

Original Article

Pretreatment clinical prognostic factors for brain metastases from breast cancer treated with Gamma Knife radiosurgery

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Abstract

Background: Brain metastases significantly affect morbidity and mortality rates for patients with metastatic breast cancer. Treatment for brain metastases lengthens survival, and options such as stereotactic radiosurgery (SRS) can increase survival to 12 months or longer. This study retrospectively analyzes the prognostic factors for overall survival (OS) for patients with one or multiple brain metastases from breast cancer treated with SRS.

Methods: Between December 2001 and May 2015, 111 patients with brain metastases from breast cancer were grouped by potential prognostic factors including age at diagnosis, Karnofsky Performance Status (KPS) score, number of brain metastases, and whether or not they received adjuvant treatments such as whole brain radiotherapy (WBRT) or surgical resection. Survival rates were determined for all groups, and hazard ratios were calculated using univariate and multivariate analyses to compare differences in OS.

Results: Median OS was 16.8 ± 4.22 months. Univariate analysis of patients with a KPS ≤ 60 and multivariate analysis of KPS 70–80 showed significantly shorter survival than those with KPS 90–100 (5.9 ± 1.22 months, 21.3 ± 11.69 months, and 22.00 ± 12.56 months, $P = 0.024$ and < 0.001). Other results such as age ≥ 65 years and higher number of brain metastases trended toward shorter survival but were not statistically significant. No difference in survival was found for patients who had received WBRT in addition to SRS ($P = 0.779$).

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Conclusion: SRS has been shown to be safe and effective in treating brain metastases from breast cancer. We found our median survival to be 16.8 ± 4.22 months, an increase from other clinical reports. In addition, 38.4% of our population was alive at 2 years and 15.6% survived 5 years. Significant prognostic factors can help inform clinical treatment decisions. This study found that KPS was a significant prognostic indicator of OS in these patients.

Key Words: Brain metastases, breast cancer, stereotactic radiosurgery

INTRODUCTION

Brain metastases are the number one cause of morbidity and mortality for approximately 1.4 million Americans who are diagnosed with cancer every year. An estimated 20%–40% of those diagnosed with cancer will develop brain metastases over the course of their illness.^[13] Breast cancer remains the second most common origin of intracranial metastases behind lung cancer, with 10%–16% of breast cancer patients developing brain metastases.^[24,35] The prognosis of these patients is generally poor: untreated patients survive an average of just 1 month.^[26] Radiotherapy in the form of whole brain radiation therapy (WBRT) alone can extend breast cancer brain metastases (BCBM) survival to 3–4 months, and surgical resection of a tumor and/or use of radiosurgery can extend that to an average of 7–12 months.^[32] Prognosis of longer survival is indicated by several factors such as Karnofsky Performance Status (KPS) score >70 , age <60 years, and a single small metastasis or small total volume of metastases.^[10]

The clinical approach to managing brain metastases comprises one or several modalities including chemotherapy, surgical resection, WBRT, and stereotactic radiosurgery (SRS). The effectiveness of radiosurgery in treating brain metastases has been well documented, and several methods are available for delivery of radiation.^[9] These equipment include linear accelerators, tomotherapy, cyclotrons, and cobalt-60-based Gamma Knife.^[28]

To date, there are several retrospective studies that outline some prognostic factors associated with radiosurgery treatment of BCBM.^[5,11,16] Much of the literature is focused on breast cancer subtype and histology, specifically how human epidermal growth factor receptor 2 (HER2)-positive, triple-negative, and estrogen receptor/progesterone receptor-positive subtypes differ in their overall survival (OS) prognostic ability. Other studies have focused on adjuvant treatment options such as trastuzumab and lapatinib.^[16,17]

In this study, we offer 111 retrospectively analyzed data from patients with BCBM treated with Gamma Knife radiosurgery (GKRS) at Gamma Knife of Spokane. Our goal is to outline several pretreatment clinical factors that have effects on prognosis for patients undergoing treatment.

MATERIALS AND METHODS

For this analysis, we examined 111 patients with a diagnosis of brain metastasis and primary tumor histology of breast cancer. These patients were treated between December 2001 and May 2015 by physicians at Gamma Knife of Spokane. The patients were grouped by age at brain metastasis diagnosis (<65 , $65+$) by whether or not they received whole brain irradiation (WBI), by whether or not they underwent resection, by KPS value, and by the number of brain metastases (1, 2–5, >5). Number of patients in these groups are shown in Table 1.

Survival curves were estimated using the Kaplan–Meier method and used to compare treatment groups, age groups, KPS groups, and brain metastases number groups. Andersen confidence intervals of 95% were constructed for the median survival time of the groups. An estimate of the standard error was used to calculate approximate confidence intervals for the log-hazard ratio (HR).

Table 1: Patient population baseline characteristics

Characteristic	Total (n = 111)
Age at diagnosis	
<65	82
≥ 65	27
Unknown	2
KPS	
90-100	12
70-80	16
≤ 60	9
Unknown	74
Brain metastases [#]	
1	37
2-5	36
>5	35
Unknown	3
Received WBI	
No	53
Yes	58
Underwent resection	
No	95
Yes	16

KPS: Karnofsky Performance Status, WBI: Whole brain irradiation

To determine whether there is statistical evidence of differences between the survival curves of the groups, log-rank tests were employed. The multivariate analysis of the treatment groups, age groups, KPS groups, and brain metastases number groups used the Cox proportional hazard model. All statistical analyses utilized StatsDirect version 2.8.0 (StatsDirect Ltd., Altrincham, UK) and SigmaPlot version 11.0 (SYSTAT Software, Inc., San Jose, CA, USA).

RESULTS

A total of 111 patients were included in the study. Their baseline characteristics are shown in Table 1. There were 82 (73.8%) patients younger than 65 years. The number of patients who were diagnosed with 1, 2–5, and 5+ brain metastases were 37 (33.3%), 36 (32.4%), and 35 (31.5%), respectively. Thirty-seven (33.3%) patients had recorded KPS scores, but 74 (66.7%) did not have KPS scores. About half of the patients (52.2%) received whole brain radiation and 16 (14.4%) patients underwent surgical resection.

Median OS was 16.8 ± 4.22 months. Kaplan–Meier survival curves for several treatment groups are found in Figures 1–3. Figure 1 shows age-related survival curves for patients > 65 or 65+. Although not statistically significant, the median survival of those patient groups was 19.0 ± 4.77 months and 15.1 ± 7.74 months, respectively ($P = 0.633$) [Table 2]. Figure 2 shows KPS score survival. Significant differences in survival were demonstrated between patients with KPS of 90–100, those of KPS 70–80, and those of KPS 60 and below ($P > 0.001$). Higher KPS correlated statistically with an increased survival rate. Figure 3 shows survival for the number of brain metastases: 1, 2–5, and 5+. No significantly different survival was indicated in those patient groups ($P = 0.349$ and 0.288 , respectively).

Univariate median survival confidence interval and HR confidence intervals are shown in Table 2. Within each category, a reference group was selected against which the other groups' HRs were tested. The univariate analysis indicated patients with KPS = 60–70 had survival experience that was statistically significantly different ($P = 0.024$) than the reference group (KPS = 90–100).

The multivariate analysis HR estimates and confidence intervals are shown in Table 3. The multivariate analysis utilized the same reference groups as the univariate analyses against which the other groups' HRs were tested. The multivariate analysis indicated patients with KPS = 70–80 and KPS ≤ 60 had survival experience that was significantly different than the reference group (KPS = 90–100).

Fifty-eight (52%) patients received WBRT in addition to SRS treatment. Median survival lengths for patients who

did and did not receive WBRT were 16.8 ± 8.14 months and 19.0 ± 6.46 months, respectively. This was not a

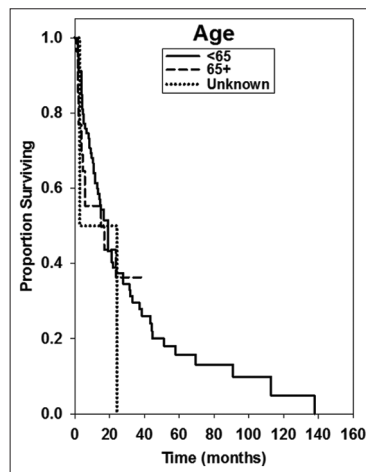


Figure 1: Overall survival curves comparing patients with ages <65, 65+ at the time of brain metastasis diagnosis

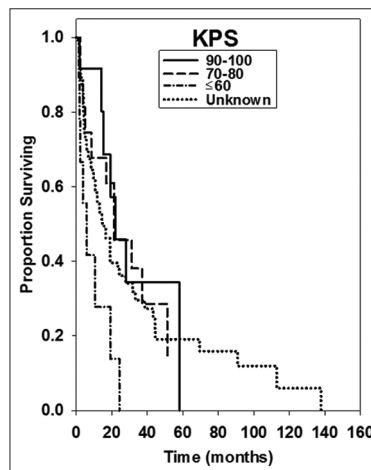


Figure 2: Overall survival curves comparing patients with Karnofsky Performance Status score of 90–100, 70–80, or ≤ 60 at initial treatment

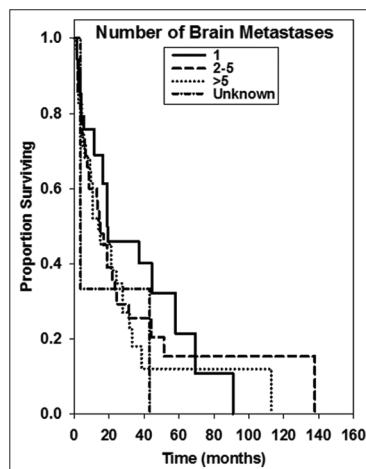


Figure 3: Overall survival curves comparing patients with 1, 2–5, or >5 brain metastases at the time of initial brain metastases diagnosis

Table 2: Univariate median survival estimates (months) and hazard ratios of patients

	Median survival		HR		
	<i>n</i>	95% CI	Estimate	95% CI	<i>P</i> **
Age at diagnosis					
<65*	82	19.00±4.77	Reference		
≥65	27	15.10±7.74	1.17	0.60-2.15	0.633
Unknown	2	2.80±incalculable	1.88	0.22-7.41	0.300
KPS					
90-100*	12	22.00±12.56	Reference		
70-80	16	21.3±11.69	1.19	0.40-4.00	0.805
≤60	9	5.90±1.22	4.13	1.16-16.45	0.024
Unknown	74	14.7±7.66	1.38	0.62-3.63	0.425
Brain metastases [#]					
1*	37	19.10±18.01	Reference		
2-5	36	14.70±5.29	1.28	0.70-2.40	0.468
>5	35	14.10±9.14	1.45	0.78-2.72	0.237
Unknown	3	3.70±0.16	2.41	0.43-8.91	0.164
WBI received					
No*	53	19.00±6.46	Reference		
Yes	58	16.80±8.14	3.10	0.59-31.06	0.251
Resection undergone					
No*	95	15.10±5.00	Reference		
Yes	16	24.20±18.57	0.67	0.31-1.32	0.296

*Reference group against which other groups' survival experience are compared, ***P* value for log-rank testing, the null hypothesis that the groups' survival experience is same as reference group. KPS: Karnofsky Performance Status, HR: Hazard ratio, WBI: Whole brain irradiation

significant difference upon multivariate or univariate analysis ($P = 0.779$ and 0.251 , respectively).

Absolute survival rates are shown in Table 4. Six-month survival was 70.8%, 1-year survival was 59.5%, 2-year survival was 38.4%, and 5-year survival was 15.6%.

DISCUSSION

Brain metastases are less common than bone or other soft tissue metastases for patients with breast cancer, but they represent a significantly poorer prognosis and are often resistant to systemic therapies.^[19] Studies have shown that the median OS for patients with brain metastases following WBRT and SRS is between 4 and 6 months.^[22] Therefore, it is imperative that more effective methods of treatment should be developed to prolong and improve the quality of life of patients with this increasingly common disease. This study aims to retrospectively analyze the effectiveness of treatment of BCBM with GKRS and to identify which patients are most likely to benefit from treatment. Several key prognostic factors are outlined by the Radiation Therapy Oncology Group (RTOG) in 1989, and revised again in 1997 to include recursive partitioning analysis (RPA) classes.^[12] These factors were associated with positive survival and include KPS score of at least 70, age <65, and low number of brain metastases (between 1 and 4). To assess the effectiveness of treatment, we compared

OS of patients receiving any combination of GKRS and whether they had adjuvant treatment such as surgical resection or WBRT.

Our study found that KPS score was a significant prognostic factor. Patients with lower KPS score on the day of treatment had significantly shorter survival than did those with high functionality. This is consistent with other reports of KPS as a strong predictor of survival for patients undergoing SRS. Kased *et al.* found that KPS score was a significant prognostic factor in both univariate and multivariate analyses for the 176 patients treated with radiosurgery or radiosurgery plus WBRT.^[15,18] They found that those with a KPS score of 70 or greater had significantly longer survival versus those with a KPS score of less than 70 ($P = 0.005$). This is supported by a long history of studies that demonstrate KPS is a significantly important prognostic indicator for patients with BCBM.^[1,14,23] The present study found a stratified difference between a KPS of 100 and a KPS of 80–90 (HR: 1.28; $P < 0.001$). There was also a statistically significant difference between KPS of 100 and a KPS of 70 or less (HR: 3.87; $P < 0.001$).

Age >60 or 65 has been found by some studies to be predictive of shorter OS following the diagnosis of brain metastases, although it generally seems to be a less reliable predictor than KPS score or RPA class indicators.^[25] A phase III prospective trial found that age, performance status, extracranial disease, and status of

Table 3: Multivariate hazard ratios, confidence intervals, and P values

	n	HR		
		Estimate	95% CI	P**
Age at diagnosis				
<65*	82	Reference		
≥65	27	1.22	0.66-2.23	0.527
Unknown	2	0.61	0.12-3.20	0.561
KPS				
90-100*	12	Reference		
70-80	16	1.28	1.11-1.47	<0.001
≤60	9	3.87	3.49-4.29	<0.001
Unknown	74	1.44	0.64-3.22	0.380
Brain metastases#				
1*	37	Reference		
2-5	36	1.33	0.74-2.39	0.349
>5	35	1.40	0.75-2.59	0.288
Unknown	3	1.77	0.51-6.16	0.372
WBI Received				
No*	53	Reference		
Yes	58	1.08	0.63-1.87	0.779
Resection Undergone				
No*	95	Reference		
Yes	16	0.74	0.35-1.54	0.420

*Reference group against which other groups' survival experience are compared, **P value for test if groups' survival experience is same as reference group, HR: Hazard ratio, CI: Confidence interval, WBI: Whole brain irradiation, KPS: Karnofsky Performance Status

Table 4: Absolute survival rates at 0.5, 1, 2, and 5 years

Year	Survival rate	95% CI
0.5	70.7	61.0-78.8
1	59.5	49.4-68.3
2	38.4	28.7-48.1
5	15.6	7.9-25.7

CI: Confidence interval

primary tumor were all significant prognostic factors on multivariate analysis.^[3]

Breast cancer-specific prognostic factors may differ from those of other tumor types, according to recent studies differentiating BCBM OS from other intracranial metastases. In 2012, Sperduto *et al.* published seminal work describing a modified graded prognostic assessment (GPA) for breast-specific cancers.^[33] They found that age and number of brain metastases were not significant indicators of prognosis, contrary to the RTOG findings, but rather tumor subtype and KPS status remained strong indicators of OS for breast cancer patients with brain metastases. Our study did not find significance in either univariate or multivariate analysis between patients aged 65 years and older and those younger than 65 years in terms of OS ($P = 0.633$). This supports the findings of Sperduto *et al.* in a single-institutional community setting. However, our

study cohort showed that the included BCBM patients younger than 65 years (73%) had a slightly longer median survival than those 65 or older, at 19.0 months and 15.1 months, respectively [Table 1].

Our multivariate survival analyses also looked at adjuvant therapies over the course of the patient's treatment, specifically the addition of surgical resection or WBRT to SRS. The literature is generally in agreement that while the addition of SRS to WBRT may improve intracranial recurrence rates, there is no significant difference in OS for patients with brain metastases from varying tumor etiologies.^[21,27,31] These findings were supported by two randomized controlled trials by Aoyama *et al.* and Chang *et al.*, who found that survival did not significantly differ between the use of WBRT plus SRS compared to SRS alone.^[3,7,15] With regard to patients with breast cancer-specific brain metastases, some older studies have demonstrated that a whole brain radiation dose ≥ 30 Gy is a significant prognostic indicator.^[8]

Our study found that there was no significant difference in OS between patients who received WBRT or surgical resection treatments in addition to SRS ($P = 0.779$ and $P = 0.42$, respectively). This finding may have biases typically associated with retrospective studies, such as that patients who received WBRT may have had more brain metastases or patients who received surgical resection may have had fewer metastases that were surgically accessible. This finding is also in agreement with the breast-GPA model developed by Sperduto *et al.* Although the GPA guidelines are intended to inform treatment decisions, they analyzed the data with intact treatment modalities and found no significant difference in median survival time.^[33]

Radiosurgery is also recently being used for patients with a greater number of metastases, and deferral of WBRT has become the standard of care for many patients.^[4,7,20] One retrospective study by Amendola *et al.* evaluated patients with breast carcinoma brain metastases who were treated with SRS.^[2] Sixty-eight patients received a total of 110 treatments to an average of 8 tumors per patient, with a median follow-up of 7.8 months. No evidence of radiation-induced dementia was noted, and survival was not significantly correlated to the number of brain metastases treated. Shultz *et al.* retrospectively analyzed 95 patients with 652 metastases (range, 1–14) who received multiple treatments of SRS for recurrent intracranial metastases.^[29] The study found that overall performance status and tumor volume, but not number of tumors, were critical in selecting patients who would do well with repeat SRS as opposed to WBRT. Local failure and OS rates were found to be consistent with numbers reported in the literature.^[7,30,36]

Presence of extracranial disease is often used as a prognostic indicator for brain metastasis OS. In breast cancer, this

prognostic value may be limited in part due to the success of systemic therapy. This is especially true since the era of trastuzumab therapy for HER2-positive breast cancers. For intracranial metastases, low levels of trastuzumab penetrate the blood–brain barrier, but this effect can be somewhat overcome after treatment with WBRT.^[34] More recently, capecitabine and lapatinib have been shown to have significant central nervous system concentrations and improve OS in previously untreated patients of HER2-positive cancers with brain metastases.^[6] Our study was not able to assess the presence of extracranial disease in our retrospective data set, but future studies should attempt to include these data.

Our study is inherently limited due to its retrospective nature. The patients who were selected for GKRS may have had better prognosis than other BCBM patients who were ineligible for SRS treatment. Because this study is not a randomized controlled trial, it has limited scope for informing clinical practice. It does, however, suggest that patients with BCBM who have good performance status (KPS ≥ 70) may have increased survival, despite other negatively influencing factors such as age ≥ 65 or multiple brain metastases. In addition, KPS scores were only available for 37 patients (33%), even though this remained our strongest predictive factor.

CONCLUSION

Our study suggests that patients with BCBM who have good performance status (KPS ≥ 70) may have increased survival, despite other negatively influencing factors such as age ≥ 65 or multiple brain metastases. In this report, the best OS rates were statistically associated with a KPS of 90 or greater. We did not find any significant survival benefit to the addition of WBRT or surgery to SRS treatment on univariate or multivariate analysis. We found encouraging long-term survival for some patients, with 15% of our cohort reaching the 5-year survival mark.

Each BCBM patient and his/her family should be informed of all treatment options and of the risks and benefits associated with each. Individual preferences and goals should also be a considered factor for physicians treating BCBM patients. SRS therapy provides the most benefit for patients with good performance status upon diagnosis of brain metastases. Repeated treatments may also be beneficial for patients who continue to have good performance status and a low gross tumor volume. GKRS continues to be a safe and effective treatment option to manage brain metastases with focal radiotherapy.

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Conflicts of interest

There are no conflicts of interest.

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