Prognostic Value of Brain Metastasis-Free Interval in Patients with Breast Cancer Brain Metastases

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■ BACKGROUND: **In patients with breast cancer brain metastases (BCBM), time between primary tumor diagnosis and appearance of brain metastases varies widely. Despite being a readily available clinical parameter, it remains unclear whether brain metastasis-free interval (BMFI) carries prognostic value among breast cancer patients. The aim of this study was to compare characteristics and overall survival among patients with varying BMFIs and to assess the prognostic role, if any, for BMFI.**

■ METHODS: **We retrospectively reviewed 3 institutional databases of adult female patients who were treated for BCBM between 1996 and 2017. Cox proportional hazards model and Kaplan-Meier survival curves were used to determine prognostic value of BMFI for survival.**

■ RESULTS: **A total of 503 patients were included. Median age at first brain metastasis was 52 (interquartile range [IQR]: 45–58) years. Median BMFI was 38 months (IQR: 18–66), and median overall survival was 17 months (IQR: 8–31). In univariate Cox proportional hazards model, younger age at BCBM, estrogen receptor (ER)+/human epidermal growth factor receptor 2 (HER2)+ tumor subtype, and the absence of liver or lung metastases were associated with longer survival. BMFI >3 years was not associated with longer survival (hazard ratio [HR] = 1.13; *P* = 0.21). In multivariate analysis, only subtype (ER+/HER2+ vs. ER–/HER2–; HR = 0.77; *P* = 0.02) and liver metastases (HR = 1.36; *P* = 0.01) were prognostic for survival. There was no significant association between BMFI and overall survival (HR = 0.99; *P* = 0.91).**

■ CONCLUSIONS: **In this large, retrospective cohort of breast cancer patients, BMFI was not prognostic for overall survival.**

INTRODUCTION

Brain metastases (BM) are common in breast cancer, occurring in approximately 10%–50% of patients with metastatic disease, depending on tumor subtype.[1-3] Recent years have seen a rise in incidence that is attributed in part to the success of systemic therapies, resulting in longer survival, and therefore, allowing more time for metastases to develop in the brain.[1,2] Although historically extracranial disease burden has been the major cause of death in metastatic breast cancer,[2,4-7] some series have reported that a substantial proportion of patients die of neurologic causes due to progressive BM[8];

Key words
- Brain metastases
- Brain metastasis-free interval
- Breast cancer
- Prognostic factors
- Survival

Abbreviations and Acronyms
BCBM: Breast cancer brain metastases
BM: Brain metastases
BMFI: Brain metastasis-free interval
ER: Estrogen receptor
HR: Hazard ratio
HER2: Human epidermal growth factor receptor 2
IQR: Interquartile range
KPS: Karnofsky Performance Status
MFI: Metastasis-free interval
PR: Progesterone receptor
SRS: Stereotactic radiosurgery

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moreover, of all metastatic sites, BM carry the least favorable prognosis.[9,10]

Predicting outcomes in breast cancer patients with BM remains challenging. However, several prognostic factors for overall survival have been suggested, including, but not limited to, age,[11,12] Karnofsky Performance Status (KPS),[11,12] molecular subtype,[13,14] number of intracranial metastases,[15-17] extracranial disease burden,[12,17,18] primary tumor size,[17] lymphopenia,[19] and various treatment modalities.[11,12,17,20] Currently, the most widely accepted prognostic model is the diagnosis-specific graded prognostic assessment, based on patient KPS, age, and molecular subtype.[11,14]

Metastasis-free interval (MFI; interval between initial breast cancer diagnosis and first diagnosis of distant metastasis in any site) has long been recognized as a prognostic factor in metastatic breast cancer.[21,22] The time between initial diagnosis of breast cancer and the appearance of the first brain metastasis varies widely, with some patients developing BM immediately after primary diagnosis and others as late as decades after.[1,9,13] This brain metastasis-free interval (BMFI) is a readily available clinical parameter that may be prognostic for overall survival.[15,23,24] However, its true prognostic value, particularly in the setting of breast cancer, remains unclear. Therefore, the aim of this study was to assess in a large cohort whether BMFI is a prognostic factor for patients with breast cancer brain metastases (BCBM).

METHODS

Study Design and Data Collection

This study was designed as a retrospective cohort study of patients from a combined neurosurgical/radiation oncological patient population; all patients were treated with either craniotomy, stereotactic radiosurgery (SRS), or both. Data were collected from 3 institutions: Brigham and Women's Hospital and Massachusetts General Hospital in Boston, Massachusetts, USA, and the University Medical Center Utrecht in Utrecht, the Netherlands. Data from Boston were collected through query of the Partners HealthCare Research Patient Data Registry and additional chart review under institutional review board approval. Dutch data were retrospectively collected from a prospective database of SRS patients. These data were determined to be exempt from the Dutch laws on medical research on human subjects by the institutional ethics committee.

Data of female patients with BCBM between January 1, 1996 and December 1, 2016 were collected. Patients with a history of primary tumors from sites other than breast were excluded unless there was histopathological confirmation that BM were from primary breast cancer.

Variables

The following variables, when available, were collected: race, date of birth, date of primary tumor, date of first BM, date and site of first extracranial metastases, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, prior treatments with neurosurgery, SRS, and/or classical radiotherapy, vital status, and time until death or censorship. When available, information on presence of additional metastases in lymph nodes, lungs, bones, and liver was collected as well. HER2 status was coded as positive if pathology reports described strong (3+) overexpression on immunohistochemical staining or moderate (2+) overexpression with HER2 amplification in fluorescent in situ hybridization (HER2/centromere 17 ratio >2.0); when HER2 expression was 2+ but no fluorescence in situ hybridization was available, HER2 status was coded as negative.

Time intervals were calculated as follows: MFI as the time between diagnosis of primary tumor and diagnosis of first metastasis; BMFI as the time between diagnosis of primary tumor and first BM; and overall survival as the time from diagnosis of first BM to death or censorship. Patients were classified based on their molecular subtype as ER−/HER2−, ER+/HER2−, ER−/HER2+, ER+/HER2+, or unknown. Patients were censored at their date of death if available, or otherwise at date of last encounter before December 1, 2017.

Statistical Analysis

Data were analyzed and visualized using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were expressed as numbers and percentages. Continuous variables were reported using mean and standard deviation if they followed a normal distribution and median and interquartile range (IQR) if they did not. Patients were stratified by quartiles of BMFI and compared. For this analysis, the χ^2 test was used for categorical variables, whereas the one-way analysis of variance test and the Kruskal-Wallis rank sum test were used for continuous variables with normal and non-normal distribution, respectively; P values were evaluated before and after Bonferroni adjustment.

Univariate and multivariate survival analyses were performed using the Cox proportional hazards model. The log-rank test was used to determine statistical significance of variables as well as interactions between BMFI and any other variable. The final model incorporated BMFI as well as any variables that were significant in univariate analysis or had an interaction with BMFI. For the survival analysis, BMFI was dichotomized at the median, and sensitivity analysis was performed for BMFI as a continuous variable. Finally, the Kaplan−Meier method was used to visualize cumulative survival differences between groups. All levels of significance were set at $P < 0.05$.

RESULTS

Patient Characteristics

A total of 611 patients were identified. Eighty-two patients were excluded because of a history of a non-breast primary tumor and an additional 26 patients had insufficient data available for our analysis. The final analysis was performed on 503 patients.

Table 1 shows the baseline characteristics of the cohort. The median age was 49 years at diagnosis of primary tumor, 51 years at first metastasis, and 52 years at first BM. In 335 patients (66.6%), extracranial metastases were present at the time of BM diagnosis. Molecular subtypes were known in 374 (74.4%) patients, with the following breakdown: 75 (14.9%) ER−/HER2−, 101 (20.1%) ER+/HER2−, 68 (13.5%) ER−/HER2+, and 131 (26.0%) ER+/HER2+. Median MFI was 24 months (IQR: 6−51 months), and median BMFI was 38 months (IQR: 18−69 months; Figure 1). At the time of censorship, 433 patients had

Table 1. Patient Characteristics Stratified by Brain Metastasis-Free Interval

BMFI in Quartiles	0–18 Months	18 Months to 3 Years	3–6 Years	>6 Years	Total	*P* Value
N	125	126	125	127	503	
Race						0.093
Asian	3 (2.4)	2 (1.6)	1 (0.8)	3 (2.4)	9 (1.8)	
Black	6 (4.8)	2 (1.6)	5 (4.0)	15 (11.8)	28 (5.6)	
Hispanic	2 (1.6)	2 (1.6)	3 (2.4)	1 (0.8)	8 (1.6)	
White	106 (84.8)	112 (88.9)	105 (84.0)	97 (76.4)	420 (83.5)	
Other	4 (3.2)	2 (1.6)	2 (1.6)	1 (0.8)	9 (1.8)	
Unknown	4 (3.2)	6 (4.8)	9 (7.2)	10 (7.9)	29 (5.8)	
Age at primary tumor (mean [SD])	50.7 (10.7)	48.5 (9.8)	48.3 (11.2)	49.0 (12.2)	49.1 (11.0)	0.31
Age at first metastasis (mean [SD])	51.1 (10.7)	49.7 (9.7)	50.3 (11.4)	53.3 (11.7)	51.1 (11.0)	0.049
Age at first brain metastasis (mean [SD])	51.4 (10.6)	50.2 (9.8)	51.5 (11.3)	55.5 (11.0)	52.2 (10.9)	0.001*
ER status						0.002
Positive	47 (37.6)	47 (37.3)	36 (28.8)	23 (18.1)	275 (54.7)	
Negative	56 (44.8)	69 (54.8)	71 (56.8)	79 (62.2)	153 (30.4)	
Unknown	22 (17.6)	10 (7.9)	18 (14.4)	25 (19.7)	75 (14.9)	
Progesterone receptor status						<0.001*
Positive	61 (48.8)	60 (47.6)	45 (36.0)	35 (27.6)	211 (41.9)	
Negative	38 (30.4)	55 (43.7)	57 (45.6)	61 (48.0)	201 (40.0)	
Unknown	26 (20.8)	11 (8.7)	23 (18.4)	31 (24.4)	91 (18.1)	
HER2 status						0.45
Positive	47 (37.6)	45 (35.7)	42 (33.6)	42 (33.1)	202 (40.2)	
Negative	46 (36.8)	57 (45.2)	53 (42.4)	46 (36.2)	176 (35.0)	
Unknown	32 (25.6)	24 (19.0)	30 (24.0)	39 (30.7)	125 (24.9)	
Subtype						0.03
ER−/HER2+	28 (22.4)	21 (16.7)	16 (12.8)	10 (7.9)	68 (13.5)	
ER+/HER2−	17 (13.6)	24 (19.0)	16 (12.8)	11 (8.7)	101 (20.1)	
ER+/HER2+	19 (15.2)	24 (19.0)	26 (20.8)	32 (25.2)	131 (26.0)	
ER−/HER2−	28 (22.4)	33 (26.2)	36 (28.8)	34 (26.8)	75 (14.9)	
Unknown	33 (26.4)	24 (19.0)	31 (24.8)	40 (31.5)	129 (25.6)	
Extracranial metastases						
Lymph nodes	40 (32.0)	62 (49.2)	59 (47.2)	58 (45.7)	219 (43.5)	0.03
Lung	24 (19.2)	37 (29.4)	40 (32.0)	46 (36.2)	147 (29.2)	0.03
Liver	19 (15.2)	31 (24.6)	38 (30.4)	41 (32.3)	129 (25.6)	0.009
Bone	32 (25.6)	49 (38.9)	63 (50.4)	56 (44.1)	200 (39.8)	0.001*
Any site	68 (54.4)	85 (67.5)	92 (73.6)	90 (70.9)	335 (66.6)	0.009
Synchronous metastases	39 (31.2)	15 (11.9)	12 (9.6)	4 (3.1)	70 (13.9)	<0.001*

BMFI, brain metastasis-free interval; SD, standard deviation; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
BMFI is the time period between the primary breast cancer diagnosis and the first (brain) metastasis.
**P* < 0.05 after Bonferroni adjustment for 27 degrees of freedom.

Continues

Table 1. Continued

BMFI in Quartiles	0–18 Months	18 Months to 3 Years	3–6 Years	>6 Years	Total	*P* Value
Treatment modalities						
Neurosurgery	51 (40.8)	50 (39.7)	38 (30.4)	57 (44.9)	196 (39.0)	0.11
Stereotactic radiosurgery	98 (78.4)	107 (84.9)	107 (85.6)	101 (79.5)	413 (82.1)	0.33
Classical radiotherapy	95 (76.0)	102 (81.0)	102 (81.6)	102 (80.3)	401 (79.7)	0.67

BMFI, brain metastasis-free interval; SD, standard deviation; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.
BMFI is the time period between the primary breast cancer diagnosis and the first (brain) metastasis.
*$P < 0.05$ after Bonferroni adjustment for 27 degrees of freedom.

died (86.1%), with a median overall survival since presentation of BM of 17 months.

BMFI Stratification

Based on rounded quartiles, patients were stratified by length of BMFI as follows: <18 months, 18 months to 3 years, 3–6 years, and >6 years. Baseline characteristics for these strata are also presented in Table 1. Patients with a longer BMFI were more likely to have extracranial metastases in any site ($P = 0.009$), especially in the bones ($P = 0.001$). They were also more likely to be ER+ ($P = 0.002$) and PR+ ($P < 0.001$), whereas there was no difference in HER2 status ($P = 0.45$). As a result, median BMFI differed for ER−/HER2− (25.6 months), ER−/HER2+ (31.0 months), ER+/HER2− (45.6 months), and ER+/HER2+ (40.0 months; $P = 0.003$ for overall comparisons). Interestingly, ER-/HER2- patients had a markedly shorter interval between first metastasis in general and first brain metastasis (3 months vs. 14.0, 13.3, and 15.6 months; $P = 0.002$ for ER−/HER2− vs. other subtypes; Figure 2). Patients

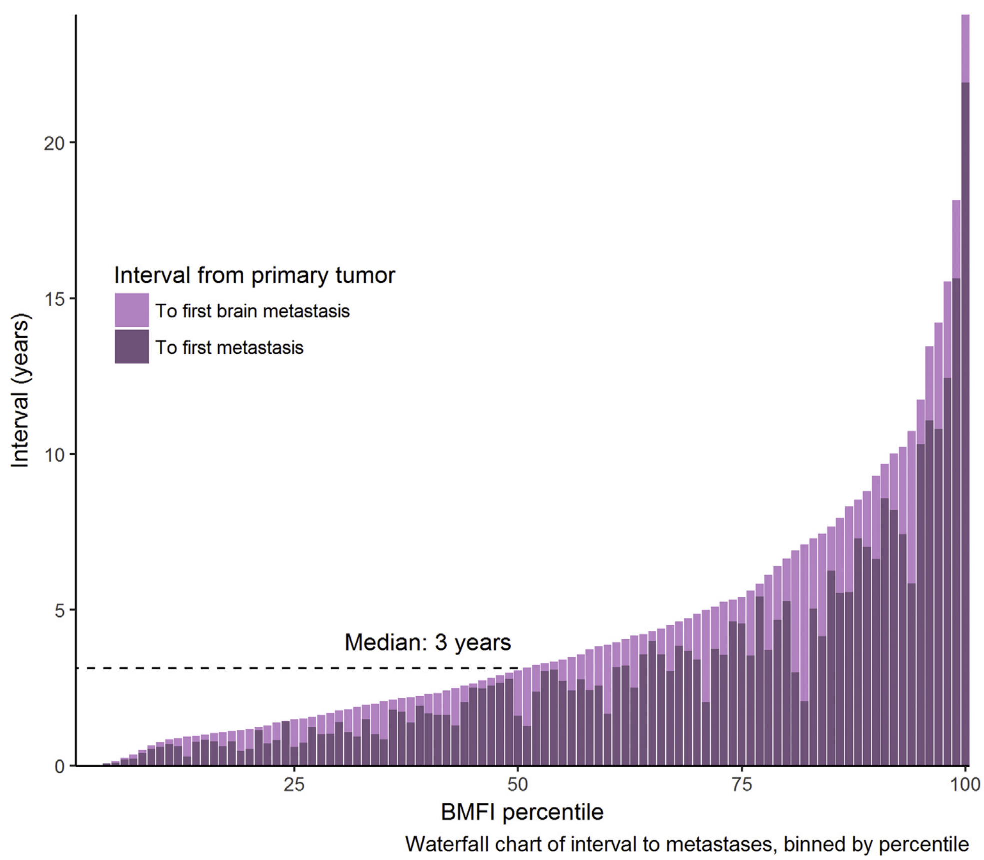

Figure 1. Waterfall chart showing distribution of metastasis-free interval and brain metastasis-free interval, binned by percentile. BMFI, brain metastasis-free interval.

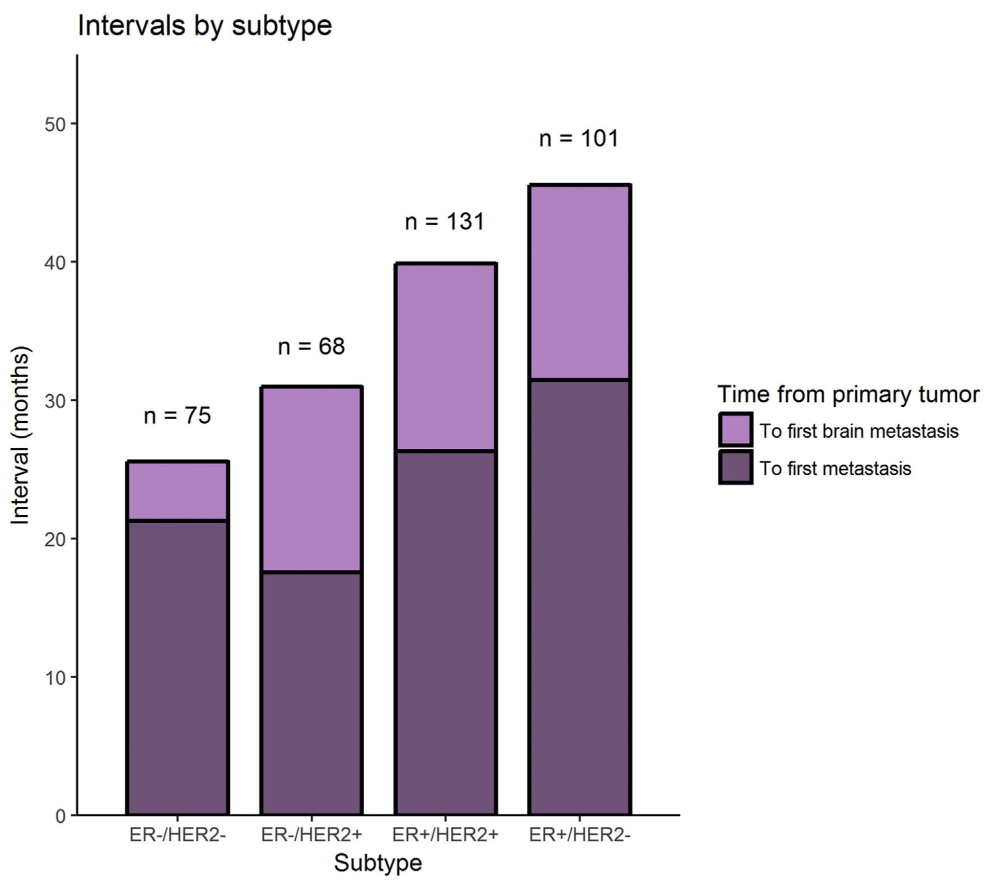

Figure 2. Metastasis-free interval and brain metastasis-free interval (BMFI) by subtype. Triple negative (ER−/HER2−) tumors had the shortest BMFI (median 26 months; $P = 0.002$) as well as the shortest time from first metastasis to first brain metastasis (median difference 3 months; $P = 0.002$ vs. other subtypes). ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

with a BMFI >6 years were older at presentation of first brain metastasis (P = 0.001), whereas there was no difference in age at the time of primary tumor diagnosis (P = 0.31). Overall survival was similar for all strata (P = 0.56). After Bonferroni correction for 27 degrees of freedom, higher age at BM, PR+ status, bone metastases, and non-synchronous onset of metastases in general were associated with longer BMFI (P < 0.05), whereas ER+ status was borderline significant (P = 0.05).

Cox Proportional Hazards Model

In univariate Cox proportional hazards model, ER+/HER2+ subtype (hazard ratio [HR] = 0.67; P = 0.01) or HER2+ status (HR = 0.68; P = 0.0007) were favorable prognostic factors, whereas age at brain metastasis >50 (HR = 1.24; P = 0.02), lung metastases (HR = 1.31; P = 0.01), and liver metastases (HR = 1.32; P = 0.01) at diagnosis of BM were associated with worse overall survival (Table 2). For black patients, BMFI >3 years was found to be a favorable prognostic factor for survival (HR = 0.33; P = 0.02). BMFI >3 years was not correlated with overall survival for all patients in univariate analysis (HR = 0.92; P = 0.37). Sensitivity analysis with BMFI as a continuous variable yielded a similar result (HR = 1.0; P = 0.43).

In multivariate analysis (Table 2), ER+/HER2+ subtype (HR = 0.77; P = 0.008), and the presence of liver metastases (HR = 1.35; P = 0.01) remained statistically significant. On sensitivity analysis, influence of subtype was found to be entirely attributable to HER2 status (HR = 0.67 for HER2 positive vs. negative; P = 0.0004). Figure 3 presents survival curves for these patient groups. There was a trend for worse survival if lung metastases were present (HR = 1.20; P = 0.10). BMFI >3 years was not correlated with survival (HR = 0.96; P = 0.70; Figure 3). When conducting sensitivity analysis for BMFI expressed as quartiles or as a continuous variable, this result did not change (all P values < 0.05).

In a multivariate interaction model, BMFI >3 years was prognostically favorable for black/African American patients (HR = 0.34; P = 0.03). In this model, black/African American patients also had poorer survival than white patients (HR = 2.04; P = 0.005).

DISCUSSION

In this large, retrospective cohort study, we found that BMFI did not affect overall survival in patients with BCBM. Following

Table 2. Cox Proportional Hazards Analysis

Variable	Univariate Analysis (HR [*P* Value])	Multivariate Analysis (HR [*P* Value])
Race (white is reference)		
Asian	0.85 (0.67)	N/A
Black	1.33 (0.17)	N/A
Hispanic	1.18 (0.69)	N/A
Other	2.04 (0.06)	N/A
Age at first brain metastasis >50	1.24 (0.02)*	1.16 (0.12)
ER+	0.88 (0.26)	
Progesterone receptor positive	0.95 (0.63)	
HER2+	0.68 (0.0007)*	0.67 (0.0004)*
Subtype (ER−/HER2− is reference)		
ER−/HER2+	0.78 (0.19)	N/A
ER+/HER2−	1.05 (0.76)	N/A
ER+/HER2+	0.67 (0.01)*	0.77 (0.008)*
Synchronous metastases	1.02 (0.88)	N/A
Extracranial metastases	1.21 (0.07)	N/A
Lymph nodes	1.09 (0.40)	N/A
Lung	1.31 (0.01)*	1.20 (0.10)
Liver	1.32 (0.01)*	1.35 (0.01)W*
Bone	1.03 (0.75)	N/A
Metastasis-free interval >2 years	1.13 (0.21)	N/A
BMFI >3 years	0.92 (0.37)	0.96 (0.70)

HR, hazard ratio; N/A, not applicable; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; BMFI, brain metastasis-free interval.
**P* <0.05.

multivariate analysis, only HER2− status and the presence of liver metastases at BM diagnosis were prognostic for worse survival in patients with BCBM. In an interaction model, black patients had worse overall survival unless they had a long BMFI. This result is based on a small sample (n = 28) and could represent a statistical outlier. Alternatively, the finding could reflect a disparity in access to health care, resulting in some patients with less access to treatment options having both a shorter disease-free interval and overall survival. To our knowledge, this cohort represents the largest study to date evaluating BMFI in breast cancer patients, as well as the only study to focus on BMFI a priori.

Strengths of our study are its large sample size and multi-institutional design. Additionally, this study was designed to be hypothesis-testing. Our cohort is comparable with breast cancer cohorts reported on in prior studies. A median age at BM of 52 years is similar to those reported by other authors (48−53 years).[14,23,25,26] The overall survival of 17 months was marginally higher than the range reported by other recent studies (9−16 months).[14,23,25-27] Moreover, the median BMFI in our cohort is approximately 3 years; this is consistent with ranges described in literature (28−54 months).[13,15,23,28] Although it is known that certain subtypes have a longer BMFI than others,[13] this study also found that ER−/HER2− patients have a shorter interval between first metastasis in any site and first brain metastasis. This is consistent with a multicenter analysis that found ER−/HER2− patients to have a shorter time from diagnosis of metastatic disease to first brain metastasis when compared with patients with other subtypes.[27]

Prior studies that have reported on the prognostic value of BMFI in BCBM patients have been conflicting. In a retrospective study of 62 patients, Kiricuta et al.[29] found no relation between BMFI and survival. More recently, Lee et al.[24] (n = 198; P = 0.06), Nieder et al.[15] (n = 86; P = 0.05), and Shen et al.[23] (n = 140; P = 0.08) identified trends for poorer survival in patients with shorter BMFI. None of these studies corrected for clinical tumor subtype, whereas 1 corrected for ER, PR, and HER2 expression as separate variables.[23] Our study lends support to the position that patients with BM have similar prognoses regardless of interval to BM development. A strength of our analysis is that we were able to control for tumor subtype, which we found to be both prognostic and associated with BMFI, and thus, could be a potential confounder in analyses that did not include subtype as a variable.

We also found that presence of extracranial metastases is not correlated with overall survival, which is consistent with the diagnosis-specific graded prognostic assessment. In their retrospective series of 642 patients used to build this model, Sperduto et al.[11,14] found that extracranial metastases were correlated to survival outcomes in univariate Cox regression, but not in multivariate analysis. Still, this finding is counterintuitive, given the fact that most BCBM patients are reported to die of extracranial disease.[2,4,5,7] A possible explanation is that not all sites of extracranial metastases are equally life-threatening. In our series, extracranial metastases were prognostically unfavorable only when present in the liver. Further studies are needed to elucidate the exact prognostic role of extracranial metastases in patients with breast cancer.

The literature regarding the prognostic impact of ER status in BCBM patients is mixed, with some studies reporting a better prognosis for patients with ER+ tumors,[6,12,13,30,31] whereas other studies report no difference.[16,19,32-34] We found ER status to correlate with longer BMFI but not overall survival, whereas HER2 status correlated with survival after the onset of BMs. Sperduto et al.[13] describe a similar association between subtype and time to BM.

The major limitation of our study is potential selection bias, as we identified patients referred for surgery and/or radiosurgery for their BM. Because patients who undergo these interventions tend to have a more favorable performance status, we cannot be sure that our results would apply to patients who are not eligible for such treatments. Indeed, our results may underestimate differences in outcomes based on tumor subtype or other potential prognostic factors. Therefore, our results should be extrapolated with caution.

This study was primarily designed to determine the prognostic value of BMFI. Other findings in the survival analysis, such as the prognostic value of liver metastases, should be interpreted in the

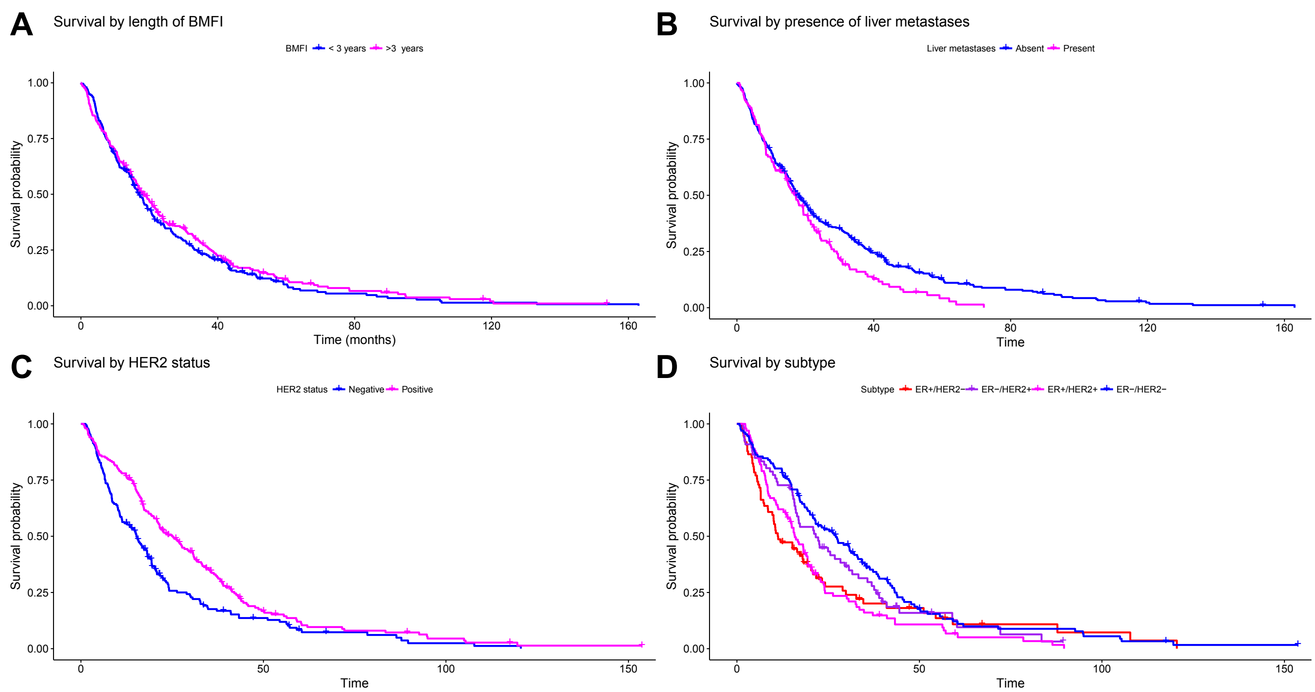

Figure 3. Survival curves by (**A**) length of BMFI, (**B**) presence of liver metastases, (**C**) HER2 status, and (**D**) tumor subtype. BMFI, brain metastasis-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

context of this limitation, and should be confirmed in independent cohorts.

In the setting of a retrospective study, we did not have presenting KPS available in many patients and were not able to include this variable in our models. We suspect that the majority of patients had KPS ≥70, given the fact that they were referred for surgery or radiosurgery, such that even if we had complete data, we would have been underpowered to evaluate the impact of low KPS on outcomes. Moreover, systemic treatment modalities, such as chemotherapy, HER2 targeted therapy, and endocrine therapy could not be reliably obtained for a considerable number of patients and were therefore not included in the analysis.

Although KPS and systemic treatments are prognostically relevant in BCBM, the aim of our study was not to build or validate a predictive model for survival in BCBM, but primarily to assess whether BMFI influences outcomes in our patients. Although it is possible that there is an interaction between systemic treatment or KPS and BMFI that we missed, we consider it unlikely that this would have substantially altered our conclusions.

CONCLUSIONS

In this large, multi-institutional review of breast cancer patients, we found no association between overall survival and interval between primary breast cancer diagnosis and first brain metastasis. BMFI varies considerably between patients but does not seem to have prognostic value in the neurosurgical and radiosurgical breast cancer population.

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