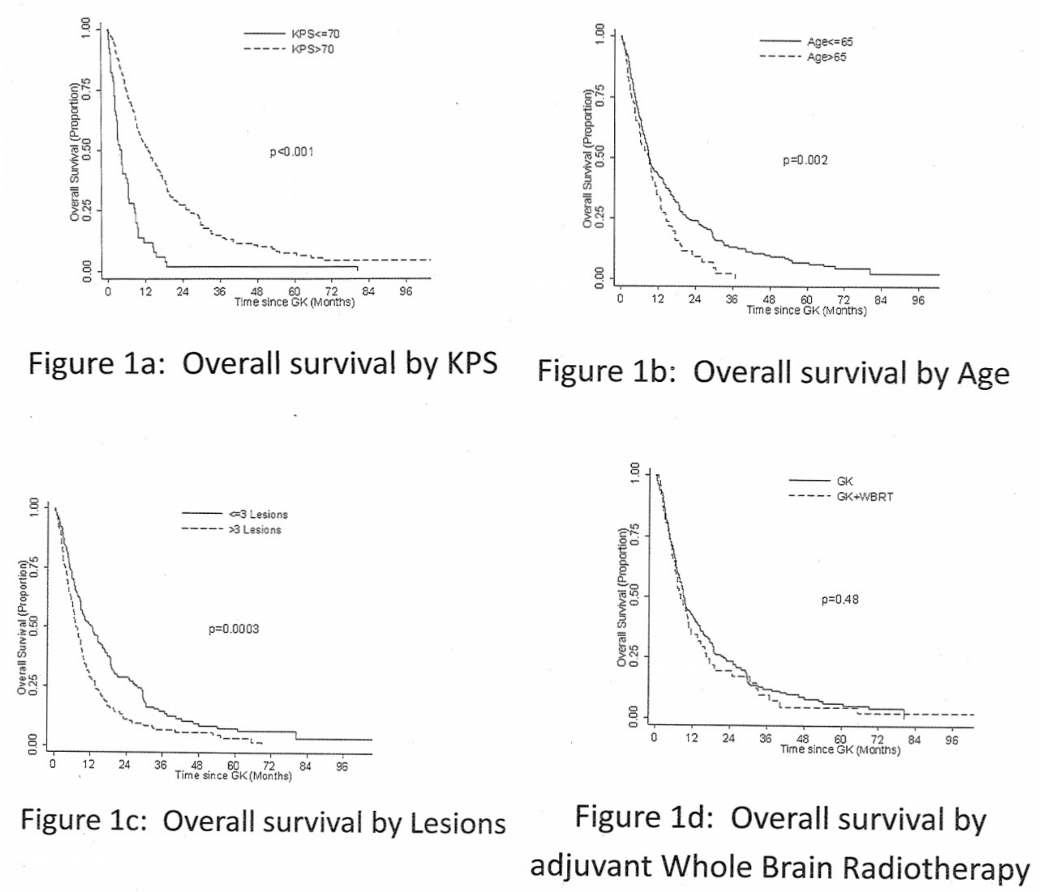

FIGURE 1: The median overall survival for the entire cohort from the time of diagnosis of brain metastases was 15.59 months (95% CI 12.5-18.68 months).

The median progression-free survival (PFS) (Figure *1a*) was 4.9 months (95% CI: 4.38-5.89) with 271 (92.80) patients progressing or dying within the follow-up time. Upon stratified analysis, PFS significantly differed between patients with fewer lesions (< 3 lesions) and more lesions (p < 0.001); KPS < 70 (p=0.001) and higher (p < 0.001); and volume of lesions with larger volume having poorer PFS (p=0.046). Multivariate analysis demonstrated the number of lesions and KPS to be independent predictors of progression.

Discussion

We present the second largest series to date examining prognostic factors and outcomes in a prospectively collected database of patients treated with GK radiosurgery for breast cancer brain metastases. In their retrospective study, Goyal, et al. [19] reviewed 43 patients with 84 lesions treated with GK for breast cancer brain metastases. They report a median overall survival of 13 months after radiosurgery, which is longer than the 9.08 months reported in the present study. Their study included patients who, on average, had better performance status, fewer metastases, and smaller tumor volumes than the present study; however, their study was consistent with ours in that multivariate analysis found that KPS and age were most predictive of survival.

Kondziolka, et al., reviewed the outcomes of 350 patients with breast cancer metastasis to the brain [29]. Median survival time in this series was 11.2 months and better prognosis was associated with extracranial control, better RPA class, higher KPS score, a smaller number of brain metastases (< 5), a smaller total tumor volume (< 8 cc), lesions located at deep cerebral or brainstem sites, and *HER2/neu* overexpression. While our series did not find an association with total tumor volume, our results are consistent with a better prognosis being associated with higher KPS class and fewer lesions. We also found that age was a significant prognostic factor, with patients younger than 65 having improved survival. Despite having comparable mean age of patients (54.4 vs 54), Kondziolza, et al. did not find an association between age and outcomes, likely because they compared survival in patients older or younger than 45 years. Predictors of higher progression-free survival (PFS) were lower RPA class, fewer lesions on SRS (< 3 metastases), no prior WBRT, smaller total tumor volume (< 8 cc), smaller volume for the largest tumor, presence of cerebellar metastases, and margin dose < 17 Gy. These results are in agreement with our study which associates better PFS with < 3 lesions, higher KPS, smaller tumor volume (< 9.1 cc). Due to lack of data, we could not evaluate the association of PFS with lesion location and RPA class.

Sook Lee, et al. [20] reviewed a series of 198 breast cancer patients with brain metastases. Twenty-two (11%) of these patients were treated with Gamma Knife and 75.3% were treated with WBRT as the primary modality of therapy. They report a median overall survival of 5.6 months, with only 23% of patients surviving over one year. When stratified by treatment modality, the median overall survival was 5.4 months for patients receiving WBRT, 14.9 months for patients receiving surgery or GK alone, and 2.1 months for patients that did not receive any treatment. Consistent with our study, Goyal, et al. also showed that performance status is a significant predictor of overall survival in multivariate analysis, with patients with a good performance status having a median survival of 6.5 months versus 3.2 months for ECOG performance status greater than or equal to three.

Another review of breast cancer patients with brain metastasis was performed by Rades and colleagues [18] who reviewed 207 patients treated with WBRT. The median survival for the entire cohort was five months, consistent with the study by Sook Lee. On multivariate analysis, they found that overall survival was significantly associated with KPS (RR 4.0, $p<0.001$) and extracranial metastases (RR 1.54, $p=0.024$). They recommend that patients with RPA class 3 (KPS < 70) receive best supportive care rather than more aggressive management because of their extremely poor prognosis. Our data are consistent with this conclusion in that patients with KPS ≤ 70 had a median overall survival of only 4.38 months, whereas patients with KPS > 70 had a median survival of 13.16 months.

Our study did not find any significant difference in the median survival of patients who were treated with radiosurgery (9.08, 95% CI: 7.7-11.35 months) only versus radiosurgery with WBRT (7.96, 95% CI 5.39-11.51 months) $p=0.48$ (Figure *1d*). Furthermore, even though addition of WBRT did enhance progression-free survival, this difference did not attain a statistical significance (GK only: 4.84, 95% CI: 4.11-5.79 versus GK+WBRT: 5.39 months, 95% CI: 3.85-6.94; $p=0.97$). A prior surgical series by Wronski, et al. [21] reported outcomes of 70 patients with primary breast cancer who underwent surgical resection of brain metastases. The median overall survival was 16.2 months after the diagnosis of a brain tumor, and 14.0 months after brain surgery. Multivariate analysis found that adjuvant WBRT after surgery and lack of meningeal carcinomatosis were the only significant predictive variables of longer survival. Survival in patients receiving WBRT was 15.8 months versus 9.6 months for those who did not. However, the vast majority of their patients did receive WBRT, which makes the results challenging to interpret.

The role of WBRT after GK for brain metastases remains controversial. Four studies have compared radiosurgery alone to radiosurgery, plus WBRT, and have failed to show a significant improvement in overall survival with combined modality therapy [16, 22-23]. On the other hand, Pirzkall, et al. [15] showed an overall survival benefit with the addition of WBRT to radiosurgery. Similarly, Regine, et al. [24] reported significantly increased rates of tumor recurrence with radiosurgery alone compared with radiosurgery, plus WBRT.

An important limitation of the present study is that the hormone receptor status of the initial breast tumors was not prospectively recorded. Prior studies, including Wronksi and colleagues, have shown that patients with positive estrogen or progesterone receptor status had a significantly longer overall survival than patients with negative hormone receptor status (21.9 months versus 12.5 months, $p<0.05$). The influence of hormone receptor status on the survival in the present cohort of patients is unknown.

Nevertheless, our study represents an important contribution to the current body of literature in that it has prospectively collected outcome data for patients treated with GK radiosurgery for breast cancer brain metastasis, and it is the second largest study to date in this patient population. There have been several large studies which have reported outcomes for patients with a wide variety of tumor histologies treated with GK radiosurgery for brain metastases [25-27]. The results of these studies are consistent with our study in reporting a significant relationship between performance status, tumor volume, and number of brain metastases on overall survival. In general, the number of patients in these studies with breast cancer was small and many showed that tumor histology was an important predictor of overall survival. For example, of the 521 patient reported by Serizawa, et al. [26], only 33 (6.3%) had breast cancer metastases.

Multiple studies have found a significant relationship between tumor histology and overall survival following radiosurgery for brain metastases. For example, Petrovich, et al. found that the 38 (8.3%) patients with a breast cancer primary had a median survival of 17 months versus nine months for all patients, six months for colon cancer, and eight months for melanoma. Similarly, Pollock, et al. [28] reported that patients with radiosensitive primaries, such as breast (21%) and lung (53%), were less likely to develop intracranial recurrences than patients with radioresistant tumors, such as melanoma, renal cell carcinoma and sarcoma (relative risk 2.43, $p=0.02$). This variation in outcomes with tumor histology highlights the importance of our breast cancer-specific analysis.

Conclusions

In summary, we examine prognostic factors and outcomes in a large prospectively collected database of patients treated with GK radiosurgery for breast cancer metastases to the brain. Our data is consistent with previous studies showing that: performance status, age, and number of brain metastases are the factors most predictive of survival. Because of the consistently poor outcomes across studies, conservative management approaches should be considered in breast cancer patients with multiple brain metastases, advanced age, and a poor performance status.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. The Institutional Review Board at Johns Hopkins Hospital issued approval N/A. **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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