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Prognostic factors of brain metastasis and subsequent survival in breast cancer patients

An 11-year, single-center, retrospective study

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Abstract

Female breast cancer is among the most prevalent cancers globally, often metastasizing to the brain. Despite advancements in treatment, brain metastasis incidence is rising, with a poor prognosis. Moreover, limited data exist on how breast cancer subtypes and patient characteristics impact survival. This study aimed to investigate prognostic factors affecting breast cancer patients with brain metastasis. We retrospectively reviewed 131 breast cancer patients with brain metastasis diagnosed at a single institution between 2010 and 2020. Demographic, clinical, pathological, and radiographic variables were analyzed. The median interval between breast cancer diagnosis and brain metastasis was 27 months. Patients diagnosed with a higher stage of breast cancer (median survival: stage 1: 97.2 months, stage 2: 44.4 months, stage 3: 38.1 months, stage 4: 13.0 months, $P < .001$) and those with ER-negative tumors (median survival: negative 25.3 months, positive 37.5 months, $P = .034$) had a shorter time between initial diagnosis and brain metastasis. Median survival after brain metastasis was 8.0 months. Multivariate analysis showed that triple-negative breast cancer was correlated to a high risk of death after brain metastasis (hazard ratio = 2.320, $P < .001$). Higher histological grade, low-performance status, extensive brain metastases, and leptomeningeal seeding was associated with shorter survival. Systemic chemotherapy after brain metastasis was the only treatment that improved survival (hazard ratio = 0.332, $P < .001$). The study suggests potential benefits of aggressive treatment, especially in nontriple-negative breast cancer subtypes, limited brain metastases, and good overall health. Further research with larger patient populations is needed.

Abbreviations: BBB = blood-brain barrier, CI = confidence interval, CNS = central nervous system, CSF = cerebrospinal fluid, ECOG = Eastern Cooperative Oncology Group, ER = estrogen receptor, HER2 = human epithelial growth factor receptor 2, MRI = magnetic resonance imaging, PR = progesterone receptor, TNBC = triple-negative breast cancer, WBRT = Whole Brain Radiation Therapy.

Keywords: brain metastasis, breast cancer, prognostic factor, survival, triple-negative breast cancer

1. Introduction

Female breast cancer was reported as the most prevalent cancer globally in 2020.[1] In Korea, as of 2021, breast cancer ranked as the most common cancer among women and the fifth most common among both men and women. Unfortunately, breast cancer is one of the malignancies that frequently metastasize to the brain, a phenomenon that significantly shortens patient survival and adversely impacts the quality of life for both patients and their families. The prevalence of brain metastasis varies according to the subtype of breast cancer and across studies. Triple-negative breast cancer (TNBC) and human epithelial growth factor receptor 2 (HER2)-overexpressing breast cancer have been documented to metastasize to the brain in up to 50% of the patients. In contrast, hormone receptor-positive and HER2-negative breast cancer exhibit the lowest incidence of brain metastasis, occurring in ≈14% of the patients.[2–4]

Over the years, survival in metastatic breast cancer has improved due to the introduction of numerous effective systemic chemotherapeutic agents. However, an insufficient effect of systemic chemotherapies in preventing metastases and the prolonged survival of patients themselves could contribute to the increased prevalence of brain metastasis.[5,6] Recent advancements in local therapy for brain metastasis, coupled

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The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval for this study was provided by the Institutional Review Board of Pusan National University Hospital (2402-020-136). Informed consent was waived owing to the retrospective nature of the study.

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with the advent of novel brain-penetrating systemic therapies have played a role in improving the prognosis of patients with brain metastasis. Despite advancements in treatment, the prognosis for breast cancer patients with brain metastases remains poor.[7,8] Moreover, there is limited data available on how specific breast cancer subtypes and patient characteristics influence survival rates. In this study, we conducted a retrospective analysis of breast cancer patients with brain metastases to identify clinicopathological features and prognostic factors associated with survival. By elucidating these factors, we aimed to suggest potential treatment strategies for patients with this challenging diagnosis.

2. Methods

2.1. Subjects

We reviewed the electronic medical records of breast cancer patients who were diagnosed between January 2010 and December 2020 at the Pusan National University Hospital in Busan, the Republic of Korea. This retrospective cohort consisted of breast cancer patients with brain metastasis. Patients were included if they had metastatic brain tumors or metastatic meningeal enhancement on brain magnetic resonance imaging (MRI), or if metastatic cancer cells were present in the cerebrospinal fluid (CSF) during the course of the disease. Patients who had malignancies other than breast cancer were excluded from the analysis. The institutional review board of Pusan National University Hospital approved the study involving human participants (2402-020-136).

2.2. Clinical data

The data were collected from the electronic medical records of individual patients with standardized case report forms. The database included the following variables: age at breast cancer diagnosis, estrogen receptor (ER)/progesterone receptor (PR)/HER2 status of primary breast lesion (generally, at the time of surgery or first biopsy), stage at breast cancer diagnosis, histological grade of primary lesion, operation of primary breast lesion, chemotherapy including trastuzumab, neurologic symptoms due to brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status, time of brain metastasis diagnosis, local treatment of brain metastases, and administration of systemic chemotherapy since the appearance of brain metastases. ER- or PR- positivity was defined as ≥ 1% of cells being positive for ER and PR, and HER2-overexpression was determined according to the 2007 American Society of Clinical Oncology/College of American Pathologists guidelines.[9] The ECOG scale was used to estimate the performance status at the time of brain metastasis diagnosis. The appearance of brain metastases was defined as when a brain MRI showed the metastatic lesions for the first time, or metastatic cancer cells were found in the CSF. Leptomeningeal seeding was defined as either the detection of metastatic cancer cells in the cerebrospinal fluid or leptomeningeal enhancement on brain MRI in the absence of brain parenchymal lesions. Survival time was defined as the interval of time from brain metastases appearance to death or the last follow-up.

2.3. Imaging data

We reviewed the radiologists' reports regarding the brain MRI findings, and subsequently, all images underwent re-evaluation by one of the authors (neurologist G.H. Lee). We perform routine brain imaging every time when we change chemotherapy regimen for stage IV patients. For other patients, we generally perform an annual brain CT scan and follow-up with an MRI if any abnormalities are detected on CT or if neurologic symptoms arise. We meticulously documented details such as the location and number of metastatic lesions in the brain, the dimensions of the most extensive brain metastases, and the presence of a cystic form (when the volume of the cystic lesions was >50% of the total volume) or leptomeningeal/pachymeningeal enhancement.

2.4. Statistical analysis

Continuous variables were expressed as mean, standard deviation, median, and interquartile range depending on their normality, while categorical variables were presented as frequency and percentage. Analysis of factors associated with time to brain metastases in breast cancer utilized linear regression models for both univariate and multivariate variables. Univariate and multivariate Cox proportional hazards models were employed for survival analysis as prognostic factors. Forward stepwise selection was used to identify independent factors in multivariate regression analysis. To satisfy the normality assumption for ER, we performed a Box-Cox analysis. The correlation between vertebral and leptomeningeal metastases was assessed using the Pearson χ^2 test. A P value <0.05 was regarded as statistically significant. Statistical analysis was performed using the R program, version 4.3.1 and SAS program, version 9.4.

3. Results

3.1. Clinical characteristics

We reviewed 151 breast cancer patients diagnosed as having metastases to the brain and analyzed 131 patients, excluding 20 patients with missing values. The missing value was histological grade of primary lesion. The median age at the time of breast cancer diagnosis was 51 years (range 28–76; Table 1). Among these patients, 43 (32.8%) were initially diagnosed at stage 4, with 7 of them presenting with brain metastases. Nine (6.9%) patients had bilateral breast cancer. The median age at the time of metastasis to the brain was 55 years (range 30–76 years). Regarding performance status, 99 (75.6%) patients had an ECOG performance status of 1 or 2, while 32 (24.4%) had a status of 3. Primary breast cancer lesions were ER-positive in 53 (40.5%) patients, PR-positive in 39 (29.8%) patients, and HER2-positive in 41 (31.3%) patients. Neurological symptoms were present in 110 (84%) patients at the time of brain metastasis diagnosis, with headache (46 patients, 35.1%) being the most common symptom, followed by hemiplegia/paresis (17, 13%). On the other hand, 21 (16%) were asymptomatic and diagnosed through screening tests.

On brain MRI, metastatic lesion findings were observed in 126 (96.2%) patients, while 13 (9.9%) patients exhibited leptomeningeal enhancement, and 10 (7.6%) patients showed pachymeningeal enhancement. In addition, 5 (3.8%) patients showed normal brain MRI findings, but tested positive for metastatic cancer cells in the CSF analysis. Among the 118 patients with brain parenchymal lesions, 36 had solitary lesions and 82 had multiple lesions (Table 1). The most extensive brain metastasis exceeded 2 cm in diameter for 70 patients. The location of brain metastases was as follow: supratentorial in 46 (35.1%) patients, infratentorial in 11 (8.4%) patients, and both supratentorial and infratentorial in 74 (56.5%) patients. While most metastatic tumors were solid, a cystic form was observed in 19 (14.5%) patients.

One hundred-and-ten patients (84%) underwent local treatment. γ-knife radiosurgery was performed in 62 (47.3%) patients, and Whole Brain Radiation Therapy (WBRT) was additionally performed in one of them (Table 1). WBRT was performed in a total of 50 (38.2%) patients. Surgery was performed in 8 (6.1%) patients, and postoperative WBRT or γ-knife radiosurgery were also administered in these patients. Of the 36 patients with solitary metastatic lesions in the brain, 7 underwent surgical removal, and 24 were treated by γ-knife.

Table 1

Baseline characteristics.

Variables	n (%)
Clinicaopathologic features	
Age at breast cancer diagnosis (yr; mean, SD)	51.6 (10.9)
Time from diagnosis of breast cancer to brain metastasis (mo; mean, SD)	42.1 (37.9)
ECOG performance status at brain metastasis diagnosis	
1	40 (30.5)
2	59 (45.0)
3	32 (24.4)
ER status of primary breast lesion, positive	53 (40.5)
PR status of primary breast lesion, positive	39 (29.8)
HER2 status of primary breast lesion, overexpressing	41 (31.3)
Triple-negative breast cancer	47 (35.9)
Bilateral breast cancer	9 (6.9)
Stage at breast cancer diagnosis	
1	10 (7.6)
2	34 (26.0)
3	44 (33.6)
4	43 (32.8)
Histological grade of primary breast lesion	
1	6 (4.6)
2	66 (50.4)
3	59 (45.0)
Trastuzumab therapy	32 (24.4)
Neurologic symptoms at brain metastasis diagnosis	110 (84.0)
Leptomeningeal seeding	23 (17.6)
Bone metastases	60 (45.8)
Lung metastases	52 (39.7)
Vertebral metastases	55 (42.0)
Brain MRI findings	
Number of brain metastases	
0	13 (9.9)
1	36 (27.5)
≥2	82 (62.6)
Size of the most extensive lesion (mm; mean, SD)	21.7 (15.6)
Size of the most extensive lesion	
<2 cm	61 (46.6)
≥2 cm	70 (53.4)
Location of brain metastases	
Supratentorial	46 (35.1)
Infratentorial	11 (8.4)
Both	74 (56.5)
Cystic form	19 (14.5)
Leptomeningeal enhancement	13 (9.9)
Pachymeningeal enhancement	10 (7.6)
Treatment modalities	
γ-Knife radiosurgery	62 (47.3)
WBRT	50 (38.2)
Surgery	8 (6.1)
Intrathecal chemotherapy	9 (6.9)
Systemic chemotherapy after brain metastases	106 (80.9)

ECOG = Eastern Cooperative Oncology Group, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, MRI = magnetic resonance imaging, PR = progesterone receptor, SD = standard deviation, WBRT = Whole brain radiation therapy.

We conducted χ^2 tests and *t* tests on baseline variables (age, ECOG performance status, receptor status, and tumor size) to compare the 20 excluded patients with the 280 included patients. No statistically significant differences (all $P > .10$) were observed.

3.2. Factors associated with time to brain metastasis in breast cancer

The median interval between breast cancer diagnosis and brain metastasis was 27 months (range 0.0–180.0). To identify factors influencing this time interval, we conducted an analysis incorporating variables such as age at breast cancer diagnosis, ER/PR/HER2 status, TNBC, bilateral breast cancer, stage at breast cancer diagnosis, histological grade and vertebral metastases (Table 2). Univariate analysis revealed that stage of breast cancer at diagnosis, and histological grade were statistically significant. Following this, a Cox proportional hazards model was used for multivariate analysis. Because ER status is historically an important prognostic factor, we evaluated the normality of relevant variables through a Box-Cox analysis. While a cube root transformation was statistically optimal (Shapiro–Wilk $P = .696$), a square root transformation also effectively satisfied the normality assumption (Shapiro–Wilk $P = .630$). Given the comparable results, we adopted the simpler square root transformation without any notable impact on the overall outcomes. Therefore, we concluded that normality was sufficiently met, and the slight difference between the cube root and square root transformations did not materially affect our results. The stage of breast cancer at diagnosis (median time: stage 1: 97.2 months, stage 2: 44.4 months, stage 3: 38.1 months, stage 4: 13.0 months, $P < .001$) was identified as an independent significant factor. Patients diagnosed with a higher stage of breast cancer at diagnosis experienced a shorter time interval between breast cancer diagnosis and the development of brain metastasis. In multivariate analysis employing linear regression, we assessed whether patients with vertebral metastases exhibited a shorter time to brain metastases. The analysis indicated no significant association, with a mean difference of 0.515 (95% confidence interval [CI], –0.491 to 1.522; $P = .313$). In addition, we explored the correlation between vertebral and leptomeningeal metastases; however, our investigation revealed no significant correlation ($P = .074$).

3.3. Prognostic factors for survival

As of the data cutoff date, the death toll was 122 (93.1%) patients. The median survival after brain metastasis was 8.0 (0.1–215.0) months, and 52 (39.7%) patients survived for >1 year (Fig. 1A). The interval between the diagnosis of breast cancer and the diagnosis of brain metastasis (more vs <1 year) did not significantly influence survival after metastasis to the brain (n = 105 vs 26, median survival = 5.7 vs 8.9 months, *P* value = .872). Multivariate survival analysis with Cox hazard model was conducted with the covariates of age at breast cancer diagnosis, ER status, PR status, HER2 status, TNBC, histological grade, ECOG performance status at brain metastasis diagnosis, symptoms from brain metastases, intrathecal chemotherapy, surgery for brain metastases, WBRT, γ-knife radiosurgery, trastuzumab therapy, chemotherapy after metastasis to the brain, number of brain parenchymal metastases, location of brain metastases, size of the most extensive metastasis to the brain, leptomeningeal seeding metastases, bone metastases, lung metastases, and vertebral metastases.

The histological grade of primary breast cancer was an independent prognostic factor in the results of the Cox hazard model for multivariate survival analysis (Table 3). A higher histological grade of primary breast cancer was associated with shorter survival after brain metastasis (Fig. 2B). We compared subsequent survival among the 3 breast cancer subtypes using Kaplan–Meier analysis. Although patients with ER-positive or PR-positive cancer had a more prolonged survival than patients with negative cancers in univariate analysis, multivariate analysis revealed that only TNBC was a statistically significant factor. The median survival time was 11.5 months (95% CI, 7.07–21.5) for the hormone receptor-positive group (n = 43), 13.1 months (95% CI, 9.97–29.5) for the HER2-positive group (n = 25), and 3.3 months (95% CI, 2.7–5.9) for the TNBC group (n = 47). A log-rank test revealed a significant difference in survival among these subtypes ($P < .0001$) (Fig. 1B). Patients with good performance (lower ECOG performance status) showed longer survivals after brain metastasis than patients with poor performance (Fig. 2C). The most

Table 2

Linear regression analysis of factors affecting time to brain metastasis in breast cancer patients.

	Univariate		Multivariate	
Variables	**Estimate (95% CI)**	***P* value**	**Estimate (95% CI)**	***P* value**
Age at breast cancer diagnosis	–0.043 (–0.088 to 0.003)	.067		
ER status	0.722 (–0.286 to 1.731)	.159	0.746 (–0.100 to 1.592)	.084
PR status	0.616 (–0.47 to 1.701)	.264		
HER2 status	–0.11 (–1.186 to 0.965)	.839		
Triple-negative breast cancer	–0.567 (–1.602 to 0.469)	.281		
Bilateral breast cancer	–1.442 (–3.398 to 0.514)	.147		
Stage at breast cancer diagnosis				
1	Reference	<.001	Reference	<.001
2	–2.224 (–3.907 to –0.541)	.010	–1.965 (–3.661 to –0.270)	.024
3	–2.814 (–4.454 to –1.175)	<.001	–2.530 (–4.188 to –0.871)	.003
4	–5.485 (–7.127 to –3.842)	<.001	–5.309 (–6.951 to –3.667)	<.001
Histological grade of primary breast lesion				
1	Reference	.017	Reference	
2	–2.492 (–4.861 to –0.123)	.037		
3	–3.253 (–5.634 to –0.872)	.008		
Vertebral metastases	0.515 (–0.491 to 1.522)	.313		
P value for Shapiro–Wilk test				.630
Adjusted R-squared				.334
Akaike information criterion				602.0626

ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor.

extensive metastatic brain lesion sizes did not affect survival after brain metastasis. The location of brain metastases was an independent prognostic factor (Table 3). Patients with metastases in both the supratentorial and infratentorial areas, including leptomeningeal seeding metastases, showed significantly shorter survival times than patients with either supratentorial or infratentorial metastases (Fig. 2D). In addition, leptomeningeal seeding metastases alone were a poor prognostic factor (median survival 2.8 vs 9.6 months, $P = .014$) (Fig. 2E). The survival time after brain metastasis did not significantly differ according to whether there were presenting symptoms at the time of brain metastases.

Regarding the treatments for brain metastases, local treatments like γ-knife radiosurgery or surgery seemed to be confer prolonged survival in univariate analysis (Table 3). However, Cox hazard model with multiple covariates revealed no significant influence on survival after brain metastases. Only systemic chemotherapy since metastasis to the brain was a good prognostic factor for survival (median survival 11.0 vs 3.3 months, $P < .001$). The patients who were given systemic chemotherapy showed significantly longer survival after brain metastases (Fig. 2F). We conducted subgroup analyses as well. Systemic chemotherapy after brain metastasis significantly led to the longer subsequent survival in Her2-positive cancer and TNBC. For local treatment, γ-knife therapy showed significantly better survival in both of these dismal subgroups and whole brain radiotherapy seemed effective only in Her2-positive subgroup (Fig. 3). To validate the Cox proportional hazards model presented in Table 3, we conducted a Schoenfeld residuals test for each covariate. None of the variables displayed significant deviations from the proportional hazards assumption (all $P > .05$). These findings support the use of our final multivariate model in predicting subsequent survival among breast cancer patients with brain metastases (Table S2, Supplemental Digital Content, http://links.lww.com/MD/O495). Harrell C-statistic was 0.761 (95% CI, 0.720–0.800), indicating moderate to good predictive performance.

4. Discussion

In this study, we aimed to investigate prognostic factors for survival in breast cancer patients with brain metastases. Several factors were identified as negative prognostic indicators in breast cancer patients with brain metastases. These included TNBC, high histological grade of the primary tumor, low-performance status, extensive brain metastasis location, and the presence of leptomeningeal metastases. Conversely, patients who received systemic chemotherapy after brain metastasis diagnosis exhibited a more favorable prognosis. While the prognosis for breast cancer patients with brain metastases remains poor, our findings suggest that active treatment may improve survival for specific patient groups. This includes patients with non-TNBC subtypes, those with limited brain metastases, and individuals with a good overall health status.

The average interval between breast cancer diagnosis and brain metastasis diagnosis was 27.0 months. Multivariate analysis revealed that the stage of breast cancer at diagnosis (with median survival time decreasing from stage 1 to stage 4) and ER status (positive test associated with increased survival time) were statistically significant factors influencing the time to brain metastases. These findings align with a study from China, which reported a higher risk of brain metastases in patients with TNBC with advanced cancer and bilateral breast cancer.[10] However, our study did not identify bilateral cancer as an independent risk factor, possibly due to the limited number of patients with TNBC with bilateral disease (only 2 out of 9). Notably, the higher the stage, the shorter the time to brain metastasis. For stage 1 and 4 patients, the time gap to brain metastasis was notably large at 97.2 months (ranging from 8 to 180 months) and 13 months (ranging from 0.0 to 110.0 months), respectively. This suggests that patients diagnosed with higher stages of breast cancer may benefit from more frequent brain metastasis screening, especially if they have other systemic metastases present.

While HER2-overexpression and TNBC are recognized risk factors for brain metastasis in breast cancer[11,12] and have been linked to poorer prognosis in breast cancer patients with brain metastases,[11,13] our study found TNBC, but not HER2-overexpression, to be an independent prognostic factor for survival following the appearance of brain metastases. Interestingly, patients with HER2-overexpressing breast cancer exhibited a longer median survival compared to those without overexpression (12.3 vs 5.9 months), although this difference did not reach statistical significance ($P = .100$).

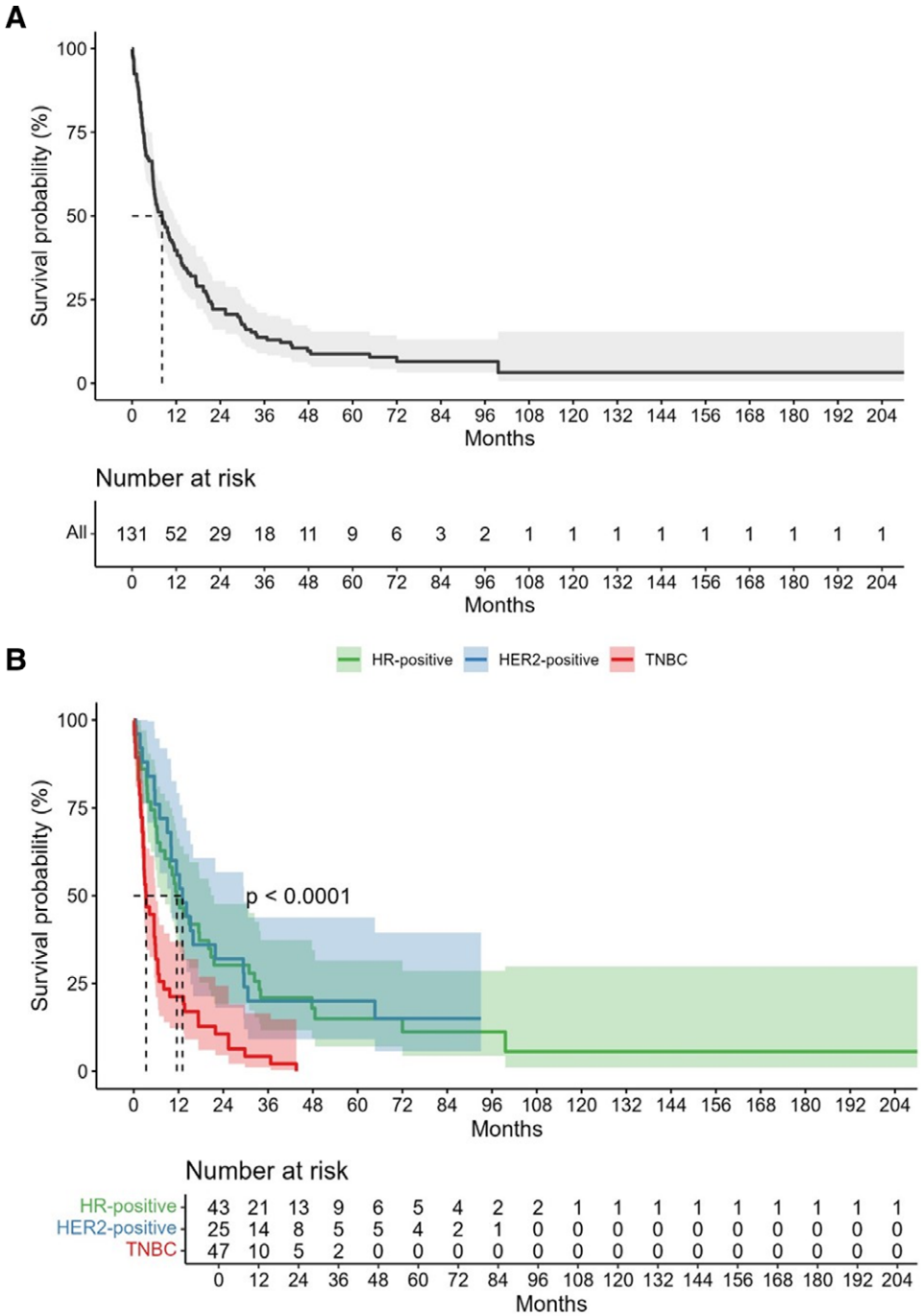

Figure 1. Overall survival after metastasis to the brain. (A) Whole population. (B) TNBC vs HER2-positive vs HR-positive. HER2=human epithelial growth factor receptor 2, HR=hormone receptor, TNBC=triple-negative breast cancer.

This observation might be attributed to the administration of HER2-targeting therapy. Despite concerns regarding the blood-brain barrier (BBB), both retrospective and prospective observational studies have indicated that systemic trastuzumab use is associated with prolonged survival in patients with brain metastases from HER2-overexpressing breast cancer.[14,15] Similarly, our study demonstrated a trend towards longer survival in patients with HER2-positive brain metastases who received trastuzumab treatment in univariate analysis (14.1 months vs 6.2 months, $P = .026$). Although this association was not statistically significant in the multivariate analysis, the median survival of Her2-positive patients appeared close to one of hormone receptor-positive subjects due to Her2-targeting therapies (Fig. 2A). In addition, TNBC was associated with significantly shorter survival after brain metastases compared to other breast cancer subtypes. Some of these differences may be attributed to TNBC having fewer effective systemic chemotherapy options. However, our study found that chemotherapy administered after brain metastasis diagnosis emerged as an independent prognostic factor, even for TNBC patients. This underscores the ongoing importance of developing improved systemic chemotherapy approaches. Researchers are actively exploring promising avenues, such as targeting molecules like TROP2 and developing methods to enhance drug delivery across the BBB using novel aptamers specifically for TNBC.[16,17]

Table 3

Cox proportional hazards model for subsequent survival in breast cancer patients with brain metastases.

	Univariate		Multivariate	
Variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Age at breast cancer diagnosis	1.005 (0.988–1.022)	.568		
ER status of primary breast lesion	0.640 (0.443–0.925)	.018		
PR status of primary breast lesion	0.621 (0.443–0.925)	.021		
HER2 status of primary breast lesion	0.723 (0.491–1.065)	.100		
Triple-negative breast cancer	2.461 (1.686–3.593)	<.001	2.320 (1.555–3.461)	<.001
ECOG performance status at brain metastasis diagnosis				
1	Reference	<.001	Reference	<.001
2	1.748 (1.138–2.688)	.011	1.485 (0.940–2.345)	.090
3	3.425 (2.079–5.650)	<.001	3.953 (2.335–6.692)	<.001
Neurologic symptoms at brain metastasis diagnosis	1.325 (0.810–2.167)	.263		
Histological grade of primary breast lesion				
1	Reference	<.001	Reference	<.001
2	1.359 (0.674–2.740)	.392	1.725 (0.844–3.528)	.135
3	2.299 (1.527–3.460)	<.001	2.833 (1.844–4.354)	<.001
Trastuzumab therapy	0.622 (0.407–0.950)	.028		
Bone metastases	1.527 (1.066–2.188)	.021		
Lung metastases	1.429 (0.993–2.056)	.054		
Vertebral metastases	1.205 (0.840–1.729)	.312		
Number of brain metastases				
0	Reference	.003		
1	0.387 (0.201–0.746)	.005		
≥2	0.743 (0.410–1.344)	.326		
Size of the most extensive lesion	0.992 (0.980–1.005)	.213		
Location of brain metastases				
Supratentorial	Reference	<.001	Reference	<.001
Infratentorial	1.359 (1.674–2.740)	.392	1.725 (0.844–3.528)	.135
Both	2.299 (1.527–3.460)	<.001	2.833 (1.844–4.354)	<.001
Leptomeningeal seeding	1.774 (1.114–2.826)	.016	1.692 (1.031–2.776)	.037
γ-Knife radiosurgery	0.530 (0.368–0.763)	.001		
WBRT	1.045 (0.724–1.508)	.814		
Surgery	0.434 (0.201–0.937)	.034		
Intrathecal chemotherapy	1.164 (0.566–2.392)	.679		
Systemic chemotherapy after brain metastases	0.364 (0.228–0.581)	<.001	0.332 (0.202–0.543)	<.001
C-index			0.761	
Akaike information criterion			912.588	

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, PR = progesterone receptor, WBRT = Whole brain radiation therapy.

Leptomeningeal disseminated metastases are known to have the poorest prognosis among central nervous system (CNS) metastases, and our study confirms this, even with a limited sample size (n = 23). The median survival time was only 2.8 months. Due to the limited number of patients who received intrathecal therapy, we were unable to conduct a separate subgroup analysis. Future larger studies are needed to evaluate the impact of intrathecal chemotherapy on survival. While standard treatment options for LM offer limited improvement, a recent study, a recent study reported a case demonstrating a sustained long-term drug response exceeding 2 years in a HER2-overexpressing cancer patient with leptomeningeal metastasis.[18] The treatment regimen included intravenous trastuzumab and pertuzumab combination therapy, intrathecal trastuzumab, and systemic trastuzumab-emtansine and trastuzumab-deruxtecan. The development of drugs like trastuzumab-deruxtecan, which can across the BBB, has shown promise in further improving the prognosis of patients with brain metastases.[19,20]

A recent retrospective study reported that bone metastasis is one of the poor prognostic factors for breast cancer patients with metastasis to the brain.[11] In this study, bone metastasis was not an independent prognostic factor in the multivariate analysis, although it showed a trend of poor prognosis in the univariate analysis. The vertebrae surround the spinal cord, which is part of the CNS, as well as the meninges, which envelop the CNS. We hypothesized that vertebral metastases might be associated with the spread of cancer to the CNS. However, our investigation revealed no correlation between vertebral metastases and the time to brain metastases or overall survival. Furthermore, while numerous reports suggest that breast cancer patients with brain metastases and no neurological symptoms have a favorable prognosis,[9,11,21] our study found that 16% of patients were asymptomatic, yet their prognosis was not notably favorable. At present, there are no definitive guidelines regarding the frequency of screening for brain metastases in breast cancer patients. Given the disparity between this study's findings and those of prior research and the authors' initial expectations, further large-scale investigations are warranted to inform the development of future screening guidelines.

In this study, the results of multivariate regression analysis revealed that local treatments such as γ-knife radiosurgery or WBRT did not exhibit a significant correlation with prolonged survival after brain metastasis. This contrasts with a German study focusing on 93 breast cancer patients who underwent surgery for brain metastases reported an average survival time of 16.0 months (ranging from 7.0 to 33.0), with poor prognosis noted for patients who developed brain metastases within 5 years after breast cancer diagnosis.[22] This survival time was relatively more prolonged than the average survival time of 8.0 months (ranging from 0.1 to 215.0) observed in our study, which included only 8 patients who underwent surgery for brain metastases. However, when examining the survival time exclusively for patients who underwent brain surgery, the median survival time significantly extended to 31 months (ranging from

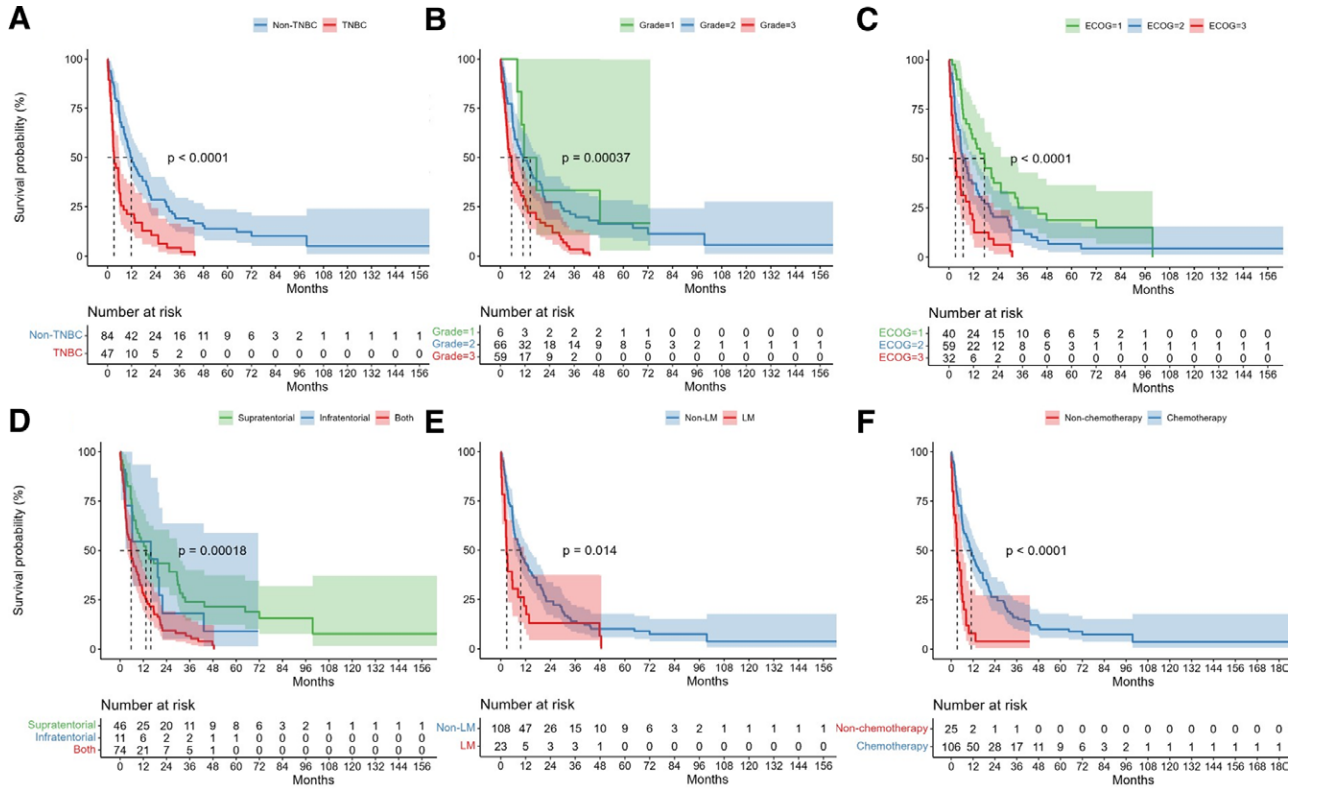

Figure 2. Survival after brain metastasis according to baseline characteristics. (A) TNBC versus non-TNBC. (B) Histological grade of primary breast cancer. (C) ECOG performance status. (D) Location of brain metastases. (E) Leptomeningeal seeding metastases. (F) Systemic chemotherapy after brain metastases. ECOG=Eastern Cooperative Oncology Group, TNBC=triple-negative breast cancer.

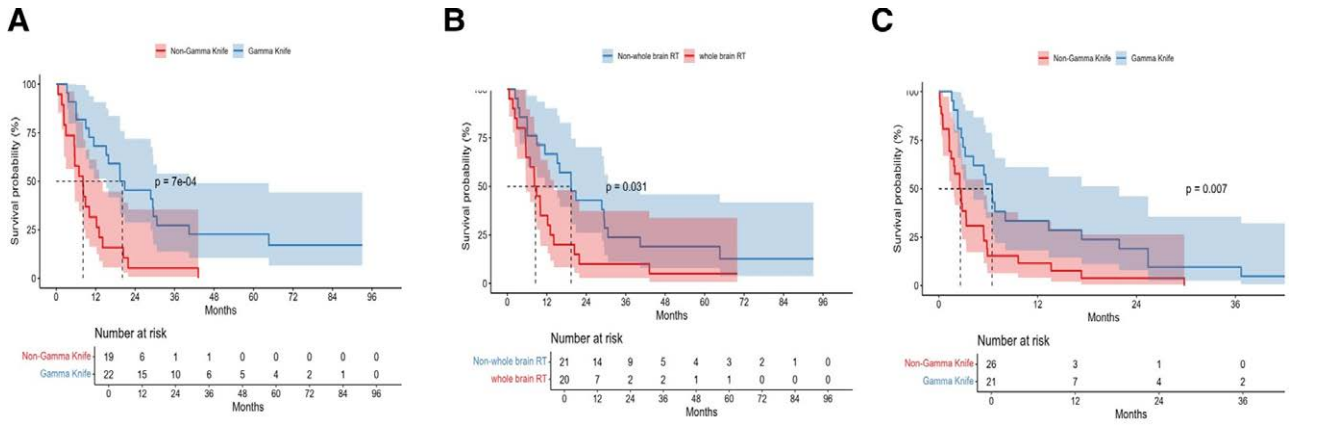

Figure 3. Survival after brain metastasis in subgroups. (A) HER2-positive cancers with and without gamma knife therapy. (B) HER2-positive cancers with and without whole brain radiation therapy. (C) TNBC with and without γ-knife therapy. HER2=human epithelial growth factor receptor 2, TNBC=triple-negative breast cancer.

15.2 to 215.0) (P = .02). Nonetheless, this finding did not attain significance in multivariate regression analysis due to the small sample size. Brain surgery itself can serve as a favorable prognostic factor; the ability to tolerate surgery might also indicate better overall health. Similarly, patients who underwent γ-knife radiosurgery exhibited prolonged survival in univariate analysis, aligning with research highlighting its low toxicity and effectiveness in palliating breast cancer brain metastases.[2,3,24] Although the overall population showed no survival benefit with local treatment, Her2-positive cancer and TNBC subgroups with γ-knife therapy showed better subsequent survival in this study. Consequently, these results emphasize the importance of considering aggressive local treatments whenever feasible for patients with breast cancer brain metastases.

As a result of the Schoenfeld residual test, which is a test of the proportional hazards assumption for the Cox model, our model satisfied the proportional hazards assumption. We provide the result of test for proportional hazard in Table S1, Supplemental Digital Content, http://links.lww.com/MD/O497. To compare the performance and accuracy of the Cox model, Harrell C-statistic and Akaike information criterion were also provided in Table 3. We have evaluated the clinical utility of our prognostic model, noting that a Harrell C-statistic ranging from 0.70 to 0.80 generally indicates moderate to good predictive performance. Such risk stratification can be highly valuable for guiding patient counseling and tailoring treatment decisions in clinical practice. We additionally conducted χ^2 test including Fisher exact test to investigate the

interaction between the ECOG performance status and other factors like type of treatment after brain metastasis or location of brain metastases (Table S2, Supplemental Digital Content, http://links.lww.com/MD/O495). γ-knife radiosurgery significantly was given to patients who had better performance status. γ-knife therapy showed better survival in HER2-positive cancer and TNBC (Fig. 3) and this suggest the better performance could influence the local treatment strategy and subsequent survival.

The primary limitation of this study stems from its retrospective, single-center design, which unavoidably introduces selection and recall biases. In addition, the relatively small sample size restricts the generalizability of the findings and the statistical power of the analyses. Furthermore, due to clinical data collection over an extended period (from 2010 to 2022), instances of missing data are inevitable. Although we considered employing propensity score matching to reduce selection bias, our sample size was insufficient for a robust propensity score matching analysis. Future research with larger cohorts should incorporate propensity score matching or other advanced methods to further minimize selection bias. Moreover, owing to the wide variety of regimens and the relatively small sample for each subtype, a meaningful subgroup analysis—such as platinum-based versus nonplatinum regimens—was not feasible. Future prospective studies should focus on more uniform treatment cohorts to clarify the impact of different chemotherapy regimens on TNBC outcomes. Finally, given the evolving nature of clinical guidelines and the introduction of new medications during the study period, diagnostic criteria, treatment modalities, and patient management strategies may have potentially influenced study outcomes.

In conclusion, we analyzed a decade-long cohort of breast cancer patients with brain metastases from a single institution. While the overall prognosis for breast cancer patients with brain metastases remains challenging, our findings suggest potential benefits from aggressive treatment in specific patient groups. This includes individuals with non-TNBC subtypes, those with limited brain metastases, and patients in good overall health. Further studies with more extensive and diverse patient populations are needed to confirm these findings and explore treatment options for specific breast cancer subpopulations.

Author contributions

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