Determinants of the interval to brain metastasis from initial breast cancer diagnosis and its relation to survival: a single-center retrospective cohort

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Abstract

Background: Brain metastasis (BM) carry short-term survival and a poor prognosis. Short-onset time to BM can lead to better survival than patients with delayed diagnosis. We intend to assess clinical factors associated with mortality and time to brain metastasis.

Methods: We retrospectively reviewed the charts of 113 patients in our institution who developed BM from primary breast cancer from 2000-2020. Demographic and clinical characteristics were reviewed. One-hundred-thirteen patients were eligible for survival analysis by univariate and multivariate COX regression. In addition, we performed statistical analysis to determine factors associated with undergoing surgery.

Results: Post-menopausal state at initial breast cancer (HR=1.66; CI 1.11-2.47, P=0.01), other ethnicities (HR=2.18; CI 1.17-4.04, P=0.01), and the subtype ER+/HER2+ (HR=2.13; CI 1.21-3.73, P=<0.05) were found on multivariate analysis to have a shorter interval to BM. Subgroup analysis of patients with ER+ tumors found that initial Stage IV at diagnosis (HR=1.83; CI 1.1-3.18, P=0.03) and HER2+ status (HR=1.81; CI 1.09-2.96, P=0.02) had shorter intervals to brain metastasis. Patients that underwent initial adjuvant endocrine therapy (HR=0.61; CI 0.39-0.95, P=0.03) and palbociclib therapy (HR=0.51; CI 0.28-0.96, P=0.04) had longer intervals to BM. In multivariate survival analysis, a BM onset shorter than 2 years (HR=0.24; CI 0.074-0.83, *P*=0.025, Figure 2C) was a protective factor.

Conclusions: Patients with early development of breast BM have better survival than patients with longer time onsets. The subtype of tumor, receptor status, systemic therapy, and high initial stage are factors related to interval from breast cancer to brain metastasis.

Background

Breast cancer remains the first cause of cancer in women and the leading cause of mortality in the United States and worldwide. [1] It is also the second cause (5–20%) of brain metastasis (BM), after lung cancer (20–56%). Breast cancer brain metastasis survival has been estimated to be up to 29.8 months in selected nationwide populations that undergo treatment, but it usually ranges from 7.1–18.9 months depending on molecular subtype and type of treatment. [2, 3]

Survival is a multifactorial event that depends on several factors including the type of treatment and severity of the disease. Patients that undergo whole brain radiation therapy (WBRT) have a limited prognosis. [4] Other factors described affecting the mortality of BM are age, Karnofsky Performance status (KPS), and molecular subtype.[5, 6] The interval from initial breast cancer to brain metastasis is a novel factor described by prior cohorts affecting survival. [7]

This interval described as brain metastasis-free interval (BMFI) by some authors has not been widely characterized yet. Several clinical characteristics are related to a shorter time for the development of BM. It is still not elucidated if this interval is also correlated to survival. Herein, we performed a retrospective study at our institution to determine the factors associated with survival and time interval from initial breast cancer to brain metastasis.

Methods

We performed a retrospective cohort of all patients admitted and treated for breast cancer that developed brain metastasis from 2000 to 2020. We extracted 254 patients with ICD-10 codes C50 and C79.31 from our clinical database at our institution. The primary exclusion criteria were primary brain tumors that differed from breast cancer.

Secondary exclusion criteria were patients with different intracranial tumors and patients presenting without parenchymal brain tumors. We excluded seventeen patients that did not have follow-up after treatment. We excluded seventeen patients that did not have follow-up after treatment. A total of 113 patients met the inclusion criteria. Supplementary figure depicts the selection process. The study was approved by the IRB at our institution.

We collected demographic and clinical characteristics of all patients. We defined staging according to the American Joint Committee on Cancer (AJCC) staging manual.[8] We considered human epidermal growth factor receptor 2 (HER2) positive tumors if pathology reports described strong overexpression (3+) on immune-histochemical (IHC) staining or moderate (2+) overexpression with HER2 amplification (> 2.0) in fluorescent in situ hybridization.[9] Tumors were considered to be estrogen receptor status positive (ER) if they had positive nuclear IHC > 1%. Patients were categorized as ER+/HER2-, ER-/HER2+, ER+/HER2+, or ER-/HER2- according to the ER and HER2 status. [10]

Categorical variables were reported as proportions. Continuous variables were expressed as means (± standard deviation) or medians [interquartile range (IQR)], depending on data normality. For continuous variables, we used the student t-test or Mann-Whitney U-test as appropriate according to the distribution of the data. Statistical significance was set at P = 0.05 for all comparisons. We calculated the time interval from initial breast cancer to BM diagnosis by image and the time from BM diagnosis to last follow-up or death. Kaplan-Meier method was used for survival analysis, and the log-rank test was used for comparison between groups. Patients were censored from the Kaplan-Meier analyses if they died during follow-up. We performed all statistical analysis in STATA 15 (StataCorp, College Station, Texas, USA).

Results

After excluding patients that did not meet our selection criteria, our sample comprised 113 female patients, the mean age of presentation of breast cancer was 53.5 (±11.27). The median interval to brain metastasis in our sample was 4.87 (IQR 2.8-11.2). Sixty-six patients (58.4%) had a breast cancer onset after 50 years. There were seventy-six patients (67.3%) with smoking history, twenty-four patients (21.2%) were African-American, eight patients were Asian (7.1%), and five (4.4%) had other ethnicities (Hispanic and Arab American). The most common type of breast cancer was invasive ductal in eighty-two patients (79.6%), followed by invasive lobular (16.5%), and four patients had other types of histology (3.9%). Most of the tumors in our sample were ER+ (73.2%), while thirty-five cases (31.3%) were HER2 positive. Breast cancer tumors were ER+/HER2- in fifty-eight patients (51.8%), ER-/HER2- in twenty-one (18.8%), ER+/HER2+ in twenty patients (17.9%), and ER-/HER2+ in thirteen patients (11.6%). In the subgroup of patients with ER+ status, forty-one patients received adjuvant endocrine therapy (48.8%), and fourteen received Palbociclib (16.7%).

Initial stage characteristics are outlined in table 1. Forty-four patients had visceral metastasis (38.9%), thirty-three had a distant lymph node metastasis (29.2%), twenty-eight had bone metastasis (24.8%), and twenty-five had vertebral metastasis (22.1%) before having intracranial disease. Sixty-eight patients (63.6%) had a low KPS (<70) during the initial BM diagnosis. Thirty-one patients underwent surgical resection as first-line treatment (27.4%), twenty-nine (25.7%) stereotactic radiosurgery (SRS), and fifty-three (46.9%) WBRT. Median time to last follow-up was 12.6 months (IQR 4.4-30.6).

Onset time to brain metastasis

Median time to brain metastasis was 53.8 months (IQR 32.2-96-1). In univariate analysis post-menopausal state at initial breast cancer diagnosis (HR=1.49; CI 1.02-2.21, P=0.04), HER2+ status (HR=2.19; CI 1.26-3.82, P=0.01), the subtypes ER-/HER2+ (Figure 1.A; HR=2.21; CI 1.22-4.01, *P=0.01*), and ER+/HER2+ (Figure 1.A, HR=2.14; CI 1.25-3.65, *P=0.01*), Hispanics and other ethnicities (Figure 1.B; HR=2.40; CI 1.02-5.63, *P=0.04*) had a shorter interval to brain metastasis from initial diagnosis. In multivariate analysis, post-menopausal state (HR=1.69; CI 1.13-2.53, *P=0.01*), Asian ethnicity (HR=2.30; CI 1.03-5.16, *P=0.043*), and the subtype ER+/HER2+ (HR=2.06; CI 1.14-3.71, *P=0.016*) had a shorter interval time. Factors associated with onset time to BM are summarized in table 2.

Subgroup analysis of the patients with ER+ status showed that patients with an initial Stage IV at diagnosis (HR=1.83; CI 1.1-3.18, *P=0.03*) and HER2+ tumors (HR=1.81; CI 1.09-2.96, *P=0.02*) had shorter intervals to brain metastasis. Patients that underwent adjuvant endocrine therapy (Figure 1.C; HR=0.61; CI 0.39-0.95, *P=0.03*) and palbociclib therapy (Figure 1.D; HR=0.51; CI 0.28-0.96, *P=0.04*) had longer onset time to brain metastasis. In multivariate analysis, high initial stage (HR=2.09; CI 1.16-3.76, *P=0.014*), Hispanic and other ethnicities (HR=3.63; CI 1.34-9.81, *P=0.011*) remained associated with a shorter time to onset. This subgroup analysis can be found in supplementary table.

Survival analysis

In the univariable Cox proportional hazard analysis, we found significantly worse OS in patients with initial lymph node positive status (HR=2.1; CI 1.01-4.3, *P=0.041*), vertebral metastasis (Figure 2A; HR=2.01; CI 1.01-4.28, *P=0.046*) and WBRT as initial treatment (Figure 2B; HR=2.7; CI 1.11-6.5, *P=0.03*). Patients with an early diagnosis (<2 years) of BM had improved survival (Figure 2C; HR=0.24; CI 0.074-0.83, *P=0.025*). In the multivariable analysis patients with an early diagnosis of BM<2 years remained statistically significant for improved survival (HR=0.22; CI 0.049-0.98, *P=0.048*). These results are displayed in Table 3.

Discussion

Brain metastasis have an average overall survival (OS) of 4 to 16 months depending on type of tumor and treatment. [11] Although median time to initial diagnosis of BM varies widely, it is estimated to be 32 months. [12] Several factors have been associated with time interval to BM, among them tumor subtype is one of the most common. [7, 13]

In our cohort we found an onset time to BM comparable and within the range of other reported studies in the literature (28–54 months).[5, 7] We found for the general group that the subtypes of receptors ER-/HER2 + and ER+/HER2 + were statistically significant and associated with a shorter time onset to BM. HER2 + status has been associated with early BM in prior studies. [13–17] HER2 gene over-expression results in a tumor with more invasive properties, increased proliferation, and tumorigenic growth.[18] Lao et al. described and association between Asian race, higher tumor grades and HER2 + subtype compared to European white women.[19] African-American and Hispanic groups suffer social disparities; that makes them less likely to have early access to healthcare and have disadvantages in access to treatment.[20] These two groups are prone to present initially with advanced disease.[20] Hispanic, Arab Americans. and Asian ethnicities had shorter onset time to BM in this study.

In the subgroup analysis of ER + tumors we found that patients who received adjuvant endocrine therapy and palbociclib had longer intervals to BM. The NSABP-P1 and the Italian clinical trial showed that tamoxifen has chemopreventive effects on the development of the contralateral breast.[21–23] Selective estrogen receptor modulator (SERM) could display these effects in addition to their adjuvant actions to delay metastasis

to other body sites, including the brain. Aromatase inhibitors (AI) have also showed these same effects and longer free disease survival in three different clinical trials.[24–26] The blood brain barrier, however, decreases permeability of chemotherapy to the brain and P-glycoprotein works as an efflux pump of these compounds.[27] Preclinical studies demonstrated that letrozole and vorozole have good distribution volumes and low clearance rates in the brain compartment.[27] Direct actions in brain tissue could explain these effects of AI. Palbociclib on the other hand, has also shown *in vivo* activity in glioblastoma multiforme xenografts, showing almost 25–35 higher quantities in tumor tissue than the normal.[28] Breast cancer metastasizes through the epithelial-mesenchymal transition process (EMT), in which cells acquire a mesenchymal phenotype and up-regulate mesenchymal markers.[29] Through decrease on COX-2 expression, PGE2 production, and down-regulation of vimentin and Snail, palbociclib exerts antimetastatic effects. [29]

Few studies have addressed the interval time from breast cancer to brain metastasis as prognostic factor of mortality.[7, 30] Hulsbergen et al. did not find a statistically significant difference between patients that had an early diagnosis (< 3 years) and those that had a late diagnosis.[7] In our study, all-causes of mortality were higher in the patients with an onset of BM after two years from initial breast cancer. Other patient specific characteristics that predicted mortality in our model were the presence of initial lymph node positive, vertebral metastasis, and first-line treatment with WBRT.

Vertebral metastasis has high mortality, with reported OS that ranges from 7 months to 17.03 months, depending on the treatment patients undergo, which accounts for the higher mortality rate of this group in our cohort. Vertebral metastasis mortality in addition to intracranial metastasis account for the higher mortality rate of this group in our cohort. [31, 32] Patients who require radiation therapy for brain metastasis have advanced intracranial disease, most cases with multiple lesions. Mix et al. has previously reported an OS of 21 months in patients who undergo stereotactic radiosurgery (SRS), while those that received WBRT had an OS of 3 months.[33] WBRT has a low survival rate of 8.8% at the third year after diagnosis in these patients. [34] Most surgical patients have a single symptomatic lesion and better prognosis.[35, 36] Leone et al. reported an OS of

5.7 years in a cohort of breast cancer patients with BM surgically resected.[37]

Our multivariate analysis model showed that a diagnosis of BM before the two years from the initial breast cancer diagnosis is associated with less mortality. Currently, guidelines only recommend initial staging with FDG PET/CT in breast cancer patients with clinical stage IIB or higher, as these patients have a higher risk of presenting with initial metastasis.[38] Other studies advocate the routine use of PET imaging for breast cancer due to a significant modification of staging. [39, 40] Brain MRI is not recommended for breast cancer patients. [38] In our study, patients presenting with BM before two years have less mortality overall. Factors associated with a short interval to brain metastasis were HER2 + status in different subtypes of tumors, some ethnical groups, and a high initial stage. Systemic therapy in the ER + group was associated with longer interval of time to BM. Our data suggests that patients with BM could benefit from an early diagnosis. This study is limited due to its retrospective nature, single center nature and size of the sample. Further prospective studies should address the importance of time onset to BM for survival and what factors are associated with it.

Conclusions

The formation of BMs is important in patients with breast cancer. We found that the HER2 + subtype, ethnicity, and high initial stage were associated with a longer onset time to BM diagnosis. Furthermore, in the ER + subgroup of patients that received adjuvant endocrine therapy or palbocilib were also found to have longer intervals to diagnosis of BMs. These longer brain metastasis interval from initial breast cancer diagnosis were associated with higher mortality. Patients with breast cancer could benefit from early screening to diagnosis BMs and decrease the mortality. Future studies should address the relationship between the factors related to interval onset and mortality.

Abbreviations

AJCC= American Joint Committee on Cancer; AI= Aromatase inhibitors; BM= Bain metastases; CI= Confidence interval; EMT= Epithelial mesenchymal-transition process; ER= Estrogen receptor; HER2= Human epidermal growth factor receptor 2; HR= Hazard ratio; IHC= immune-histochemical; IQR= interquartile range; KPS= Karnofsky Performance status; OR= Odds ratios; OS= Overall survival; SERM= Selective estrogen receptor modulator; SRS= stereotactic radiosurgery; WBRT= Whole brain radiation therapy.

Declarations

Supplementary information: The online version contains supplementary material

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Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

Ethics declarations

Conflicts of interest

The authors declare that they have no conflict of interest

Ethical approval

This retrospective study was approved by the Institutional Review Board at our institution

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Tables

Table 1. Demographics and clinical characteristics

Variable	N= 113
Age	53.5 (±11.27)
Age >50	66 (58.4%)
Smoking history	31 (27.4%)
Race	
White	76 (70%)
African-American	24 (18.5%)
Asian	8 (7.1%)
Other (e.g., Hispanic)	5 (4.4%)
Type of histology (n=103)	
Ductal	82 (79.6%)
Lobular	17 (16.5%)
Other	4 (3.9%)
ER+ (n=112)	82 (73.2%)
HER2+ (n=112)	35 (31.3%)
Subtype (n=112)	
ER+/HER2-	58 (51.8%)
ER-/HER2+	13 (11.6%)
ER+/HER2+	20 (17.9%)
ER-/HER2-	21 (18.8%)
Initial tumor grade (n=92)	
T1-T2	33 (35.9%)
T3-T4	59 (64.1%)
Initial positive lymph node (n=95)	20 (21.1%)
Initial stage IV (n=104)	24 (23.1%)
Bone metastasis	28 (24.8%)
Vertebral metastasis	25 (22.1%)
Visceral metastasis	44 (38.9%)
Distant lymph node metastasis	33 (29.2%)
Low KPS at the initial BM diagnosis (n=107)	68 (63.6%)
Brain metastasis treatment	
Surgery	31 (27.4%)
SRS	29 (25.7%)
WBRT	53 (46.9%)

BM=Brain metastasis; ER= Estrogen receptor; HER2= Human epidermal growth factor receptor 2; SRS=Stereotactic radiosurgery; WBRT=Whole brain radiation therapy

Table 2. Univariate and multivariate Cox proportional analysis of factors affecting time to BMs

Variable	Univariate analysis (HR; CI, P value)	Multivariate analysis (HR, CI, P value)
Age >50 at breast cancer diagnosis	1.45 (CI 0.98-2.15, P=0.06)	NA
Post-menopausal state	1.49 (CI 1.02-2.21, *P=0.04*)	1.69 (CI 1.13-2.53, *P=0.01*)
Smoking history	1.05 (CI 0.69-1.59, P=0.81)	NA
Ethnicity		NA
White	1	
African-american	1.16 (CI 0.73-1.84, P=0.54)	1.21 (CI 0.75-1.96, P=0.43)
Asian	1.73 (CI 0.79-3.79, P=0.17)	2.30 (CI 1.03-5.16, *P=0.043*)
Other (e.g., Hispanic)	2.40 (CI 1.02-5.63, *P=0.04*)	2.45 (CI 0.98-6.07, P=0.053)
High Tumor grade: III-IV	0.91 (CI 0.59-1.41, P=0.69)	NA
Initial lymph node positive	1.26 (CI 0.76-2.1, P=0.36)	NA
Initial high stage: IV	1.41 (CI 0.89-2.23, P=0.15)	NA
Bone metastasis	0.89 (CI 0.58-1.38, P=0.62)	NA
Vertebral metastasis	0.81 (CI 0.52-1.26, P=0.35)	NA
Visceral metastasis	0.77 (CI 0.53-1.13, P=0.19)	NA
Distant lymph node metastasis	0.90 (CI 0.59-1.37, P=0.63)	NA
ER+	0.76 (CI 0.49-1.16, P=0.21)	NA
HER2+	2.19 (CI 1.26-3.82, *P=0.01*)	1.27 (CI 0.37-4.27, P=0.71)
Subtype receptor		
ER+/HER2-	1	
ER-/HER2+	2.21 (CI 1.22-4.01, *P=0.01*)	2.39 (CI 0.65-8.85, P=0.19)
ER+/HER2+	2.14 (CI 1.25-3.65, *P=0.01*)	2.06 (CI 1.14-3.71, *P=0.016*)
ER-/HER2-	0.89 (CI 0.53-1.49, P=0.66)	0.99 (CI 0.59-1.65, P=0.97)
Type of histology		
Invasive ductal	1	
Invasive lobular	0.81 (CI 0.49-1.34, P=0.41)	NA
Other	0.93 (CI 0.43-2.03, P=0.18)	NA

ER= Estrogen receptor; HER2= Human epidermal growth factor receptor 2; HR=Hazard ratio; CI=Confidence interval

Table 3. Univariate and multivariate Cox proportional analysis of factors affecting survival after BMs

Variable	Univariate analysis (HR; CI, P value)	Multivariate analysis (HR, CI, P value)
Age >50 at breast cancer diagnosis	1.54 (CI 0.75-3.16, P=0.24)	NA
Age: >55 at brain metastasis diagnosis	2.02 (CI 0.91-4.44, P=0.083)	NA
Post-menopausal state	1.77 (CI 0.89-3.5, P=0.1)	NA
Smoking history	1.54 (CI 0.78-3.01, P=0.21)	NA
Race		NA
White	1	
African-american	0.88 (CI 0.33-2.33, P=0.79)	NA
Asian	1.49 (CI 0.44-5.05, P=0.52)	
Other (e.g., Hispanic)	0.89 (CI 0.14-3.86, P=0.89)	NA
Low KPS at initial BM diagnosis	1.64 (CI 0.73-3.7, P=0.23)	NA
High Tumor grade: III-IV	1 (CI 0.48-2.07, P=0.99)	NA
Initial lymph node positive	2.1 (CI 1.01-4.3, *P=0.041*)	1.76 (CI 0.84-3.7, P=0.13)
Initial high stage: IV	1.7 (CI 0.9-3.5, P=0.13)	NA
Vertebral metastasis	2.01 (CI 1.01-4.28, *P=0.046*)	1.17 (CI 0.54-2.54, P=0.68)
Bone metastasis	1.43 (CI 0.72-2.84, P=0.3)	NA
Visceral metastasis	0.94 (CI 0.47-1.87, P=0.86)	NA
Distant lymph node metastasis	1.57 (CI 0.78-3.17, P=0.21)	NA
ER+	1.66 (CI 0.72-3.83, P=0.23)	NA
Her2+	1.01 (CI 0.49-2.04, P=0.89)	NA
Subtype receptor		
ER+/HER2-	1	
ER-/HER2+	0.69 (CI 0.24-2.01, P=0.49)	NA
ER+/HER2+	1.58 (CI 0.69-3.57, P=0.27)	NA
ER-/HER2-	1.17 (CI 0.41-3.29, P=0.76)	NA
Type of histology		
Invasive ductal	1	
Invasive lobular	1.72 (CI 0.79-3.72, P=0.17)	NA
Other	0.25 (CI 0.033-1.85, P=0.18)	NA
Diagnosis during the first 2 years	0.24 (CI 0.074-0.83, *P=0.025*)	0.22 (CI 0.049-0.98, P=0.048)
Initial BM treatment		
Surgery	1	
SRS	1.7 (CI 0.63-4.6, P=0.29)	NA
WBRT	2.7 (CI 1.11-6.5, *P=0.03*)	1.18 (CI 0.76-1.84, P=0.45)

BM=Brain metastasis; CI=Confidence interval; ER= Estrogen receptor; HER2= Human epidermal growth factor receptor 2; HR=Hazard ratio; KPS=Karnofsky Performance Status; SRS=Stereotactic radiosurgery; WBRT=Whole-brain radiation therapy.

Figures

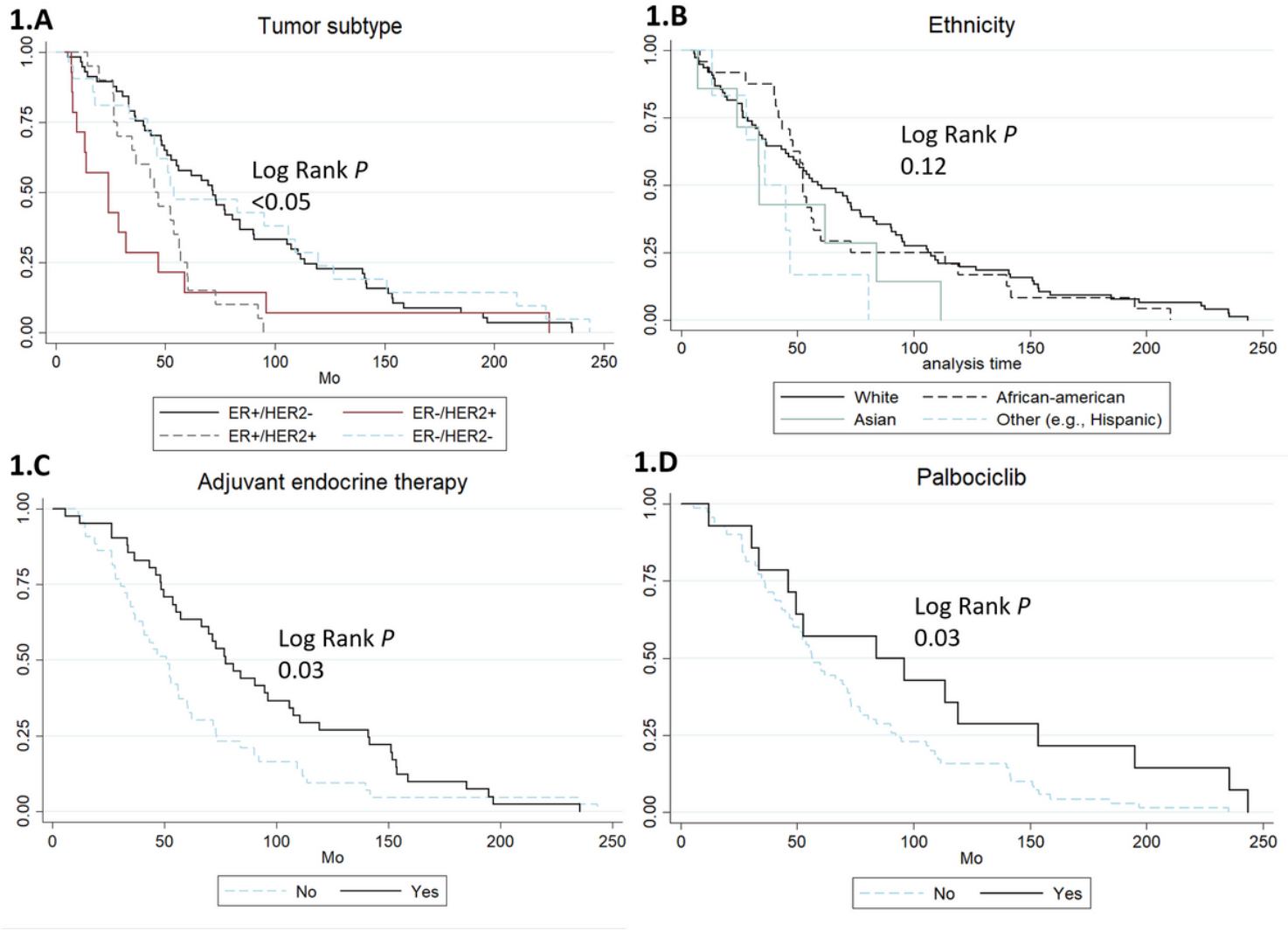

Figure 1

Kaplan-Meier survival curve of patients from breast cancer to brain metastasis grouped by tumor subtype (A), ethnicity (B), adjuvant endocrine therapy (C), and palbociclib (D).

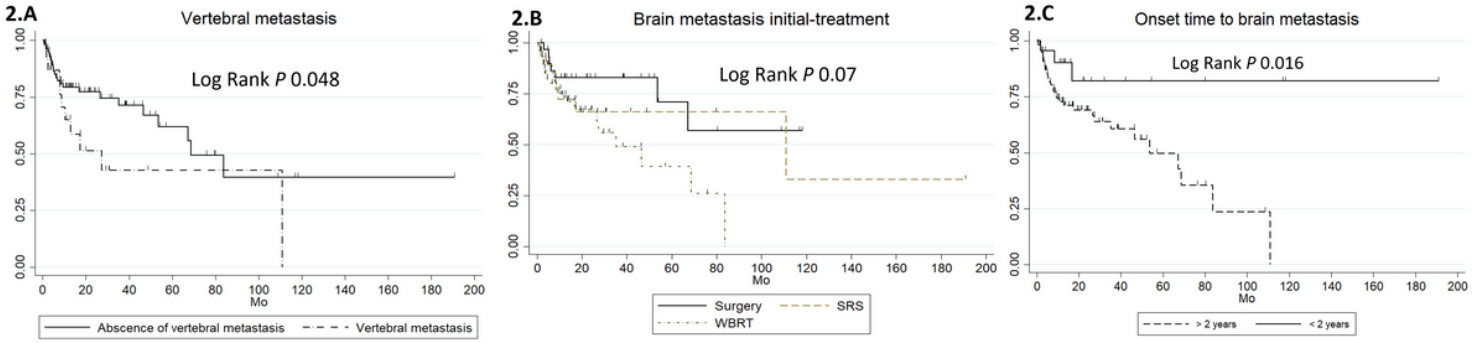

Figure 2

Kaplan-Meier survival curve of patients grouped by vertebral metastasis (A), initial treatment of brain metastasis (B), onset time to brain metastasis (C).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable.UnivariateandmultivariateCoxproportionalanalysisoffactorsaffectingtimetobrainmetastasisinbreastcancerERtypes.docx
- Supplementaryfigure.png