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Retrospective Review for Prevalence and Survival in Metastatic Breast Cancer with Brain Metastasis in Two Patient Cohorts: One Collected 2000-2005 and the Second Collected 2006-2011

Laura Bourdeanu[1], Linlin Chen[2], Thehang Luu[3]

[1]Department of Nursing, Excelsior College, Albany, NY, USA
[2]Department of Mathematics, Rochester Institute of Technology, Rochester, NY, USA
[3]OncoGambit, Irvine, CA, USA
Email: lbourdeanu@oncogambit.com, lxcsma@rit.edu, tluu@oncogambit.com

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Abstract

Purpose: To determine whether the new treatments for breast cancer CNS metastases improve survival by comparing the survival between two cohorts: 2000-2005 and 2006-2011. Patients and Methods: A retrospective, comparative, correlational chart review was performed. Data from 172 women diagnosed with CNS metastases between 2000 and 2011, was evaluated. Results: Approximately 10% of patients diagnosed with invasive breast cancer between 2000 and 2011 developed CNS metastases. The cohort was separated into four groups: luminal A (ER+ and/or PR+, HER2-), luminal B (ER+ and/or PR+, HER2+), HER2+ (ER-, PR-, HER2+) and TN (ER-, PR-, HER2-). There was a statistically significant difference in the overall survival between luminal A and luminal B (5.55 months vs. 15.3 months, respectively, p = 0.048). There was also a statistically significant difference in the overall survival between luminal B and TN (15.3 months vs. 7.49 months, respectively, p = 0.0181). There was no significant difference in overall survival between luminal B and HER2+ (15.3 months vs. and 10.98 months, respectively, p = 0.105), TN and HER2+ (7.49 months vs. 10.98 months, respectively, p = 0.514), and between luminal A and TN or HER2+ (5.55 months vs. 7.49 months, respectively, p = 0.428, or 5.55 months vs. 10.98 months, respectively, p = 0.491). Overall median survival of the patients in 2000-2005 and 2006-2011 were 6.64 months vs. 10.58 months, respectively (p = 0.0592). Conclusion: The results of our study showed that despite the new therapies there is little improvement in survival for brain metastasis in breast cancer.

Keywords

Breast Cancer, Brain Metastases, Cancer Treatment, Cancer Survival

1. Introduction

Breast cancer is one of the most common causes of central nervous system (CNS) metastases, second only to lung cancer, with 10% - 30% of patients experiencing brain metastases [1] [2] [3]. Typically, CNS metastasis occurs later during the course of metastatic disease. This diagnosis is associated with poor survival rates, due largely to the inability of chemotherapeutic and biological agents to cross the blood-brain barrier [4] [5].

In recent years, the incidence of CNS metastases has increased. Many researchers postulate that this increase is due to improvements in data collection, diagnostic capability, and systemic disease control [6] [7]. In addition, there has been a notable increase in breast cancer tumors that have a higher likelihood of recurring or progressing in the brain, such as estrogen/progesterone/Her-2/neu negative (triple-negative, TN) and Her2/neu positive breast cancer [8] [9] [10] [11]. The treatment of CNS metastases has also undergone rapid growth in the last 5 to 7 years with the introduction of various new modalities, such as targeted therapies stereotactic radiation and craniotomy [3]. In this study, we reviewed and analyzed data of patients with CNS metastatic breast cancer treated at City of Hope (COH) in two cohorts separated by time, 2000-2005 and 2006-2011, toward the purpose of determining the effect of new treatment modalities on survival.

2. Methods and Patients

A retrospective, comparative, correlational chart review was performed to analyze all relevant variables. After obtaining Institutional Review Board approval, data was collected on 1890 women diagnosed with stage I, II, III, or IV breast cancer who had received treatment between 2000 and 2011 at City of Hope Medical Center, a National Cancer Institute designated comprehensive cancer center in Duarte, CA. Of these, 172 (9.1%) developed solitary or multiple brain metastases or leptomeningeal disease during the defined period and were included in this study. The medical records were reviewed for demographic information, pathologic data, treatment, and clinically relevant dates.

The time of brain metastasis was defined as the time when a brain scan via computed tomography (CT) or magnetic resonance imaging (MRI) documented the presence of brain metastases. Overall survival time after brain metastasis was measured in months from the date of diagnosis of the brain metastasis to the date of death or last known follow-up. Variables were analyzed using the Chi-square, Fisher's exact test, or proportion test. Kaplan-Meier survival curves were used to determine survival, and the difference in survival was compared using

the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model. R data analysis software was used for all analyses, and a P-value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

Patient characteristics and treatment of all the patients with CNS metastases that were included in this study are presented in Table 1. There were 172 patients diagnosed with CNS metastases, with 47 patients treated between 2000 and 2005 (comprising the 2000-2005 group) and 125 patients treated between 2006 and 2011 (comprising the 2006-2011 group). Most of the CNS metastases were due to the progression of current metastatic disease versus *de novo* tumor formation [80.8% *vs.* 14.5% (4.7% were unknown)]. The predominant histology was ductal carcinoma, accounting for 66.3 % of the patients ($N = 114$). A total of 23 patients (13.4%) received no adjuvant chemotherapy, 105 (61.1%) received no adjuvant anti-hormonal therapy, and 84 (48.8%) underwent mastectomy for the primary tumor. The median time from the diagnosis of metastatic disease to CNS metastases for all patients was 10.58 months (range 0 - 190.2 months).

The CNS metastatic lesions were categorized into three groups based on the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER-2/neu) status of the tumors. Tumors were designated positive (+) or negative (−) based on their expression of each receptor: Group 1 was ER+ and/or PR+ and HER-2/neu- (ER/PR+); Group 2 was ER-, PR−, and HER-2/neu- (TN); Group 3 was ER+/−, PR+/−, and HER-2/neu+ (HER-2/neu+). The sample consisted of 32 ER/PR+ patients, 35 TN patients, and 65 HER-2/neu+ patients. Information regarding the type of chemotherapy the patients received prior to the diagnosis of CNS metastases was not available at the time of data collection.

The survival of patients with brain metastases among those with HER-2/neu+, TN, or ER/PR+ tumors was calculated based on the patients with available data only. The patients with missing information were eliminated from the survival analysis. In this cohort, the overall median survival for all patients with brain metastases was 10.58 months (95% CI: 6.64, 15.93) (Figure 1). Only 27.3% of patients ($N = 47$) were still alive after one year. The median survival times for patients with brain metastasis was found to be 5.39 months (95% CI: 3.38, 22.31) for patients with HER-2/neu+ tumors, 7.49 months (95% CI: 2.46, 17.94) for patients with TN tumors, and 12.3 months (95% CI: 8.9, 20.3) for patients with ER/PR+ tumors. There was no statistically significant difference in the survival between ER/PR+ and TN tumors ($P = 0.327$) (Figure 2). However, there was a statistically significant difference in the survival of patients with TN tumors *vs.* HER-2/neu+ tumors ($P = 0.0423$) and HER-2/neu+ tumors *vs.* HER-2/neu− tumors ($P = 0.0419$), with better overall survival in HER-2/neu+ patients (Figure 3 and Figure 4). The survival ER/PR+ *vs.* HER-2/neu positive was not significant ($P = 0.447$).

Table 1. Descriptive data.

	All patients (N = 172) N (%)	2000-2005 (N = 47) N (%)	2006-2011 (N = 125) N (%)
Age at any metastases diagnosis	52 (24 - 87)	50 (27 -6 8)	52 (24 - 87)
Age at CNS metastases	53 (24 - 87)	51 (28 - 68)	52 (24 - 87)
Race/ethnicity n (%)			
White	80 (46.5)	23 (48.9)	54 (43.2)
Hispanic	44 (25.6)	12 (25.5)	35 (28)
AA	12 (7)	5 (10.6)	7 (5.6)
Asian	28 (16.2)	7 (15)	21 (16.8)
Missing	8 (4.7)		8 (6.4)
Marital Status			
Married	110 (63.9)		74 (59.2)
Single	18 (10.5)	42 (89.4)	14 (11.2)
Divorced/separated	22 (12.8)	4 (8.5)	16 (12.8)
Widowed	13 (7.6)	1 (2.1)	13 (10.4)
Unknown	9 (5.2)		8 (6.4)
CNS mets diagnosis			
De novo	25 (14.5)	4 (8.5)	21 (16.8)
Progression	139 (80.8)	43 (91.5)	96 (76.8)
Missing	8 (4.7)		8 (16.4)
Type			
Leptomeningeal	17 (10)	1 (2.1)	16 (12.8)
Brain lesions	155 (90)	46 (97.9)	109 (87.2)
Extracranial metastases site			
Lung	3 (1.7)	2 (4.2)	1 (0.8)
Liver	2 (1.2)	2 (4.2)	
Bone	26 (15.1)	8 (17)	18 (14.4)
Skin	2 (1.2)	1 (2.1)	1 (0.8)
Multiple sites	139 (80.8)	34 (72.5)	105 (84)
ER			
Negative	79 (45.9)	20 (42.5)	59 (47.2)
Positive	84 (48.8)	20 (42.5)	64 (51.2)
Unknown	9 (5.3)	7 (15)	2 (1.6)
PR			
Negative	103 (59.9)	27 (57.4)	76 (60.8)
Positive	59 (34.3)	13 (27.7)	46 (36.8)
Unknown	10 (5.8)	7 (14.9)	3 (2.4)
HER2			
Negative	90 (52.3)	21 (44.7)	69 (55.2)
Borderline	2 (1.2)	1 (2.1)	1 (0.8)
Positive	66 (38.4)	16 (34)	50 (40)
Unknown	14 (8.1)	9 (19.2)	5 (4)
Histology			
Ductal	114 (66.3)	30 (63.8)	84 (67.2)
Metaplastic	1 (0.6)	1 (2.1)	1 (0.8)
Lobular	8 (4.7)	4 (8.6)	7 (5.6)
Nos	12 (6.9)	11 (23.4)	8 (6.4)
Inflammatory	18 (10.5)	1 (2.1)	7 (5.6)
Mixed	9 (5.2)		8 (6.4)
Missing	10 (5.8)		10 (8)

Continued

Surgery of primary breast lesion			
Mastectomy	84 (48.8)	24 (51.1)	60 (48)
None	24 (13.9)	9 (19.1)	15 (12)
Lumpectomy	50 (29.1)	13 (27.7)	37 (29.6)
Unspecified	2 (1.2)	1 (2.1)	1 (0.8)
Unknown	12 (7)		12 (9.6)
Chemotherapy for primary tumor			
Yes	139 (80.8)	39 (83)	100 (80)
No	23 (13.4)	8 (17)	15 (12)
Missing	10 (5.8)		10 (8)
Radiation for primary tumor			
Yes	73 (42.4)	22 (46.8)	51 (40.8)
No	85 (49.4)	25 (53.2)	60 (48)
Missing	14 (8.2)		14 (11.2)
Hormone therapy for primary tumor			
Yes	57 (33.1)	13 (27.6)	44 (35.2)
No	105 (61.1)	34 (72.4)	71 (56.8)
Missing	10 (5.8)		10 (8)
Treatment modalities for brain metastases			
Stereotactic	25 (14.5)	17 (36.1)	46 (36.8)
Whole brain radiation	68 (39.5)	1 (2.1)	21 (16.8)
Chemotherapy	7 (4.1)	7 (14.9)	34 (27.2)
(intrathecal)		36 (76.6)	79 (63.2)
Craniotomy	2 (1.2)	13 (27.7)	46 (36.8)
Combination	70 (40.7)		

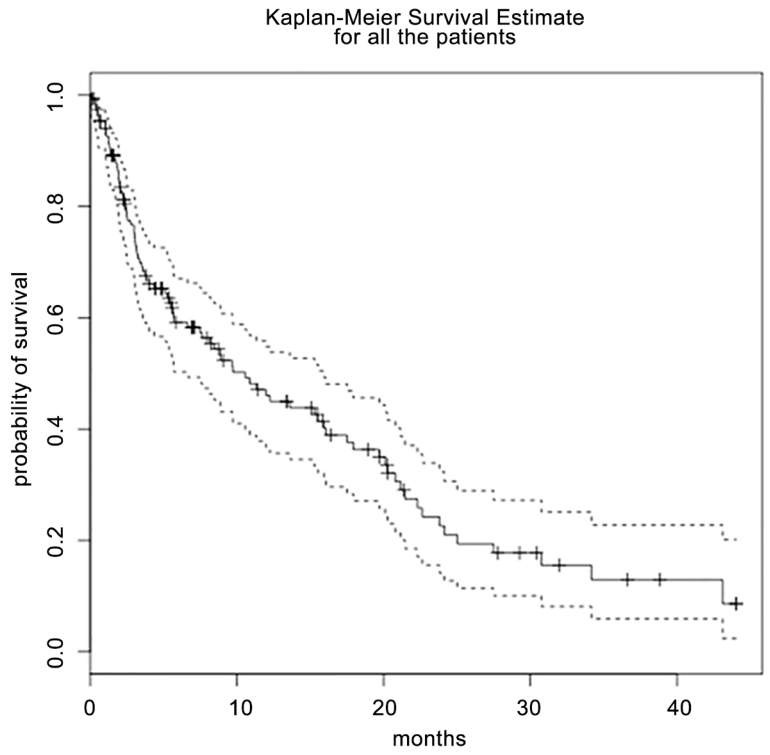

Figure 1. Survival of all patients.

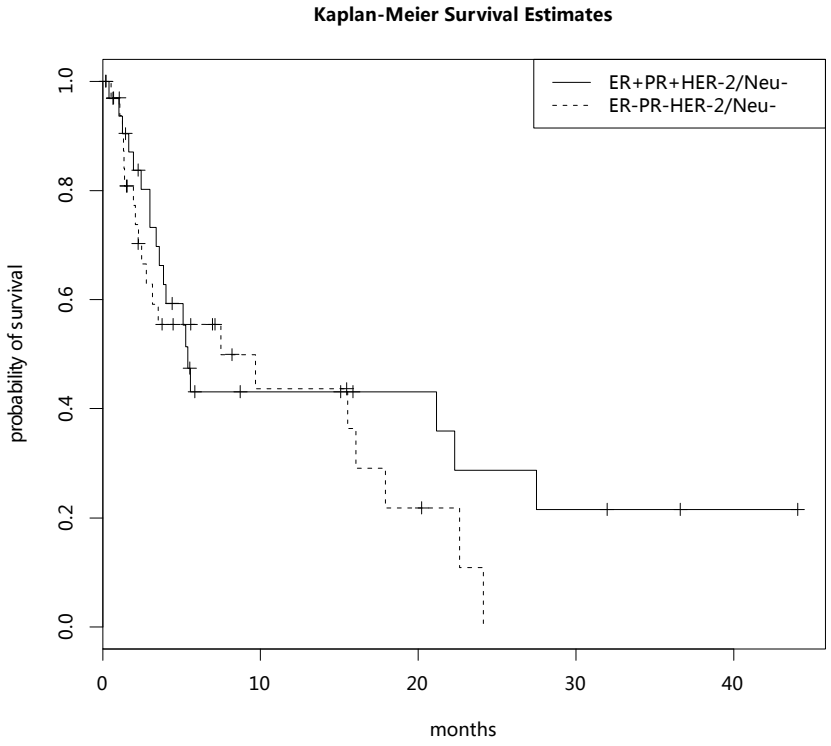

Figure 2. Survival for TN vs ER/PR+.

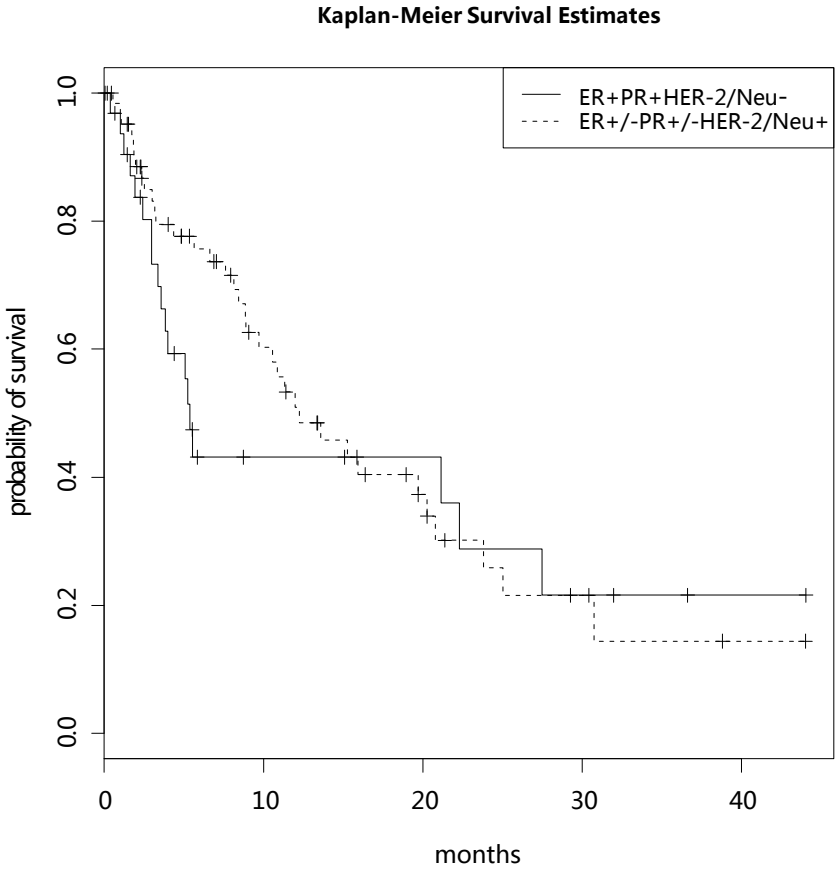

Figure 3. Survival of TN versus HER2+.

Next, the patients were separated into four groups: luminal A (ER+ and/or PR+, HER2/neu-), luminal B (ER+ and/or PR+, HER2/neu+), HER2/neu+ (ER-, PR-, HER2/neu+) and TN (ER-, PR-, HER2/neu-) (Figure 4). There was a statistically significant difference in the overall survival between luminal A and luminal B (5.55 months, 95% CI: 3.58, 21.16, and 15.3 months, 95% CI: 8.9, 30.8, $P = 0.048$). There was also a statistically significant difference in the overall survival between luminal B and TN (15.3 months, 95% CI: 8.9, 30.8 and 7.49 months, 95% CI: 2.46, 17.94, $P = 0.0181$). There was no significant difference in overall survival between luminal B and HER2+ (15.3 months, 95% CI: 8.9, 30.8and 10.98 months 95% CI: 5.65, 20.27, $P = 0.105$), between TN and HER2+ (7.49 months, 95% CI: 2.46, 17.94, and 10.98 months, 95% CI: 5.65, 20.27, $P = 0.514$), or between luminal A and either TN (5.55 months, 95% CI: 3.58, 21.16 and 7.49 months, 95% CI: 2.46, 17.94, $P = 0.428$,) or HER2+ (5.55 months, 95% CI: 3.58, 21.16, and 10.98 months, 95% CI: 5.65, 20.27, $P = 0.491$). Figure 5 depicts the survival curves of all four groups.

The patients were then separated into two groups. Group A included patients with brain metastases diagnosed between 2000 and 2005. Group B included patients with brain metastases diagnosed between 2006 and 2011. There were 47 patients in Group A (2000-2005) and 125 patients in Group B (2006-2011). Patient characteristics and treatment modalities are presented in Table 2. The

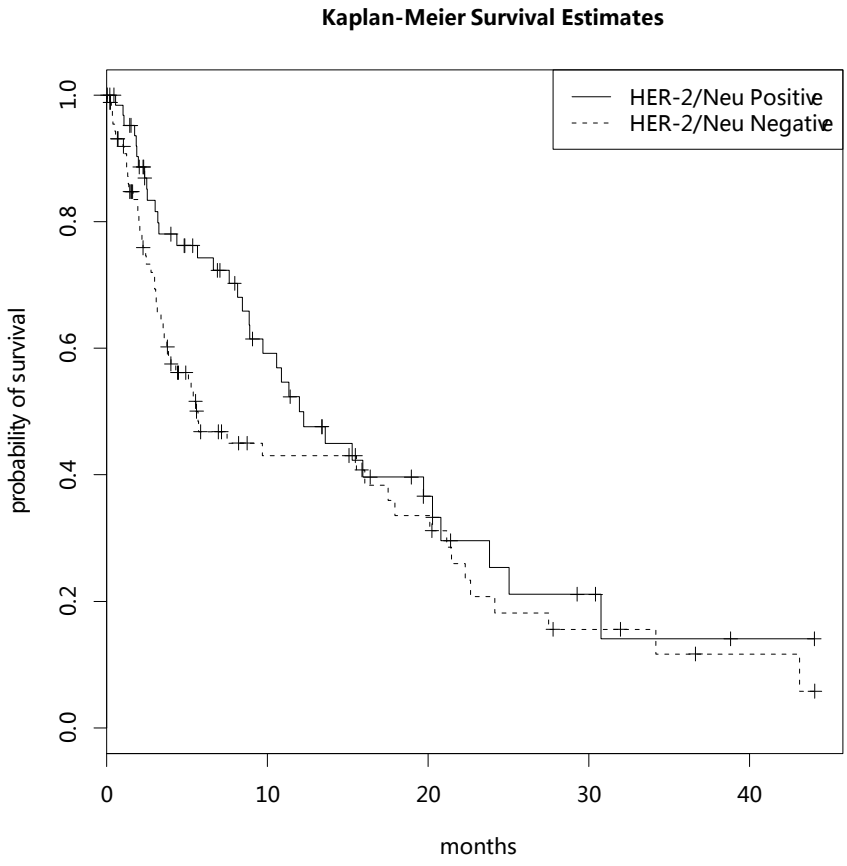

Figure 4. Survival of HER2+ versus HER2−.

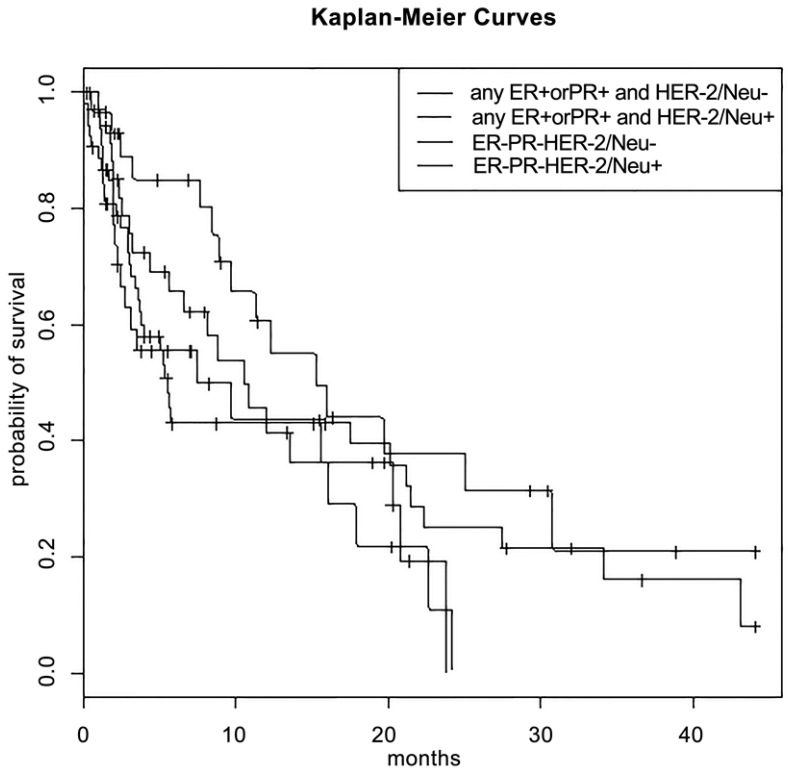

Figure 5. Survival of the four groups.

Table 2. Median survival and 95%CI.

	median	95%CI	*N*
ER/PR+	5.39	3.38, 22.31	32
TN	7.49	2.46, 17.94	35
Her2/neu+	12.3	8.9, 20.3	65
Her2neu+	11.99	8.90, 20.8	66
Her2/neu-	5.68	3.84, 17.9	89
Luminal A	5.55	3.58, 21.16	53
Luminal B	15.3	8.9, 30.8	31
TN	7.49	2.46, 17.94	35
HER2+	10.58	5.65, 20.27	36
Asian	15.54	5.55, NA	28
African American Hispanic	5.65	5.09, NA	12
Caucasian	5.68	3.84, 17.5	44
Unknown	15	8.90, 23.8	78
	0.28	1.87, NA	8
	2.99		
2000-2005	6.64	4.01, 18.3	47
2006-2011	10.58	7.59, 19.7	125
Age <50	9.72	7.49, 18.3	58
Age >50	9.69	5.55, 20.1	110

median age at CNS metastases diagnosis was 51 years old (range 28 - 68) for the patients in Group A and 52 years old (range 24 - 87) for the patients in Group B. The brain was the first site of metastatic involvement with or without extracranial metastases in 4 (8.5%) and 21 (16.8%) patients for Group A and Group

B, respectively. The most common single metastatic site was bone (17% and 14.4%, respectively) for both groups; however most patients had several metastatic sites (72.5% and 84%, respectively). The median times for CNS metastases from the diagnosis of breast cancer metastases for groups A and B were 7.8 months (range 0 - 78.8 months) and 10.0 months (range: 0 - 190.2 months), respectively. Although not significant, there was a higher incidence of patients with TN and HER2/neu+ disease in the 2006-2011 cohort than in the 2000-2005 cohort (23.2% *vs.* 12.8%, 40.8% *vs.* 34.0%, $P = 0.095$).Whole brain radiation as primary treatment was given to 27 patients (60%) in Group A, but only 42 patients (33.6%) in Group B ($P = 0.004$) Stereotactic radiation as a single treatment was administered to 6 (12.8%) in Group A and 19 (15.2%) patients in Group B. Only one (2.1%) patient in group A and six (4.8%) patients in Group B received chemotherapy. No patient in Group A and two (1.6%) patients in Group B underwent craniotomy for resection of brain metastases. The sample of patients receiving stereotactic radiation, chemotherapy, and craniotomy as single treatments was insufficient to determine significance for either group A or group B.

Overall median survival of the patients in Group A was 6.64 months (95% CI: 4.01, 18.3), while overall survival in Group B was 10.58 months (95% CI: 7.59, 19.7). This difference neared statistical significance with a *P*-value of 0.0592 (Figure 6). Because the two survival curves cross early in the curve, we performed an extended cox regression mode by defining a time-dependent covariate instead of using the log-rank test. With this analysis, the p-value was significant ($P < 0.0001$).

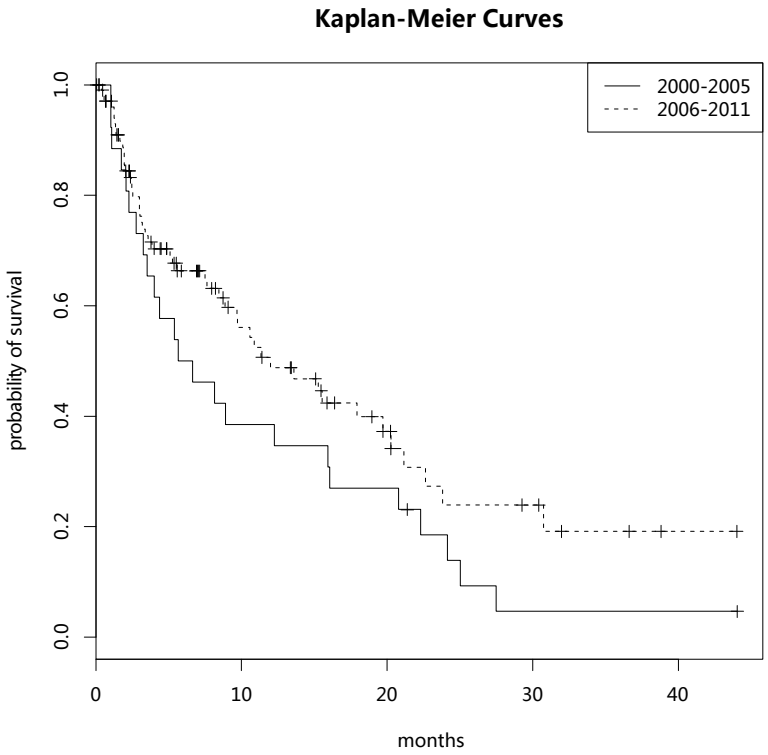

Figure 6. Survival of 2000-2005 versus 2006-2011.

3.2. Secondary Analysis

There was no significant difference in the overall survival between women <50 years and women >50 years of age diagnosed with metastatic breast cancer to the brain; women ≤50 years old survived 9.72 months (95% CI: 7.49, 18.3) and women >50 years old survived 9.69 months (95% CI: 5.55, 20.1) after diagnosis ($P = 0.815$, Figure 7). At early stages of tumor development, women over the age of 50 years had a higher survival probability; however, after approximately 12 months, women less than 50 years old had a higher survival probability.

Next, we compared the overall survival of Caucasian, African-American, Asian, and Hispanic women with brain metastases and found a statistically significant difference in the overall survival among these different ethnic groups. Caucasian patients survived 15.28 months (95% CI: 8.90, 23.8), African-American patients survived 5.65 months (95% CI: 5.09, NA), Asian patients survived 15.54 months (95% CI: 5.55, NA), and Hispanic patients survived 5.68 months (95% CI: 3.84, 17.5), ($P = 0.0488$, Figure 8). African American and Hispanic women had a worse survival when compared to either Caucasian or Asian women. We found no relationship between age or race and tumor sub-type (ER/PR+, TN, Her-2/neu+) ($P = 0.8185$, P = 0.8324, respectively). The breakdown of tumor sub-types according to age and race are summarized in Table 3 and Table 4, respectively. A total of 25 patients (14.5%) had brain metastasis as their first site of recurrence compared to 139 patients (80.8%) who experienced

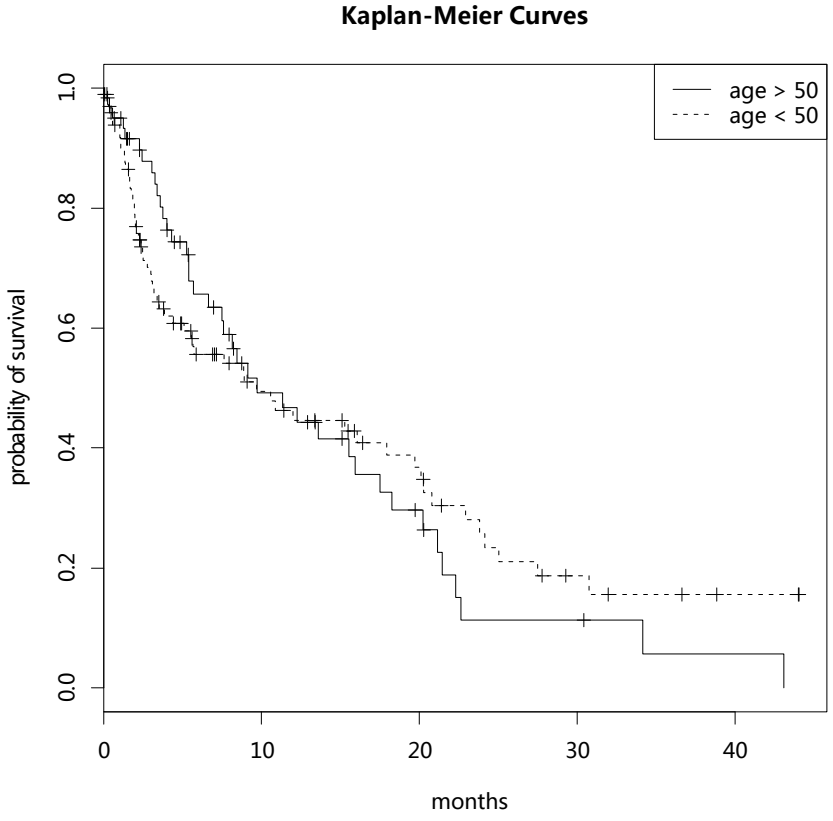

Figure 7. Survival by age.

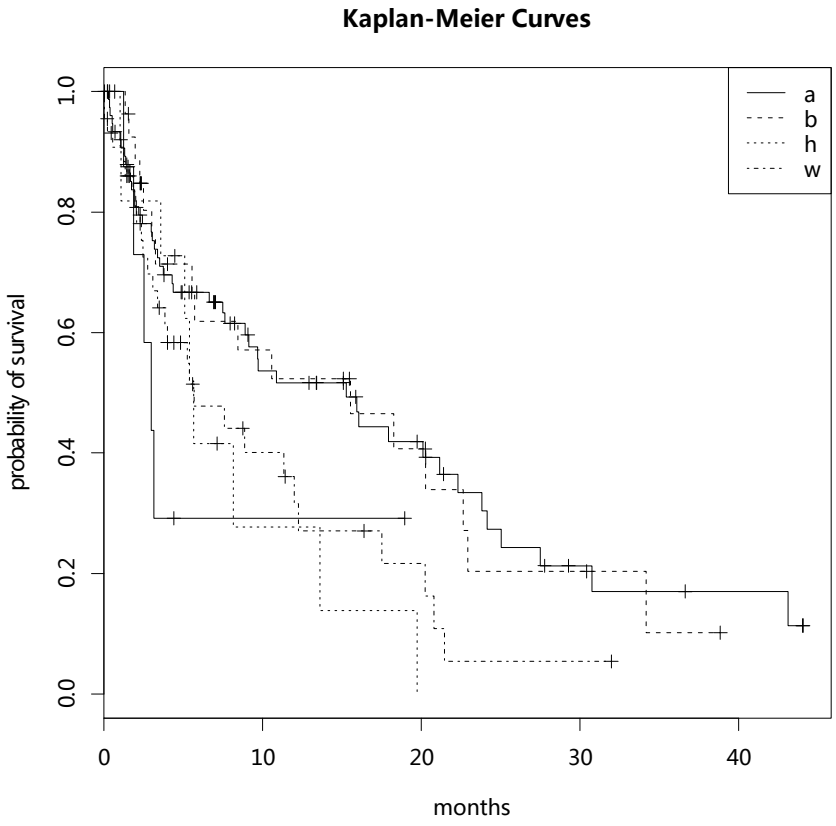

Figure 8. Survival by race.

Table 3. Subtypes by age.

Age	<50 *N*(%)	>50 *N*(%)	Not available *N*(%)
HR+	10 (24.4)	19 (22.9)	4 (50)
TN	11 (26.8)	23 (27.7)	1 (12.5)
Her2+	20 (48.8)	41 (49.4)	3 (37.5)

Table 4. Subtypes by race.

	Caucasian *N*(%)	African American *N*(%)	Hispanic *N*(%)	Asian *N*(%)	Not available *N*(%)
HR+	15 (23.8)	4 (36.3)	7 (24.1)	3 (14.3)	3 (37.5)
TN	19 (30.2)	2 (18.2)	6 (20.7)	7 (33.3)	1 (12.5)
Her2+	29 (46.0)	5 (45.5)	16 (55.2)	11 (52.4)	4 (50.0)

progression of metastatic disease. There was no significant difference in the overall survival between patients who presented with *de novo* brain metastases and patients with metastatic breast cancer progression, 12.25 months and 8.87 months, respectively ($P = 0.067$) (Figure 9).

4. Discussion

Here, we present a single-institution, retrospective cohort study comparing the

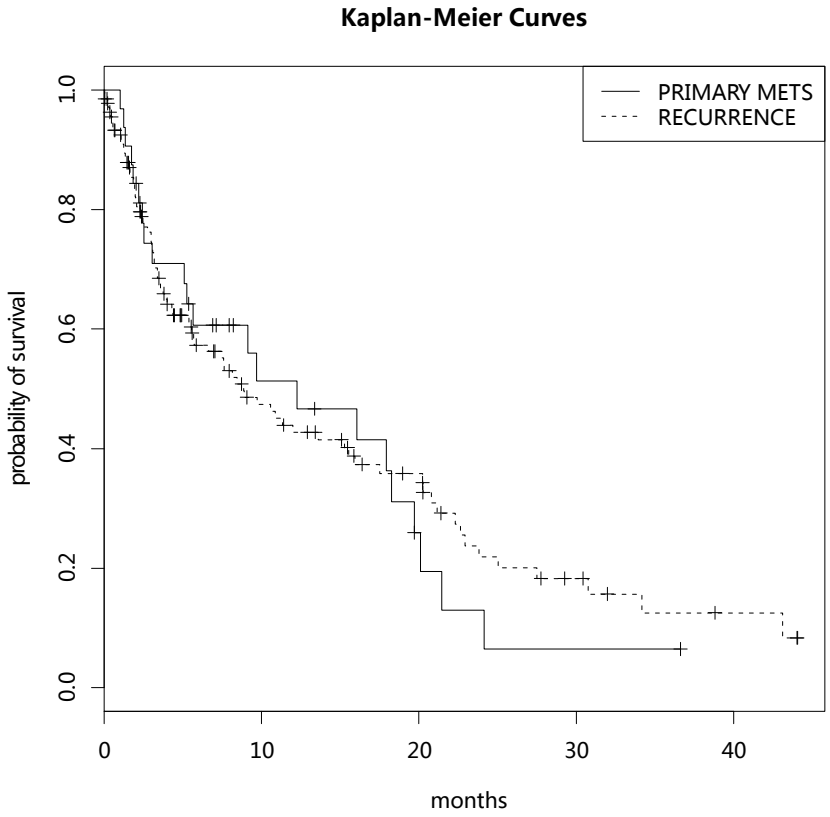

Figure 9. Survival of CNS de novo versus recurrence.

survival of patients diagnosed with brain metastases between 2000 and 2005 and those diagnosed between 2006 and 2011. The results of our study demonstrated that, despite the advent of new therapies and improved diagnostic capabilities, there was no significant improvement in the overall survival for breast cancer patient with brain metastasis. The survival curve demonstrates that, after a certain period of time, patients diagnosed between 2006 and 2011 had a significantly better survival. This may be in part due to treatment with trastuzumab for the primary tumor or the recurrent tumor, or the treatment for the brain metastases. There is a significant difference in the treatment of patients seen between 2000-2005 and 2006-2011, with more people receiving whole brain radiation in the former ($P = 0.004$). This may also affect the survival because stereotactic surgery and resection have not been shown to improve survival relative to whole brain radiation alone [12] [13]. Unfortunately, the information regarding the number of lesions was not available at the time of data collection, making it difficult to rule out the potential of patients in the 2000-2005 group having more brain lesions than the 2006-2011 group, which may affect survival.

In the overall cohort of patients seen between 2000 and 2011, the median age at the time of first diagnosis of brain metastases was 52 years. This value is consistent with that of other studies, which have found the median age of patients with metastatic breast cancer to the brain to be 45 to 55 years [3] [14]. The overall median survival was 10.58 months, which compares to the median overall

survival of 4 to 16 months reported in previous analyses of breast cancer patients with brain metastases [15] [16] [17]. Several studies showed that TN status increased the risk of mortality among metastatic breast cancer patients with CNS metastases [15] [18] [19] [20]. However, our results showed that and ER/PR+ tumors have the lowest survival rate among metastatic breast cancer patients after the diagnosis of CNS metastases, although this was not significantly different than the TN tumors (5.39 months *vs.* 7.49 months, $P = 0.327$).

Our study revealed that patients with Her2/neu+ status had significantly better survival than patients with Her2/neu− patients (11.99 months *vs.* 5.68 months, p = 0.0419).This is in concordance with other studies showing survival to 9 to 24 months in patients with HER-2/neu+ breast cancer [15] [17] [19] [20]. When the patients were grouped into luminal A, luminal B, HER2+, and TN categories, the overall survival was significantly better in luminal B patients when compared to luminal A or TN patients. This is similar to previous findings reported by Niikura and colleagues [15]. However, our study found that TN patients did not have a significantly worse overall survival when compared to luminal A or HER2+ patients, as previously reported [15]. This discrepancy may be due to the small sample size in this study. Neurosurgery, whole brain radiation, and stereotactic radiation were used alone or in combination. The improved survival may be due to the combination therapies; however, this finding should be interpreted with caution because the choices of treatment were most likely correlated with the disease and functional status of the patient.

Ethnicity seems to influence the survival, with African American and Hispanic women experiencing a poorer survival probability. This result is in contrast to a previous report that found no significant differences in the overall survival between Caucasians and non-Caucasians [21]. We found no significant association between ethnicity and tumor subtype, which might have accounted for this discrepancy. The socioeconomic factors or delays in diagnosis cannot be excluded as reasons for this difference; however this information was not available at the time of data collection. These findings were based on a convenient sample, which may not be representative of the actual ethnicity composition of patients with breast cancer. Despite these contingencies, this finding warrants the development of a larger, prospective study to determine how or why ethnicity influences survival.

Although not significant, there was a higher incidence of patients with TN, Her2/neu+, and ER/PR+ disease in the 2006-2011 as compared to 2000-2005 (23.2% vs. 12.8%, 40.8% vs. 34.0%, 36% vs. 53.2%, $P = 0.095$, respectively).The difference in the tumor biology may be explained by the fact that COH is a tertiary cancer center, and thus women with more aggressive types of breast cancer may present at COH for clinical trials not available elsewhere. In summary, we found that patients who received treatment after 2006 were associated with a better survival, although the findings were not statistically significant.

This study has several limitations. The results were limited by the small sample size of the 2000-2005 cohort ($N = 47$) compared to the 2006-2011 cohort (N

= 125). This difference may be in part due to the more frequent use of screening studies in the second cohort. We did not include the systemic treatment after the diagnosis of brain metastases, as it may not have been used to determine survival due to high degree of variation in treatment regimens among these patients. However, it is reasonable to assume that the treatments were selected based on the NCCN guidelines. Patients with missing data were excluded from the analysis, although the number of patients excluded may not have affected the results. Lastly, the study was conducted at one institution, making the results less generalizable than studies conducted at multiple institutions.

5. Conclusion

The results of this study demonstrate that, despite new treatments for CNS breast metastases; there has been little improvement in the overall survival of patients with metastatic breast cancer to the brain. These results further confirm that the current treatment is aimed at reducing tumor burden and not the biology of the tumor. Studies aimed to develop novel chemotherapeutics and targeted approaches are warranted.

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