International Journal of Clinical Oncology (2022) 27:332–339
https://doi.org/10.1007/s10147-021-02049-w

ORIGINAL ARTICLE

HER2-low breast cancer could be associated with an increased risk of brain metastasis

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Received: 16 July 2021 / Accepted: 3 October 2021 / Published online: 18 October 2021

Abstract

Purpose The HER2-low breast cancer is a newly recognized entity with the clinical characteristics is yet to be defined. We hypothesized that HER2-low breast cancer could lead to an increased rate of brain metastases in patients with localized breast cancer. We tested this hypothesis in a large cohort of breast cancer patients with long follow-up.

Methods We included 2686 adult breast cancer patients followed up in Hacettepe University Cancer Center. Patients with 1 + positive HER2 expression and 2 + HER2 expression with a negative FISH were categorized as HER2-low disease. We evaluated the brain metastasis risk with binary logistic regression analyses and reported odds ratios (OR) with 95% confidence intervals (CI).

Results During a median 95.4 (IQR 72.6–123.1) month follow-up, 184 patients developed brain metastasis (6.9%). The brain metastases were developed in 5.1% of the patients with HER2-negative disease, 8.5% of the patients with HER2-low disease, and 10.1% of the patients with HER2-positive disease. A multivariable binary logistic regression model demonstrated an increased risk of brain metastasis in patients with HER2-low disease (OR: 1.611, 95% CI 1.055–2.460, $p = 0.027$) and in HER2-positive patients (OR: 1.837, 95% CI 1.308–2.580, $p < 0.001$). Additionally, HR + -HER2-low disease was associated with a decreased DFS compared to HR + -HER2-negative disease ($p = 0.008$).

Conclusion In this study, we observed an increased risk of brain metastasis in localized breast cancer patients with HER2-low disease. We think that a high level of vigilance and a low threshold for brain imaging could benefit HER2-low breast cancer patients similar to the patients with HER-positive disease.

Keywords Brain metastasis · Breast cancer · HER2 · HER2-low

Introduction

Breast cancer is the most common malignancy and a leading cause of mortality in women with more than two million cases and 600,000 deaths in 2018 [1]. Breast cancer has four well-defined clinical subtypes, Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2) positive, and triple negative (TN), affecting the prognosis and guiding treatment decisions [2, 3]. The HER2-positive disease is a distinct subgroup characterized by the endocrine resistance and uncontrolled proliferation due to over-expression of epithelial growth factor receptors and clinically characterized by the high rate of brain metastases and early relapses [4–7]. While the HER2-positive disease was previously associated with poor survival outcomes, the survival outcomes are significantly improved with the advent of effective anti-HER2 treatments in the last 2 decades [8, 9].

The HER2-positive breast cancer was defined by a 3 + HER2 expression in immunohistochemistry (IHC) or in situ hybridization (ISH) positivity, and these patients are candidates for anti-HER2 treatments. However, the IHC 1 + and 2 + HER-positive breast cancers have a significant degree of HER-2 expression in cellular surfaces [10, 11], which could contribute to the disease progression. This

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notion led the researchers to test the anti-HER2 agents like trastuzumab and trastuzumab emtansine in these patients to improve outcomes, both in the metastatic and adjuvant settings [12, 13]. However, the results were largely disappointing and led to the limitation of clinical trials with anti-HER2 agents to HER2 3 + or HER2 ISH positive patients only. However, new-generation antibody–drug conjugates (ADC) like trastuzumab deruxtecan and trastuzumab duocarmazine demonstrated a significant degree of activity in patients with low HER2 expression in the metastatic setting [14, 15]. These findings reignited the interest in anti-HER2 treatments in hormone-positive (HR) and TN patients with 1 + and 2 + HER2 expression, and several clinical trials are being conducted in the HER2-low breast cancer with ADCs [16–18].

The HER2-low breast cancer is a newly recognized entity with the potential to be amenable to novel anti-HER2 agents. However, the clinical characteristics and the prognosis of this subtype are yet to be defined [16, 17]. Several studies evaluated the association between prognosis and low-level HER2 positivity in early breast cancer with variable HER2 expression cut-offs (> 0 + or 2 +) and methodologies (transcriptomic vs immunohistochemistry), and reported different affected subgroups (node-positive or negative/HR-positive or negative), leading to inconclusive results [19–21]. Besides, whether there are clinical similarities in metastasis patterns between HER2-positive and HER2-low disease was not evaluated. From these points, we hypothesized that HER2-low breast cancer could lead to decreased survival times and an increased rate of brain metastases in patients with localized breast cancer. In this study, we tested this hypothesis in a large cohort of breast cancer patients with long follow-up.

Methods

Study cohort

For this retrospective cohort study, we evaluated the data of 3151 adult breast cancer patients followed up between 01.01.2000 and 30.12.2016 in Hacettepe University Cancer Center. We included all patients treated within the prespecified dates other than patients treated in clinical trials, patients with incomplete clinical and survival data, and patients with metastatic disease at baseline. HER2 status was determined via IHC and expression levels were graded as negative, 1 +, 2 + and 3 + according to relevant ASCO CAP guidelines [22] at the time of tumor evaluation. Fluorescent in situ hybridization (FISH) was performed for the IHC 2 + cases. Patients with 1 + positive HER2 expression and 2 + HER2 expression with a negative FISH were categorized as HER2-low disease as previously suggested [16, 22]. Due to prohibitions in our country, the HER2 statuses were not re-evaluated for the study.

We recorded baseline demographics (age, sex, marital status), menopause status, patient weight and height, tumor T-N-M stage, tumor hormone, and HER2 expression status, lymphovascular invasion (LVI), perineuronal invasion (PNI), surgery and radiotherapy history, comorbidities and regular medications together with survival data. Additionally, the presence or absence of brain metastasis development during follow-up was recorded. The patients were diagnosed with brain metastasis with the imaging studies that were conducted due to symptoms and no routine cranial imaging was performed during the follow-up, as suggested in the guidelines [23, 24]. Comorbidities were categorized according to Charlson Comorbidity Index (CCI) [25]. The disease-free survival (DFS) events were defined as the development of metastases or new breast tumors under follow-up and/or death. The overall survival (OS) time was defined as the period from diagnosis to the last follow-up and/or death, and DFS time was defined as the period between diagnosis to disease progression and/or death.

Statistical analyses

We presented the descriptive characteristics by the medians and interquartile ranges (IQR) for continuous variables and percentages for categorical variables. We compared baseline characteristics with Kruskal–Wallis and Chi-square tests. We evaluated the predisposing factors for brain metastasis development with Chi-square and Fisher's exact tests. We constructed a binary logistic regression model for brain metastasis development with the statistically significant parameters in the univariate analyses. We used Kaplan–Meier survival curves and Cox regression analyses for univariate and multivariable survival analyses, respectively. We reported odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CI) for the variables included in the multivariable models. We used Statistical Package for Social Sciences version (SPSS) version 25.0 (IBM Inc., Armonk, NY, USA) in the analyses and considered p values below 0.05 statistically significant.

Results

Baseline characteristics

After excluding patients with incomplete data ($n = 171$) and patients with metastatic disease at baseline ($n = 294$), we included a total of 2686 patients who followed up between the prespecified dates. The cohort's median age was 48 (IQR 41–56), and 49.3% of the patients were premenopausal at diagnosis. Most patients had T1 or T2 disease (84%)

and more than half of the patients had node positive disease (53.3%) (Table 1). Six hundred seventy-three patients (25.1%) had HER2-positive disease, while 1723 (64.1%) had HR + and 290 (10.8%) had TN breast cancer. Hypertension was the most frequent comorbidity (22.5%), and the median CCI was 1. The HER2 expression was 0 in 1625 (60.5%), + 1 in 172 (6.4%), 2 + in 265 (9.9%) and + 3 in 624 (23.2%) patients. Additionally, HER2 FISH was positive in the 49 patients with + 2 HER2 expression. The HER2 1 + and 2 + patients were included together as the HER2-low group in the analyses ($n = 388$). The large portion of patients with HER2-low disease had HR positivity ($n = 347$, 89.6%), while TN-HER2-low disease was present in the minority ($n = 41$, 10.6%). Compared with HER2-negative tumors, HER2-low and HER2-positive tumors had higher T and N stages (Table 2). The median age of HER2-negative cohort was slightly higher and the frequency of hypertension was higher in HER2-negative and HER2-low patients compared to HER2-positive patients (Table 2).

Table 1 Baseline patient characteristics of study population

Clinical feature	*n* (%)
Sex	
Male	17 (0.6)
Female	2669 (99.4)
Histological subtype	
NOS	1969 (73.3)
ILC	125 (4.7)
Mixed histology	348 (12.9)
Other	244 (9.1)
Molecular subtype	
Hormone positive	1723 (64.1)
HER2-positive	673 (25.1)
Triple negative	290 (10.8)
Menopause status	
Premenopause	1325 (49.3)
Perimenopause	196 (7.3)
Postmenopause	1165 (43.4)
Lymphovascular invasion	
Absent	1916 (71.3)
Present	770 (28.7)
Perineuronal invasion	
Absent	2374 (88.4)
Present	312 (11.6)
Tumor T stage	
T1	928 (34.5)
T2	1327 (49.5)
T3	355 (13.2)
T4	76 (2.8)
Tumor N stage	
N0	1255 (46.7)
N1	786 (29.3)
N2	363 (13.5)
N3	282 (10.5)

NOS not otherwise specified, *ILC* invasive lobular carcinoma

Survival analyses

During a median 95.4 (IQR 72.6–123.1) months follow-up, 539 (20.1%) patients died, and 710 (26.4%) patients had any DFS events. The median OS and DFS were not reached. The T3–T4 primary, lymph node positivity, diabetes, and higher CCI (2 vs. 0–1) were associated with decreased OS ($p < 0.001$ for each) in univariate analyses. Similarly, these factors were associated with decreased PFS ($p < 0.001$ for T3–T4 primary, lymph node positivity and higher CCI and $p = 0.004$ for diabetes) in univariate analyses. The patients with LVI or PNI had decreased OS and DFS, while the survival difference between normal and overweight patients did not reach statistical significance ($p = 0.092$ for OS and $p = 0.439$ for DFS). Low levels of HER2 expression (vs. remaining cohort including HER2-negative and HER2-positive patients) did not have a statistically significant association with OS ($p = 0.981$) and DFS ($p = 0.294$). Similarly, the patients with HER2-low disease had similar OS compared to HER2-negative patients ($p = 0.393$). In contrast, low-level HER2 expression was associated with decreased DFS compared to negative HER2 expression (Fig. 1). The adverse effect of low-level HER2 expression was statistically significant in HR + -HER2-low disease ($p = 0.008$), while the difference did not reach statistical significance in TN-HER2-low disease ($p = 0.242$). A multivariable model was constructed with statistically significant variables in univariate OS analyses. In multivariable analyses, all included parameters other than the history of diabetes retained a significant negative association with OS. The DFS analyses were consistent with OS analyses (Table 3).

Evaluation of brain metastasis risk

During the follow-up, 184 patients developed brain metastasis (6.9%). The risk of brain metastases development was increased in premenopausal patients and node-positive patients, and patients with T3–T4 tumors. Additionally, brain metastasis development risk was increased in HER2-low and HER2-positive patients ($p = 0.001$). The brain metastases were developed in 5.1% of the patients with HER2-disease, 8.5% of the patients with HER2-low disease, and 10.1% of the patients with HER2-positive disease (Fig. 2). A multivariable binary logistic regression model demonstrated an increased risk of brain metastasis in patients with HER2-low disease (OR: 1.611, 95% CI 1.055–2.460, $p = 0.027$) and in HER2-positive patients (OR: 1.837, 95% CI 1.308–2.580, $p < 0.001$) (Table 3,

Table 2 Comparison of baseline characteristics across different HER2 expression levels

	HER2 negative ($n=1625$)	HER2 low ($n=388$)	HER2 positive ($n=673$)	p Value
Age (median, IQR)	49 (42–57)	48 (42–56)	48 (40–55)	0.008
Menopausal status				
Premenopausal	780 (48)	195 (50.3)	350 (52)	0.133
Perimenopausal	122 (7.5)	20 (5.2)	54 (8)	
Postmenopausal	723 (44.5)	173 (44.5)	269 (40)	
Body mass index				
<25 kg/m^2	548 (35.7)	112 (32.5)	209 (33)	0.328
>25 kg/m^2	988 (64.3)	233 (67.5)	425 (67)	
Diabetes mellitus				
Absent	1454 (89.5)	352 (90.7)	615 (91.4)	0.347
Present	171 (10.5)	36 (9.3)	58 (8.6)	
Hypertension				
Absent	1235 (76)	290 (74.7)	556 (82.6)	0.001
Present	390 (24)	98 (25.3)	117 (17.4)	
Charlson Comorbidity Index				
0 or 1	1258 (77.4)	300 (77.3)	544 (80.8)	0.174
2 or higher	367 (22.6)	88 (22.7)	129 (19.2)	
T stage				
T1–T2	1399 (86.1)	318 (82)	538 (79.9)	0.001
T3–T4	226 (13.9)	70 (18)	135 (20.1)	
N stage				
N0	830 (51.1)	169 (43.6)	256 (38)	<0.001
N+	795 (48.9)	219 (56.4)	417 (62)	

IQR interquartile range, *kg* kilogram, m^2 square-meter

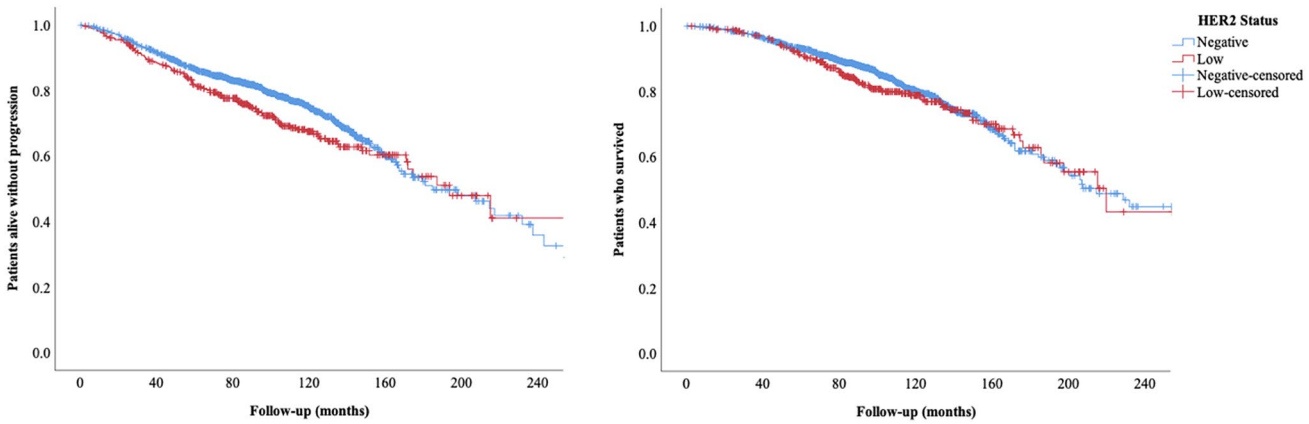

Fig. 1 The association between HER2-expression levels and disease-free (left) and overall survival (OS)

Fig. 3). The increased risk of brain metastasis remained significant in patients with HR + -HER2-low disease (OR: 1.655, 95% CI 1.041–2.664, $p=0.033$). The association between brain metastasis development risk and HER2-low disease did not reach statistical significance in patients with TN-HER2-low disease (OR: 1.590, 95% CI 0.568–4.450, $p=0.377$).

Discussion

Breast cancer is the second leading cause of brain metastasis and development of brain metastases is related to significant mortality [26–28]. The risk of brain metastasis is subtype-dependent in breast cancer with a predilection for

Table 3 Multivariable analyses for brain metastasis risk, overall survival and disease-free survival

Clinical factor	Brain metastasis development		Overall survival		Disease-free survival	
	OR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
HER2-low disease (1 + –2 +) (vs. HER2-negative disease)	1.611 (1.055–2.459)	0.027				
HER2-positive disease (vs. HER2-negative disease)	1.865 (1.330–2.615)	< 0.001				
T stage (T3–T4 vs. T1–T2)	1.813 (1.280–2.568)	0.001	1.737 (1.431–2.108)	< 0.001	1.587 (1.333–1.889)	< 0.001
Node positivity (N + vs. N0)	1.978 (1.407–2.781)	< 0.001	1.999 (1.637–2.440)	< 0.001	1.849 (1.563–2.187)	< 0.001
Diabetes (present vs. absent)			1.143 (0.876–1.490)	0.325	1.189 (0.930–1.521)	0.166
CCI (2 or higher vs. 0–1)			1.926 (1.601–2.318)	< 0.001	1.388 (1.172–1.645)	< 0.001
Lymphovascular invasion (present vs. absent)			1.400 (1.168–1.678)	< 0.001	1.248 (1.063–1.465)	0.007
Perineuronal invasion (present vs. absent)			1.133 (0.892–1.440)	0.307	1.082 (0.872–1.344)	0.474

OR odds ratio, *HR* hazard ratio, *CCI* Charlson Comorbidity Index

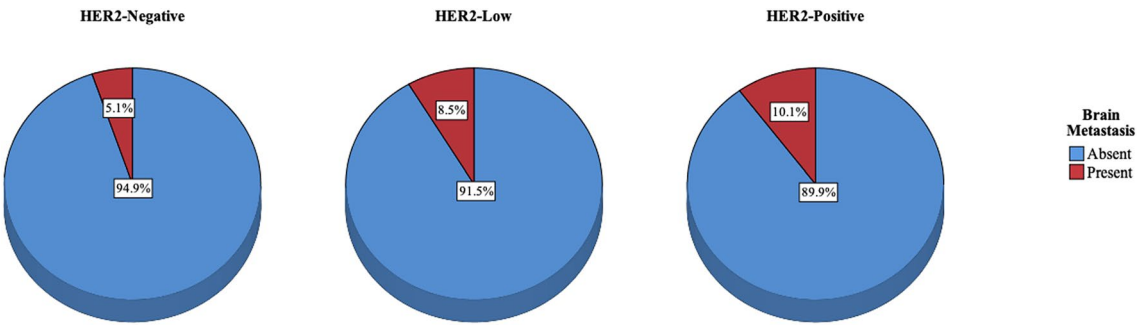

Fig. 2 The percentage of patients with brain metastasis according to HER2 expression levels

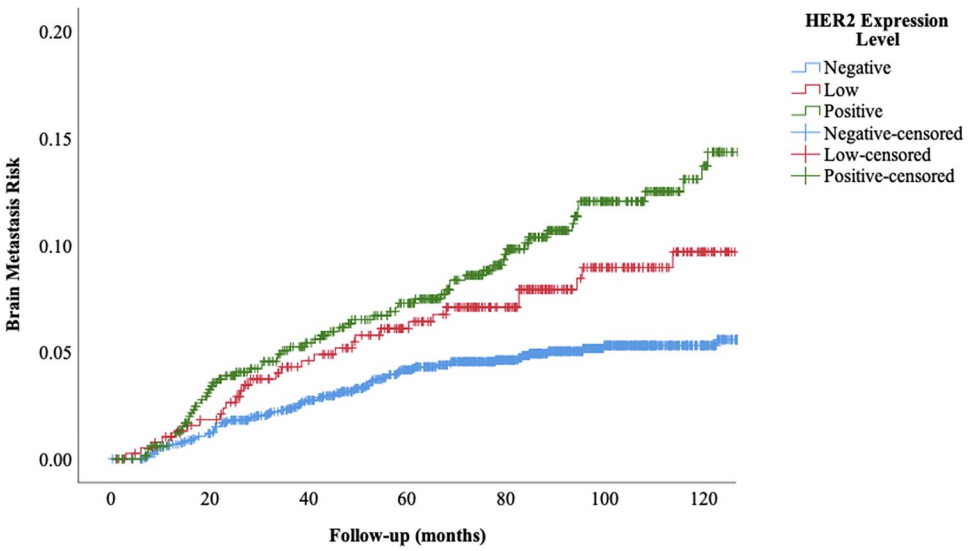

Fig. 3 Risk of brain metastasis development according to HER2 expression levels

increased risk in HER2-positive tumors [29, 30]. The brain tropism in HER2-positive tumors is possibly related to an interplay of several factors in the tumor microenvironment and blood–brain barrier [31], and HER2 oncogene postulated to be at the center of these interplay [31, 32]. The HER2-low breast cancers also contain a significant level of HER2 receptors on the cell surface [11]. However, whether a similar tropism for brain metastases is present in HER2-low breast cancers is unknown.

In the present study, we observed a 61% increased risk of brain metastasis in HER2-low breast cancer compared to HER2-negative patients. If this association is supported by prospective evidence, the patients with HER2-low breast cancers could be candidates for new therapeutic strategies in the adjuvant setting to prevent brain metastasis. The increased brain metastasis risk did not reach statistical significance in the TN group. We think that the small sample size ($n=289$) and a limited number of events ($n=26$) could be the reasons for the lack of association, and the association between HER2 expression and brain metastasis risk should be evaluated in larger TN breast cancer cohorts. In contrast, the brain metastasis risk was significantly increased in the HR + -HER2-low group independent of tumor T and N stages. While the HR + tumors conventionally have a better prognosis and a lower brain metastasis risk, low levels of HER2 expression could define a biologically more aggressive subtype with an increased brain metastasis risk, possibly due to similar biologic mechanisms with HER2-positive tumors.

We observed similar OS in patients with HER2-low tumors and HER2-negative tumors, while the DFS was significantly lower in patients with HER2-low tumors, especially in the HR + -HER2-low subgroup (Fig. 1). The effect of low-level HER2 expression on survival was investigated in several studies in localized breast cancer and demonstrated conflictive results [21, 33, 34]. In one of the pioneer reports by Camp et al., both the high and normal levels of HER2 expression were associated with poor outcomes, while the intermediate HER2 expression was associated with better DFS in a cohort of 300 breast cancer patients. The authors used a histogram to define the HER2 expression and reported that 71.3% of the breast cancers had intermediate HER2 expression [35]. A latter report with a moderate sample size ($n=91$) suggested that any level of HER2 expression was associated with decreased DFS ($p=0.001$) and OS ($p=0.001$) in node lymph-positive breast cancer patients [21], albeit the HER2-low disease was comprised a significantly lower portion of their cohort (14% HER2 1 + and 5% HER2 2 +) similar to our study. The negative prognostic effect was more pronounced in the HR + -HER2-positive cohort [21], similar to our study. Rossi et al. included a larger cohort of patients ($n=1150$) with HER2-negative and HER2-low disease and observed lower DFS in HER2 2 + patients compared to HER2-negative and HER2 1 + patients. In the study, the 1 + HER2 expression was higher than our cohort (39% vs. 6.4%), while the 2 + HER2 expression rates were similar (10% vs. 9.9%). The adverse effect of 2 + HER2 expression was time dependent and observed after an early survival advantage [34]. Interestingly, in the most comprehensive study (> 5000 patients), researchers from Germany reported lower DFS (HR: 1.217, 95% CI 1.052–1.408, $p=0.008$) but similar breast cancer-specific survival (HR = 1.045, 95% CI 0.926–1.178, $p=0.474$) in HR + patients with moderate HER2 expression [36]. However, the DFS difference did not reach statistical significance in HR− patients. These data [36] and our observations in the HR + subgroup only made us think that HER2-low status could be an additional prognostic factor in HR + patients, which traditionally have a better prognosis than the TN disease [37, 38].

Our study has several limitations. First, the study's retrospective nature and the small number of patients in some subgroups limited the generalizability. Our study was conducted in a tertiary reference center that may have created shifts in our case distribution as the increased percentage of younger patients. The 1 + HER2 expression was possibly underreported in our study as recent studies reported more than 30% 1 + HER expression levels [39], while 2 + HER expression rates in our study were similar to the literature [36, 39]. This issue could prevent our results' generability, although we think that our results are still hypothesis-generating. We could not exclude the possibility of an undetected brain metastasis due to a lack of regular interval cranial imaging to detect brain metastasis in accordance with the international oncology guidelines. Additionally, the maturation rates for OS and DFS levels were low limiting the power of survival analyses. However, despite these limitations, we observed a significant increase in the risk of brain metastasis in patients with HER-2-low breast cancer. To best our knowledge, this is the first report on the brain metastasis risk in this newly defined disease phenotype.

Conclusion

In this study, we observed an increased risk of brain metastasis in localized breast cancer patients with HER2-low disease and a lower DFS in HR + -HER2-low disease. We think that a high level of vigilance and a low threshold for brain imaging could benefit HER2-low breast cancer patients similar to the patients with HER-positive disease until our observation is further tested in the larger prospective datasets.

Author contributions DCG and SA have planned the work. DCG, MBK, BF, MO, HCY, KK, NK, OD, AU, and SA participated in patient care and data collection. All authors, namely DCG, MBK, BF, MO, HCY, KK, NK, OD, AU, and SA participated have made significant and substantive contributions to the reporting of the work. All authors have participated in the review of relevant literature, drafting of the manuscript, review and revisions of the final draft. DCG, MBK and SA have analysed the data and determined the main conclusions. DCG has prepared the first draft of the manuscript. All authors reviewed and participated in the preparation of the revised and final version of the manuscript. DCG and SA are responsible for the overall content as guarantors. All co-authors qualify the criteria for authorship according to Vancouver protocol.

Funding The authors received no financial support for this article.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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