Original Study

$ER^+/HER2^+$ Breast Cancer Has Different Metastatic Patterns and Better Survival Than $ER^-/HER2^+$ Breast Cancer

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Abstract

This study examined the metastatic pattern and prognosis of both estrogen receptor-positive (ER^+)/human epidermal growth factor receptor 2-positive ($HER2^+$) and estrogen receptor-negative (ER^-)/$HER2^+$ breast cancer. A total of 54,147 patients with $HER2^+$ breast cancer from the National Cancer Database and 31,946 patients with $HER2^+$ breast cancer from the Surveillance, Epidemiology, and End Results database were examined. We found that patients with $ER^+/HER2^+$ and $ER^-/HER2^+$ breast cancers had different metastatic patterns, and $ER^-/HER2^+$ patients had worse prognosis.

Background: Human epidermal growth factor receptor 2–positive ($HER2^+$) breast cancer is generally treated with HER2-targeted therapy combined with chemotherapy. Patients with $HER2^+$ and estrogen receptor–positive (ER^+) cancer are additionally treated with long-term hormone therapy. This study examined the metastatic pattern and prognosis of both $ER^+/HER2^+$ and $ER^-/HER2^+$ breast cancer. **Patients and Methods:** A total of 54,147 patients with $HER2^+$ breast cancer from the National Cancer Data Base (NCDB, 2010-2013) and 31,946 patients with $HER2^+$ breast cancer from the Surveillance, Epidemiology, and End Results Program (SEER, 2010-2014) were examined. Sites of metastasis and overall survival (OS) were examined in the NCDB, while OS and breast cancer–specific survival were examined in the SEER database. **Results:** Compared to $ER^-/HER2^+$ breast cancer, $ER^+/HER2^+$ breast cancer was more likely to metastasize to bone but less likely to brain, liver, and lung and less likely to result in multiple metastases. In univariate analysis based on the NCDB, patients with $ER^-/HER2^+$ breast cancer had worse OS in all metastasis subsets, including patients who received HER2-targeted therapy. This poor survival for $ER^-/HER2^+$ persisted in patients with metastasis to bone and lung, and multiple metastases. In multivariate analysis adjusting for age, tumor grade, surgery, chemotherapy, HER2-targeted therapy, and hormone therapy, $ER^-/HER2^+$ patients with bone metastasis still had worse OS. In the SEER, $ER^-/HER2^+$ patients had both worse OS and breast cancer–specific survival in univariate analysis. **Conclusion:** This large study showed patients with $ER^+/HER2^+$ and $ER^-/HER2^+$ breast cancers had different metastatic patterns. Patients with $ER^-/HER2^+$ breast cancer may require more aggressive treatment.

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Introduction

Breast cancer is the most common cancer in women worldwide, with almost 2 million new breast cancer diagnoses each year.[1] In the United States, there were an estimated 268,670 cases of invasive cancer in 2018, 6% of which presented as stage IV disease.[2] Survival for patients with metastatic breast cancer has steadily improved over the last several decades.[3,4] Ruiterkamp et al[4] noted median overall survival (OS) for de novo stage IV breast cancer increased from 1.42

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Table 1 Characteristics of HER2$^+$ Breast Cancer Patients From NCDB Diagnosed From 2010 to 2013 and SEER Diagnosed From 2010 to 2014

Characteristic	NCDB (N = 54,147)	SEER (N = 31,946)
Age at Diagnosis		
< 50 years	14,796 (27.33)	9,548 (29.89)
≥ 50 years	39,351 (72.67)	22,398 (70.11)
ER		
Positive	37,922 (70.04)	21,722 (68.00)
Negative	16,225 (29.96)	10,224 (32.00)
PR		
Positive	29,276 (54.07)	16,435 (51.45)
Negative	24,730 (45.67)	15,401 (48.21)
Unknown	141 (0.26)	110 (0.35)
Stage		
I	25,248 (0.47)	11,852 (0.37)
II	19,295 (0.36)	12,156 (0.38)
III	7,718 (0.14)	5,416 (0.17)
IV	1,886 (0.03)	2,522 (0.08)
Tumor Grade		
1	3,034 (5.60)	1,588 (4.97)
2	20,104 (37.13)	11,360 (35.56)
3	31,009 (57.27)	18,998 (59.47)
Surgery		
Yes	53,250 (98.34)	29,167 (91.30)
No	897 (1.66)	2,779 (8.70)
Chemotherapy		
Yes	44,944 (83.00)	23,605 (73.89)[a]
No	9,203 (17.00)	8,341 (26.11)[a]
Unknown	—	
HER2-Targeted Therapy		
Yes	9,916 (18.31)	—
No	44,231 (81.69)	—
Hormone Therapy		
Yes	34,576 (63.86)	—
No	19,571 (36.14)	—
Radiotherapy		
Yes	32,179 (59.43)	14,505 (45.40)[a]
No	21,706 (40.09)	17,441 (54.60)[a]
Unknown	262 (0.48)	

Data are presented as n (%). Dash indicates no data available.
Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NCDB = National Cancer Data Base; PR = progesterone receptor; SEER = Surveillance, Epidemiology, and End Results.
[a]Number of patients who received chemotherapy or radiotherapy from SEER might be inaccurate mainly because treatment information might be missing by registry if received outside of hospital setting. No/unknown chemotherapy was one category in SEER database.

years (1995-1999) to 1.95 years (2005-2008). Patient outcomes and length of survival are dependent on many factors, including receptor status and site of metastasis.[5-9] It is often the heterogenous nature of breast cancer that causes tailoring of treatment for these patients to be a challenge for clinicians.[10,11]

Table 2 Characteristics of ER$^+$/HER2$^+$ and ER$^-$/HER2$^+$ Breast Cancer Patients in NCDB

Characteristic	ER$^+$/HER2$^+$ (N = 37,922)	ER$^-$/HER2$^+$ (N = 16,225)
Age at Diagnosis		
< 50 years	10,853 (28.62)	3,943 (24.30)
≥ 50 years	27,069 (71.38)	12,282 (75.70)
PR		
Positive	28,372 (74.82)	904 (5.57)
Negative	9,431 (24.87)	15,299 (94.29)
Unknown	119 (0.31)	22 (0.14)
Stage		
I	18,130 (0.48)	7,118 (0.44)
II	13,584 (0.36)	5,711 (0.35)
III	5,037 (0.13)	2,681 (0.17)
IV	1,171 (0.03)	715 (0.04)
Tumor Grade		
1	2,762 (7.28)	272 (1.68)
2	16,342 (43.09)	3,762 (23.19)
3	18,818 (49.62)	12,191 (75.14)
Surgery		
Yes	37,383 (98.58)	15,867 (97.79)
No	539 (1.42)	358 (2.21)
Chemotherapy		
Yes	30,865 (81.39)	14,079 (86.77)
No	7,057 (18.61)	2,146 (13.23)
HER2-Targeted Therapy		
Yes	7,023 (18.52)	2,893 (17.83)
No	30,899 (81.84)	13,332 (82.17)
Hormone Therapy		
Yes	33,202 (87.55)	1,374 (8.47)
No	4,720 (12.45)	14,851 (91.53)
Radiotherapy		
Yes	23,270 (61.36)	8,909 (54.91)
No	14,500 (38.24)	7,206 (44.41)
Unknown	152 (0.40)	110 (0.68)

Data are presented as n (%).
Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NCDB = National Cancer Data Base; PR = progesterone receptor.

Targeted therapy for breast cancer, especially metastatic disease, has been utilized for over 100 years. Endocrine therapy for metastatic breast cancer is one of the oldest effective therapies, with Beatson[12] noting the benefits of oophorectomy in the 1800s. Work by various researchers on tamoxifen and the estrogen receptor (ER) in the 1960s led to the institution of targeted therapy in the 1970s.[13] The Early Breast Cancer Trialists' Collaborative Group results solidified support for targeted therapy for hormone receptor positive breast cancer.[14]

Further targeted therapy was developed after the discovery of human epidermal growth factor receptor 2 (HER2) as a potential target in breast cancer.[15] Early studies by Slamon et al[16] examined the effect of trastuzumab added to chemotherapy in the metastatic

Table 3 Distribution of Metastatic Sites in ER+/HER2+ and ER−/HER2+ Breast Cancers in NCDB

Subtype	Single Metastasis				Multiple Metastases	No Metastasis
	Bone	Brain	Liver	Lung		
ER+/HER2+ (n = 26,296)	552 (1.46)	16 (0.04)	188 (0.50)	119 (0.31)	360 (0.95)	36,687 (96.74)
ER−/HER2+ (n = 13,171)	139 (0.86)	19 (0.12)	202 (1.24)	133 (0.82)	240 (1.48)	15,492 (95.48)

Data are presented as n (%).
Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NCDB = National Cancer Data Base.
$P < .0001$ (chi-square test).

setting and noted a longer time to disease progression and an increase in median OS in patients with HER2+ breast cancer by 5 months. In the Cleopatra trial, the addition of another HER2-targeted agent, pertuzumab, to trastuzumab and docetaxel improved median OS to 56.5 months, versus 40.8 months with trastuzumab and docetaxel alone.[17] More recent studies examined T-DM1 (trastuzumab emtansine), with improvements in median OS of 25% to 32% in previously treated patients with metastatic HER2+ breast cancer.

Survival has improved based in part on the emergence of these targeted therapies. Interestingly, relatively little is known about the relationship between hormone receptor (HR) and HER2 status in terms of survival and sites of metastasis in metastatic breast cancer. This study attempted to better define that relationship.

Patients and Methods

Patient Information

We searched breast cancer patients in the American College of Surgeon and American Cancer Society's National Cancer Data Base (NCDB) and in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. SEER collects cancer data from cancer registries covering approximately 34.6% of the US population (https://seer.cancer.gov/about/overview.html). The total number of breast cancer patients was 420,520 in NCDB and 300,451 in SEER from 2010 to 2013. We identified 54,147 HER2+ breast cancer patients diagnosed from 2010 to 2013 in the NCDB; the follow-up time was up to 71.72 months (median, 36.99 months). We identified 31,946 HER2+ breast cancer patients diagnosed from 2010 to 2014 in the SEER database; the follow-up time was up to 59 months (median, 24 months). All metastatic disease information in the NCDB and SEER data was collected at the time point of diagnosis.

In the NCDB, we collected the following patient information: age at diagnosis, status of ER and progesterone receptor (PR), clinical stage, tumor grade, site of metastasis, OS, and treatment information including surgery, chemotherapy, hormone therapy, HER2-targeted therapy, and radiotherapy. In the SEER database, we collected age, status of ER and PR, stage, tumor grade, surgery, chemotherapy, radiotherapy, OS, and breast cancer–specific survival (BCSS). Hormone therapy and HER2-targested therapy information was not available in the SEER database.

Because the SEER database did not have information on hormone therapy and HER2-targeted therapy, we focused survival analysis on the NCDB and used the SEER database for a validation analysis.

Statistical Analysis

Demographic and clinicopathologic characteristics of HER2+ patients, including patient age, ER and PR status, stage, tumor grade, surgery, systemic therapies (chemotherapy, HER2-targeted

Table 4 Univariate and Multivariate Analysis Comparing Overall Survival of ER+/HER2+ Versus ER−/HER2+ Patients With Different Metastatic Disease in NCDB

Characteristic	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
All patients	0.57 (0.53-0.60)	< .0001*	1.00 (0.91-1.09)	.96
Patients received HER2-targeted therapy	0.41 (0.33-0.51)	< .0001*	0.97 (0.68-1.39)	.88
Metastatic Site				
No metastasis	0.58 (0.54-0.62)	< .0001*	1.01 (0.91-1.12)	.88
Bone	0.51 (0.38-0.69)	< .0001*	0.54 (0.37-0.79)	.0015*
Brain[a]	0.45 (0.17-1.18)	.10	0.40 (0.07-2.38)	.31
Liver	0.82 (0.58-1.17)	.27	1.41 (0.91-2.18)	.12
Lung	0.67 (0.44-1.00)	.049*	1.33 (0.79-2.24)	.29
Multiple	0.69 (0.56-0.86)	.0011*	0.95 (0.73-1.24)	.36

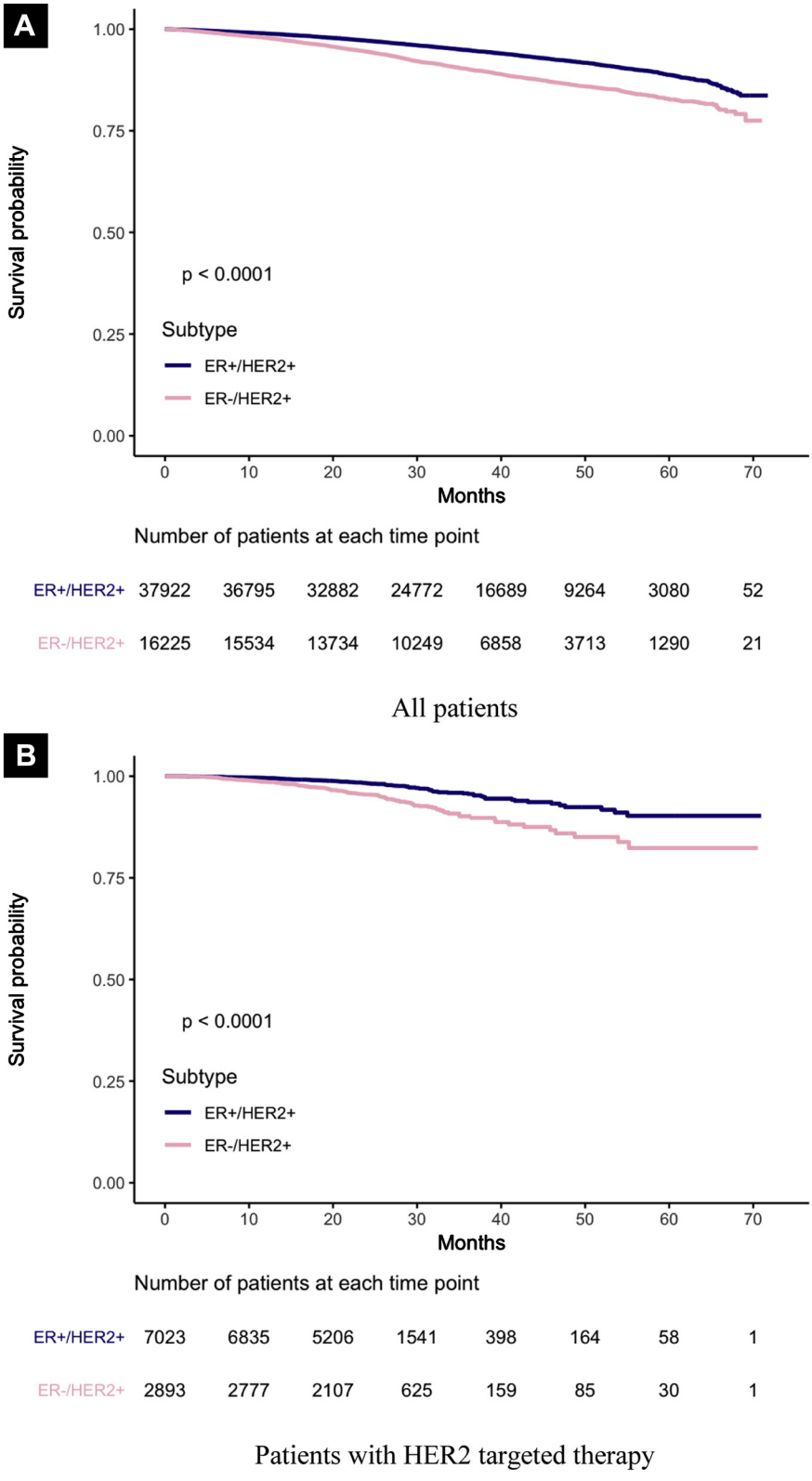
Multivariate analysis was adjusted for age, stage, tumor grade, surgery, chemotherapy, HER2-targeted therapy, and hormone therapy.
Abbreviations: CI = confidence interval; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; NCDB = National Cancer Data Base.
[a]Only 35 patients had brain metastases, including 16 ER+/HER2+ patients and 19 ER−/HER2+ patients.
*Statistically significant ($P < .05$).

Table 5 Survival Probabilities at Each Time Point in NCDB

Characteristic	Subtype	Time (Months)							Median Survival (Months)
		10	20	30	40	50	60	70	
Overall	$ER^+/HER2^+$	0.992	0.978	0.960	0.940	0.917	0.888	0.837	—
	$ER^-/HER2^+$	0.983	0.957	0.921	0.889	0.859	0.827	0.775	—
Patients received HER2-targeted therapy	$ER^+/HER2^+$	0.997	0.988	0.971	0.944	0.924	0.902	—	—
	$ER^-/HER2^+$	0.990	0.966	0.928	0.887	0.850	0.823	—	—
Metastatic Site									
No metastasis	$ER^+/HER2^+$	0.994	0.984	0.968	0.950	0.929	0.902	0.855	—
	$ER^-/HER2^+$	0.988	0.967	0.936	0.907	0.881	0.852	0.798	—
Bone	$ER^+/HER2^+$	0.956	0.895	0.823	0.756	0.664	0.589	0.515	—
	$ER^-/HER2^+$	0.891	0.748	0.667	0.527	0.505	0.415	0.415	49.12
Brain	$ER^+/HER2^+$	0.933	0.862	0.689	0.689	0.473	0.473	—	46.23
	$ER^-/HER2^+$	0.789	0.632	0.386	0.386	0.289	0.000	—	27.33
Liver	$ER^+/HER2^+$	0.904	0.812	0.761	0.701	0.639	0.598	—	64.66
	$ER^-/HER2^+$	0.924	0.844	0.746	0.644	0.499	0.459	—	49.81
Lung	$ER^+/HER2^+$	0.966	0.840	0.735	0.666	0.644	0.423	—	55.43
	$ER^-/HER2^+$	0.924	0.791	0.636	0.516	0.456	0.258	—	41.36
Multiple	$ER^+/HER2^+$	0.839	0.713	0.583	0.507	0.428	0.314	—	40.64
	$ER^-/HER2^+$	0.781	0.625	0.462	0.374	0.231	0.173	—	28.06

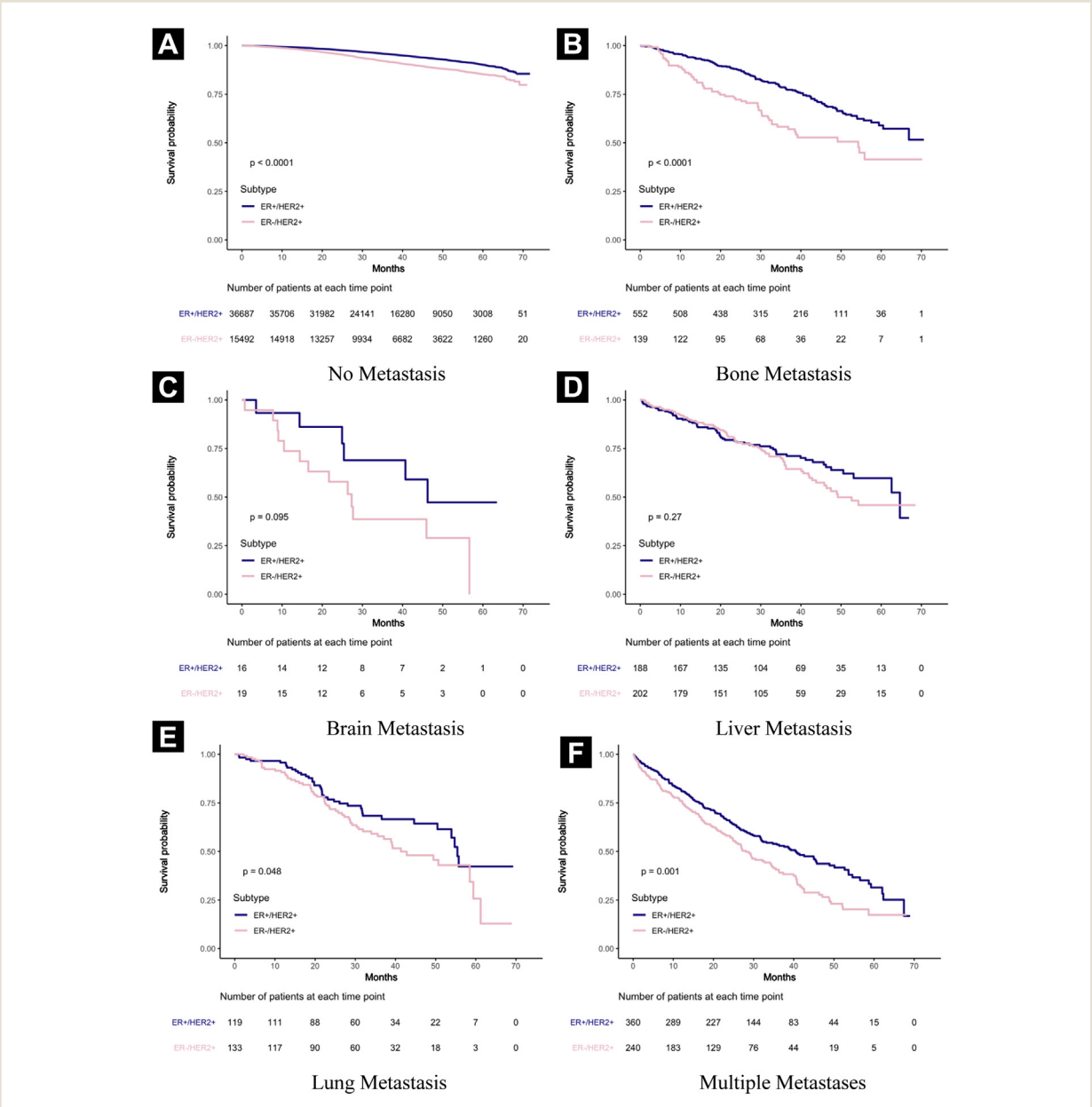
Dash indicates no data available.
Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NCDB = National Cancer Data Base.

Figure 1 Kaplan-Meier Curves of OS. (A) OS of All ER+/HER2+ and ER−/HER2+ Patients in NCDB Regardless of Metastatic Status. (B) OS of Patients Who Received HER2-targeted Therapy



Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NCDB = National Cancer Data Base; OS = overall survival.

Figure 2 Kaplan-Meier Curves of OS by Site of Metastasis. OS Comparing $ER^+/HER2^+$ and $ER^-/HER2^+$ Cancer Patients With No Metastasis (A), Bone Metastasis (B), Brain Metastasis (C), Liver Metastasis (D), Lung Metastasis (E), and Multiple Metastases (F) in NCDB



Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NCDB = National Cancer Data Base; OS = overall survival.

therapy, or immunotherapy), radiotherapy, and metastatic site were summarized by absolute and relative frequencies. Age was categorized as < 50 or ≥ 50 years. Three PR status groups (positive, negative, unknown) were considered. For tumor grade, the undifferentiated and anaplastic tumor groups were considered to be grade 3. Differences between breast cancer subtypes ($ER^+/HER2^+$, $ER^-/HER2^+$) with regard to metastatic sites (bone, brain, liver, lung, multiple, or no metastasis) were evaluated by a chi-square test.

Kaplan-Meier survival curves were used to estimate the OS stratified by metastatic site and the BCSS for patients with $ER^+/HER2^+$ and $ER^-/HER2^+$ cancers. Log-rank tests and univariate Cox proportional hazards model were performed to assess the difference in OS and BCSS between $ER^+/HER2^+$ and $ER^-/HER2^+$ subtypes in all patients and in patients with different metastatic sites. We performed multivariate Cox regression analyses to estimate the effects of subtypes on OS while adjusting for other prognostic factors including age, stage, tumor grade, surgery, and systemic

Table 6 Survival Probabilities at Each Time Point in SEER Database

Survival	Subtype	Time (Months)				
		10	20	30	40	50
OS	ER+/HER2+	0.975	0.955	0.927	0.901	0.874
	ER−/HER2+	0.958	0.923	0.881	0.846	0.811
BCSS	ER+/HER2+	0.982	0.969	0.949	0.931	0.914
	ER−/HER2+	0.966	0.938	0.903	0.876	0.849

Abbreviations: BCSS = breast cancer–specific survival; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; OS = overall survival; SEER = Surveillance, Epidemiology, and End Results.

therapies. Results were regarded as statistically significant at $P < .05$. All analyses were performed based on available cases and were performed by SAS 9.4 software (SAS Institute, Cary, NC).

Results

Patient Demographic and Clinical Information

Table 1 summarizes the demographic and clinicopathologic characteristics of the patients in both NCDB and SEER. The patient distribution in age, ER and PR status, and tumor grade was similar in NCDB and SEER. ER positivity was 70.04% in NCDB and 68.00% in SEER. A small number of cancers were grade 1 (5.60% in NCDB and 4.97% in SEER). The majority of patients received both surgery and chemotherapy.

The clinicopathologic characteristics of patient with ER+/HER2+ and ER−/HER2+ breast cancer in NCDB was summarized in Table 2. As expected, ER+/HER2− cancers had more PR positivity (74.82% vs. 5.57% in ER−/HER2+) and were more likely to be grade 1 tumor (7.28% vs. 1.68%); 87.55% of patients with ER+/HER2+ cancers received hormone therapy. The patient distribution regarding age and receipt of chemotherapy and HER2-targeted therapy was similar between ER+/HER2+ and ER−/HER2+ cancers.

ER+/HER2+ and ER−/HER2+ Breast Cancers Have Different Metastatic Patterns

Analysis of NCDB data showed that compared to ER−/HER2+ breast cancers, ER+/HER2− breast cancers were more likely to metastasize to bone and are less likely metastasize to brain, liver, and lung, and are less likely to manifest as multiple metastases (Table 3). The different metastatic pattern between ER+/HER2+ and ER−/HER2+ cancers was significant ($P < .0001$). The most frequent metastatic site was bone in ER+/HER2− cancer and liver in ER−/HER2+ cancer (Table 3).

Table 7 Univariate Analysis of Survival Comparing ER+/HER2+ Versus ER−/HER2+ Patients in SEER Database

Survival	HR	95% CI	*P*
OS	0.62	0.57-0.67	< .0001*
BCSS	0.53	0.49-0.58	< .0001*

Abbreviations: BCSS = breast cancer–specific survival; CI = confidence interval; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; OS = overall survival; SEER = Surveillance, Epidemiology, and End Results.
*Statistically significant ($P < .05$).

Patients with ER−/HER2+ breast cancers with single bone metastasis had worse survival than patients with ER+/HER2+ breast cancer with single bone metastasis in both univariate and multivariate analysis in NCDB. Univariate analysis showed patients with ER−/HER2+ breast cancer had worse OS than ER+/HER2+ cancer patients in all, and notably in patients who received HER2-targeted therapy (Tables 4 and 5; Figure 1). When stratified by metastasis status, univariate analysis showed that patients with ER−/HER2+ breast cancer had worse OS in all categories except for patients with brain or liver metastasis (Table 5; Figure 2). The number of patients with brain metastasis was small (16 ER+/HER2+, 19 ER−/HER2+), which may result in a lower power to detect the difference. In multivariate analysis adjusting for age, stage, tumor grade, surgery, chemotherapy, HER2-targeted therapy, and hormone therapy, patients with ER−/HER2+ cancer had worse OS in patients with bone metastasis ($P = .0015$; Tables 4 and 5).

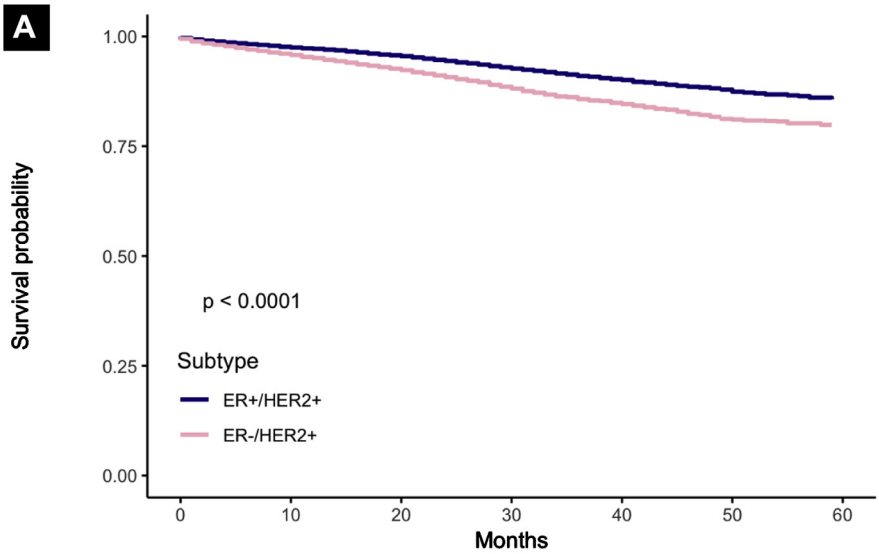
Patients with ER−/HER2+ breast cancer had worse OS and BCSS in the SEER database. Because hormone and HER2-targeted therapy information was not available in SEER, we used univariate analysis to compare OS and BCSS. Similar to the results from the NCDB, univariate analysis showed patients with ER−/HER2+ breast cancer had worse OS and BCSS than patients with ER+/HER2+ breast cancer in SEER (Tables 6 and 7; Figure 3).

Discussion

The outcomes of breast cancer patients with metastatic disease is known to vary on the basis of the receptor status of the tumor. The analysis of HER2+ metastatic breast cancer has often been a combined analysis, with disregard for the ER status of the disease.[18,19] This detailed analysis of data from NCDB and SEER clearly defines the role of ER status in HER2+ breast cancer in terms of site of distant metastasis, OS, and BCSS.

The site of metastasis in breast cancer often contributes to the patient's OS. Patients with bone metastasis from their breast cancer often have a notably increased survival over patients with visceral or brain metastasis.[20] In this analysis, ER+/HER2+ patients were noted to have a higher rate of bone metastasis than ER−/HER2+ patients. Conversely, patients with ER−/HER2+ cancer had significantly more liver metastasis as well as higher rates of metastasis to brain and lung, as well as higher rates of multiple metastases, than patients with ER+/HER2+ cancer. These results are consistent with the findings of many other researchers. Patient with ER−/HER2+ cancer have often been noted to have more visceral metastases as well as metastasis at an earlier time period than comparable patients with ER+/HER2+ cancer.[5,21-26] In several studies examining the

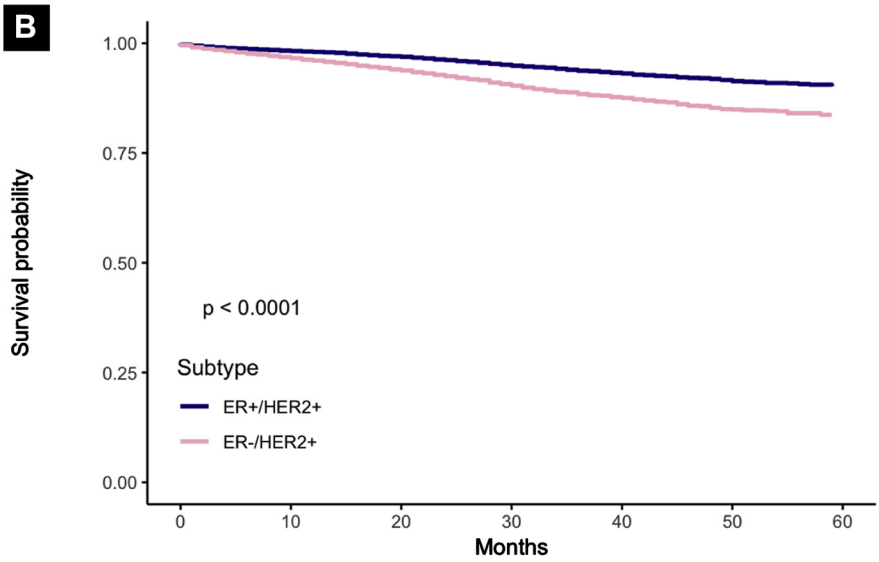
Figure 3 Kaplan-Meier Curves of OS in SEER Database. (A) OS and (B) Breast Cancer–specific Survival (B) Comparing $ER^+/HER2^+$ and $ER^-/HER2^+$ Patients in SEER Database



Number of patients at each time point

ER+/HER2+	21722	16736	12716	9073	5683	2629	0
ER-/HER2+	10224	7802	5920	4140	2567	1194	0

Overall Survival



Number of patients at each time point

ER+/HER2+	21722	16736	12716	9073	5683	2629	0
ER-/HER2+	10224	7802	5920	4140	2567	1194	0

Breast Cancer-Specific Survival

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth actor receptor 2; OS = overall survival; SEER = Surveillance, Epidemiology, and End Results.

SEER database, although both subtypes had higher rates of bone metastases than to other sites, patients with ER+/HER2+ cancer had higher rates of bone metastasis compared to patients with ER−/HER2+ cancer.[22,25] A recent examination of SEER, although examining only patients presenting with metastatic disease, noted higher rates of bone metastasis in HR+/HER2+ breast cancer compared to either HR−/HER2+ or triple-negative breast cancers.[27] Garcia Fernandez et al[24] noted similar findings, although in a smaller cohort. In a study comparing ER+/HER2+ versus ER−/HER2+ cancer, Smid et al[23] also found higher rates of bone metastasis in the ER+ subgroup.

The site of metastasis is often linked to OS in breast cancer, with bone being more favorable than brain or visceral locations.[20] In this large study of SEER and NCDB, ER−/HER2+ patients with bone metastasis had significantly poorer OS than similar ER+/HER2+ breast cancer patients with bone metastasis. Thus, metastasis to the same location confers a different rate of survival based on the receptor subtype of the breast cancer. Interestingly, the significant difference in survival based on site of metastasis and tumor receptor subtype was not replicated in any other sites, with statistically equivalent survival for ER−/HER2+ and ER+/HER2+ patients with brain, liver, and lung metastases as well as multiple metastases. Kast et al[21] described the improved survival for patients with bone metastasis compared to visceral or brain metastases. Thus, clinicians may need to differentiate HER2+ patients with bone metastasis on the basis of hormone receptor status in terms of aggressiveness of systemic therapy.

This modern analysis of information in NCDB and SEER supports the notion that patients with ER+/HER2+ breast cancer have better BCSS and OS; interestingly, this survival advantage was not affected by the receipt (or lack thereof) of HER2-targeted therapy. The finding of improved survival for ER+/HER2+ patients over ER−/HER2+ patients is consistent with previously published reports.[3,21,24,28,29] In an examination of metastasis, survival, and receptor subtype, Molnar et al[28] noted similar findings with ER+/HER2+ patients displaying improved OS versus ER−/HER2+, regardless of the receipt of HER2-targeted therapy. Similarly, Lobbezoo et al[30] described improved OS in ER+/HER2+ patients and found receptor status to be an independent prognostic factor for patients with metastatic breast cancer. Sanpaolo et al[31] examined luminal B (ER+/PR+/HER2+) and HER2+ (ER−/PR−) patients and noted significantly improved BCSS and OS for the luminal B subset. They further noted that luminal A patients had improved BCSS and OS compared to the luminal B and HER2+ patients, which may indicate a poorer response to endocrine therapy for the luminal B subset.

This improved survival is likely due in part to the preferential bone metastasis in the ER+/HER2+ receptor subgroup. There is also a role for the relationship between hormone receptors and HER2 receptors, and a differential response to therapy. Specifically, there is evidence of cross-talk between the ER and HER2 pathways that can lead to impaired response to endocrine therapy and possible modification of the tumor's response to HER2-targeted therapy. In both clinical and laboratory studies, this cross-talk has been noted to decrease tamoxifen's effectiveness.[32-34] More recently, studies examining the response of HER2+ tumors to neoadjuvant HER2+-targeted therapy have noted decreased complete responses in ER+/HER2+ as opposed to ER−/HER2+ patients.[35,36]

There were limitations to this study. Specifically, although rigorously examined for accuracy, the NCDB and SEER databases still suffer from issues with data entry and completeness of the treatment record. Of note, although the data were collected on a modern cohort of patients treated from 2010 to 2013, the NCDB noted that only 18% of HER2+ patients were treated with HER2-targeted therapy. This would be expected to be an error in recording. On the basis of a recent examination of the National Comprehensive Cancer Network Breast Cancer Outcomes Database, 83% of HER2+ women received HER2-targeted therapy with trastuzumab.[37] Thus, it is likely that the majority of this patient population did indeed receive HER2-targeted therapy at one point in the management of their breast cancer. Another limitation may be the relatively short follow-up time for the patients included. Unfortunately, NCDB and SEER did not record the HER2 status until 2010; thus, this examination provides the longest possible follow-up for these data sets. Although longer follow-up may reveal more metastases in the ER+ subgroup, it would not likely alter the preferential metastasis to bone for these tumors, or their better BCSS and OS.

This large study shows ER+/HER2+ and ER−/HER2+ breast cancers have different metastatic patterns. ER+/HER2+ breast cancer patients can be treated with targeted agents against both ER and HER2 receptors, and thus have improved survival compared to ER−/HER2+ patients. Meanwhile, ER−/HER2+ cancer patients, with their relatively worse prognosis in comparison to ER+/HER2+ breast cancer, may require a more aggressive approach, even when presenting with oligometastatic bone metastasis.

Clinical Practice Points

- Relatively little is known about the relationship between ER and HER2 status in terms of survival and sites of metastasis in breast cancer.
- This study examined the metastatic pattern and prognosis of both ER+/HER2+ and ER−/HER2+ breast cancer with 54,147 patients with HER2+ breast cancer from the NCDB (2010-2013) and 31,946 patients with HER2+ breast cancer from the SEER program (2010-2014).
- This large study showed that patients with ER+/HER2+ and ER−/HER2+ breast cancers had different metastatic patterns and patients with ER− /HER2+ breast cancer had worse prognosis.
- Patients with ER−/HER2+ breast cancer may require more aggressive treatment.

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Disclosure

The authors have stated that they have no conflict of interest.

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