The Frequency of Low HER2 Expression in Breast Cancer and A Comparison of Prognosis Between Patients With HER2-Low and HER2-Negative Breast Cancer By HR Status

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Abstract

Purpose

The DESTINY-Breast04 clinical trial is currently investigating whether trastuzumab deruxtecan (T-DXd) is effective in HER2-low as well as HER2-positive breast cancer. This highlights the interest in treatment strategies for patients with HER2-low breast cancer. The current study was therefore designed to determine the frequency of HER2-low among all breast cancers, and to compare the prognosis of HER2-low patients with that of HER2-negative patients.

Methods

We retrospectively reviewed the biological data from 4,918 of 4,977 primary breast cancer patients who attended our institute. We quantified the overall frequency of breast cancer patients with a new HER2-low subtype that was defined by an immunohistochemistry score of IHC1+ or IHC2+/ISH-. We then compared the clinical characteristics and prognosis of HER2-low patients with that of patients who did not have HER2 amplification (HER2-0).

Results

Low HER2 expression was found in 3169 (64.4%) patients; 2860 (58.1%) were HR-positive and 309(6.3%) were HR-negative. Among HER2-0 patients, 681(13.9%) were HR-positive and 157(3.2%) were HR-negative. The HER2-0 group tended to have more poor prognostic factors than the HER2-low group, irrespective of HR status. There were no statistically significant differences between the prognosis of HER2-low and HER2-0 patients, regardless of HR status. However, patients in the HER2-low group tended to have better prognosis than those in the HER2-0 group.

Conclusion

HER2-low patients did not have a significantly different prognosis than HER2-0 patients, regardless of HR status. However, we should consider tailoring therapies for patients with HRE2-low early breast cancer according to their HR status.

Introduction

Approximately 15 to 20% of breast cancer patients have overexpression of human epidermal growth factor receptor 2 (HER2) [1, 2], and breast cancer patients with high levels of HER2 have a worse prognosis than those who are HER2-negative [1, 3-5]. However, the advent of humanized anti-HER2 monoclonal antibodies such as trastuzumab and pertuzumab has significantly improved the prognosis for patients with HER2-positive breast cancer [6-8]. Moreover, the EGFR and HER2 tyrosine kinase inhibitor lapatinib, has also been approved for use in HER2-positive breast cancer [9]. More recently, HER2 targeting antibody-drug conjugates (ADCs) including trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), have been developed in order to treat HER2-positive breast cancer [10, 11].

American Society of Clinical Oncology (ASCO)/ College of American Pathologist (CAP) guidelines have been widely used to estimate the HER2 score in many countries. According to the guidelines, there are three categories of HER2 status that are based on immunohistochemistry (IHC) analysis, as follows. Patients are HER2-negative if the IHC score is 0 or 1+, HER2-equivocal if the score is 2+, and HER2-positive if the score is 3+. The HER2 status of patients with equivocal IHC scores are further examined using in situ hybridization (ISH). ISH-positive and ISH-negative tumors and then classified as HER2-postive and -negative, respectively [12, 13]. Several HER2 targeting therapies, such as trastuzumab, pertuzumab, lapatinib and T-DM1 have been specifically approved only for HER2-positive breast cancer as defined in the ASCO/CAP guidelines. These therapeutic options are therefore not available to patients with IHC1+ or IHC2+/ISH- scores; even though they have slightly elevated HER2 levels they are categorized as HER2-negative [12, 14]. However, it has recently been suggested that T-DXd may be effective not only in HER2-positive breast cancer, but also in HER2-low breast cancer, which would include patients with IHC1+ and IHC2+/ISH- scores [15].

Given these observations, we suggest that it is critical to understand both the frequency and prognostic significance of HER2-low status in breast cancer. If, for example, HER2-low status was associated with a poorer prognosis than HER2-positive status, this would prompt a re-evaluation of the utility of anti-HER2 therapies in HER2-low patients. Although there is one report in which the prognoses of HER2-low and HER2-0 breast cancer were compared [16], further studies are required. We therefore carried out a retrospective analysis of HER2-low versus HER2-negative patients. The results of this analysis are described herein, and include stratification of cases based on hormone receptor (HR) status.

Methods

We retrospectively reviewed the data from 4,977 primary breast cancer patients who had received treatment at our institute between January 2005 and December 2015 (Fig. 1). The data collected included HER2 status, HR status, age, tumor size, the number of metastatic lymph nodes and histological grade from clinical records. We excluded patients for whom biological data were not available. We then investigated the proportion of patients that had low HER2 expression and compared the prognosis and background of the HER2-low group with the same parameters in the HER2-0 group; these data were stratified by HR status.

Pathological assessment and definition of molecular subtypes

Histopathological diagnoses of breast cancer were made by several pathologists at Aichi Cancer Center Hospital. HER2 score was determined by IHC; if the IHC score was equivocal, samples were subjected to ISH. The criteria of the Trastuzumab Pathology Group, which is referred to in the ASCO/ CAP guidelines, were used to determine the HER2 score. Tumors were defined as HR-positive if they yielded an Allred score of 3 or more for ER or PgR. We categorized new HER2 subtypes as follows. HER2-high if IHC3+ or IHC2+/ISH+, HER2-low if IHC 1+ or IHC 2+/ISH-, HER2-negative (HER2-0) if there was no HER2 staining. The categorization of new HER2 subtypes is shown in Table 1.

Statistical analysis

The baseline characteristics were evaluated using Pearson's χ2 test. The endpoint of our study was comparison of 5-year overall survival (OS) and 5-year disease-free survival (DFS) between the HER2-0 group and the HER2-low group, according to HR status. DFS was defined as the time from the day of surgery to the day of recurrence or death from any cause. OS was defined as the time from the day of surgery to the death from any cause. Differences in five-year DFS and OS between HER2-low and HER2-0 patients and according to HR status were estimated using the log-rank test and the Kaplan-Meier method. A *p* value less than 0.05 was considered statistically significant in our analysis. All data analysis was carried out using Stata Ver15.

Results

Patients

We obtained biological data from 4918 breast cancer patients (Fig. 1). In the new subtype categories, low HER2 expression was found in 3169 (64.4%) of all breast cancer patients. There were 2860 HR-positive/HER2-low patients (58.1%), and 309 HR-negative/HER2-low patients (6.3%). There were 838 HER2-0 patients (17.1%) overall; 681 were HR-positive (13.9%) and 157 were HR-negative (3.2%) (Table 2). The baseline characteristics of the HER2-low group and the HER2-0 group by HR status are shown in Table 3. Patients in the HR-negative/HER2-0 group tended to have larger tumors than those in the HR-negative/HER2-low group, whereas those in the HR-negative/HER2-low group had a higher frequency of in situ carcinoma. As observed in the HR-negative group, the HR-positive/HER2-0 group had larger tumors and worse historical grade (HG) when compared with the HR-positive/HER2-low group. The frequency of ILC was higher in the HR-positive/HER2-low group than in the HR-positive/HER2-0 group. Regardless of HR status, there were no statistical differences between the HER2-low group and the HER2-0 group regarding lymph node metastasis, adjuvant chemotherapy or adjuvant endocrine therapy.

DFS and OS

The median follow-up time was 5.5 years. Five-year DFS in the HR-positive/HER2-low group and the HR-positive/HER2-0 groups was 91.6% and 90.1%, respectively; these rates were not significantly different (p = 0.151; Fig. 2-A). There was also no significant difference in 5-year OS between the HR-positive/HER2-low group and the HR-positive/HER2-0 group (96.7% and 94.9%, respectively, p = 0.215; Fig. 2-B).

HR-negative cases had a poorer overall prognosis than HR-positive cases. Specifically, 5-year DFS was 74% in the HR-negative/HER2-0 group and 78.7% in the HR-negative/HER2-low group; these values were not significantly different (p = 0.306; Fig2-C). A similar result was seen for 5-year OS among HR-negative patients (Fig2-D).

Discussion

According to previous studies, between 40% and 50% of patients with breast cancer have tumors with low HER2 expression [15-17]. Here we observed a slightly higher proportion of HER-low cases (64% of all breast cancers). The reason for the differences in frequency are currently unclear. However, one explanation is that there may be differences in the methods of quality control for the HER2 test, as we describe below. We also found that the overall incidences of HR-positive/HER2-low and HR-negative/HER2-low cases were 58.1% and 6.3%, respectively.

There have been several reports regarding the prognosis of breast cancer patients with low HER2 expression. Ignatov et al. reported that patients with an intermediate HER2 score (defined as IHC 2+ and ISH-negative) had a worse prognosis than HER2-negative patients (defined as IHC 0 or 1+) breast cancer [18]. However, their study did not further stratify the patients based on HR status, which is an important parameter in the clinic. Francesco et al. were the first to compare the prognosis of HER2-low and HER2-0 by HR status, and found no statistically significant differences these two groups, regardless of HR status [16]. We suggest that it is more important to determine whether HER2-low or HER2-0 status is associated with a poorer prognosis in luminal or triple negative breast cancer. Our current study was designed to address this question, and the results suggest that HER2-low patients did not have a significantly different prognosis than HER2-0 patients, which is consistent with Francesco et al. However, we did find that the HER2-low group tended to have a better prognosis than the HER2-0 group regardless of HR status, although the differences were not statistically significant. We infer that this is because patients in the HER2-0 group tended to have more factors associated with poor prognosis than those in the HER2-low group. Further studies are required to fully understand the prognostic significance of different levels of HER2 expression in breast cancer.

There are currently no approved guidelines that recommend anti-HER2 therapy for breast cancers with low HER2 expression. However, several studies have assessed anti-HER2 therapy in HER2-low breast cancer patients. The use of trastuzumab as adjuvant therapy in this setting did not improve DFS [19], nor did trastuzumab emtansine (T-DM1) improve DFS in metastatic breast cancer with low HER2 expression [20]. On the other hand, T-DXd may be effective for the treatment of breast cancer patients with low HER2 expression. T-DXd is a novel, HER2targeted ADC that is composed of a humanized monoclonal antibody attached by a cleavable peptide-based linker to a potent topoisomerase I inhibitor payload [21]. In the DESTINY-Breast 01 phase□study, T-DXd seemed to be effective in 44% patients with metastatic disease and low HER2 expression [21]. These results lead to the DESTINY-Breast04 phase III randomized trial, which is currently evaluating T-DXd for the treatment of HER2-low metastatic or advanced breast cancer (ClinicalTrials.gov identifier: NCT03734029). In our current study, there was no statistical difference between HER2-0 and HER2-low patients with regard to prognosis, irrespective of HR status. However, if T-DXd and other anti-HER2 therapies are demonstrated to be effective in patients with HER2-low breast cancer, this should improve their overall prognosis. In particular, the prognosis of HR-negative/HER2-low breast cancer is poor, and novel therapeutic agents to treat patients in this group are clearly needed. HER2-low status may eventually be used as a predictive factor of the efficacy of novel therapeutics in early breast cancer, in much the same way that HER2-positive status is now used to stratify patients for T-DXd treatment.

The limitations of our current study are that it was carried out at a single institution, was retrospective and relied on inconsistent evaluation of HER2 scores. Moreover, different types of formalin solution can lead to different HER2 scores, which could contribute to inter-institutional discrepancies [22, 23]. In addition, the HER2 scoring scale was different in each study due to the continual updating of ASCO/CAP guidelines. However, our study is one of only a few that have determined the frequency and prognostic value of low HER2 expression in breast cancer in the context of of HR status.

Conclusion

There was no difference in prognosis between HER2-low and HER2-0 breast cancer patients regardless of HR status. However HER2-low patients, who will be candidates for new HER2-ADC drugs in the near future, accounted for over half of all early breast cancer patients. The therapeutic strategies for treatment of HER2-low early breast cancer patients should be considered in the context of HR status.

Declarations

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Author contributions

NH performed the planning study and the statistical analysis and drafted the manuscript. YA and HI were involved in the drafting and revision of the manuscript. MS, MH, AY, HK, AK, KS, YO, YE, DT and KN participated in information and data collection. All authors read and approved the fnal manuscript.

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Conflicts of interest: The authors declare that they have no conflict of interest.

Ethics approval: Our study adhered to the Declaration of Helsinki principles and was approved by the Institutional Review Board of Aichi Cancer Center Hospital. An opt-out approach was used, and was accessible to patients via or website, (https://www.pref.aichi.jp/cancer-center/cc/01gaiyo/rinri/2020-1-319.pdf).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1 The categorization of new HER2 subtypes

IHC ISH	3+	2+	1+	0
Positive	HER2-high	HER2-high	HER2-high	HER2-high
Negative	(ISH was not tested)	HER2-low	(ISH was not tested)	(ISH was not tested)

Table 2 The frequency of breast cancer patients with new HER2-low subtypes

	HER2-high (IHC3+, IHC2+/ISH+) (%)	HER2-low (IHC1+, IHC2+ /ISH-) (%)	HER2-0 (%)	Total (%)
HR+	508(10.3)	2860(58.1)	681(13.9)	4049(82.3)
HR□	403(8.2)	309(6.3)	157(3.2)	869(17.7)
Total	911(18.5)	3169(64.4)	838(17.1)	4918(100)

Frequencies shown are percentages of the overall total of patients in this study

Table 3 Baseline characteristics between the HER2-low group and the HER2-0 group by HR status

	HR-positive			HR-negative		
	HER2-low □=2860(%)	HER2-0 n=681(%)	P	HER2-low □=309(%)	HER2-0 □=157(%)	P
Age			<0.001			0.06
<65	2262(79.1)	496(72.8)		219(71.0)	124(79.0)	
≧65	598(21.0)	185(27.2)		90(29.1)	33(21.0)	
T			0.04			0.002
Tis	483(16.9)	101(14.8)		66(21.4)	15(9.6)	
<2cm	1796(62.8)	414(60.8)		139(45.0)	94(59.9)	
2~5cm	501(17.5)	136(20.0)		82(26.5)	31(19.8)	
> 5	49(1.7)	22(3.2)		17(5.5)	15(9.6)	
unknown	31(1.1)	8(1.2)		5(1.6)	2(1.3)	
N			0.25			0.95
0	1764(61.7)	431(63.3)		198(64.1)	104(66.2)	
1–3	521(18.2)	109(16.0)		56(18.1)	27(17.2)	
□4	227(7.9)	46(6.8)		30(9.7)	13(8.3)	
unknown	348(12.2)	95(14.0)		25(8.1)	13(8.3)	
HG			<0.001			0.05
1	943(33.0)	273(40.1)		19(6.2)	3(1.9)	
2	1290(45.1)	268(39.4)		64(20.7)	30(19.1)	
3	319(11.2)	91(13.4)		200(64.7)	117(74.5)	
Unknown	308(10.8)	49(7.2)		26(8.4)	7(4.5)	
Histological type※□			<0.001			0.005
IDC	2083(72.8)	472(69.3)		226(73.1)	130(82.8)	
ILC	192(6.7)	31(4.6)		9(2.9)	4(2.6)	
Other	82(2.9)	71(10.4)		26(8.4)	17(10.8)	
Chemotherapy			0.193			0.213
Neoadjuvant Chemotherapy	136(4.8)	43(6.3)		56(18.1)	32(20.4)	

Adjuvant Chemotherapy	637(22.3)	135(19.8)		154(49.8)	82(52.2)	
No chemo	1983(69.3)	474(69.6)		81(26.2)	29(18.5)	
Unknown	104(3.6)	29(4.3)		18(5.8)	14(8.9)	
Endocrine therapy	1994(69.7)	468(68.7)	0.686	-	-	
No endocrine	744(26.0)	179(26.3)		-	-	
Unknown	122(4.3)	34(5.0)		-	-	
Anti-HER2 therapy			<0.001			0.790
Adjuvant anti-HER2 therapy	13(0.5)	0		1(0.3)	1(0.6)	
No anti-HER2	2014(70.4)	433(63.6)		179(57.9)	87(55.4)	
unknown	833(29.1)	248(36.4)		129(41.8)	69(44.0)	

※1 excluding in situ carcinoma and a histological sample that could not be categorized

Figures

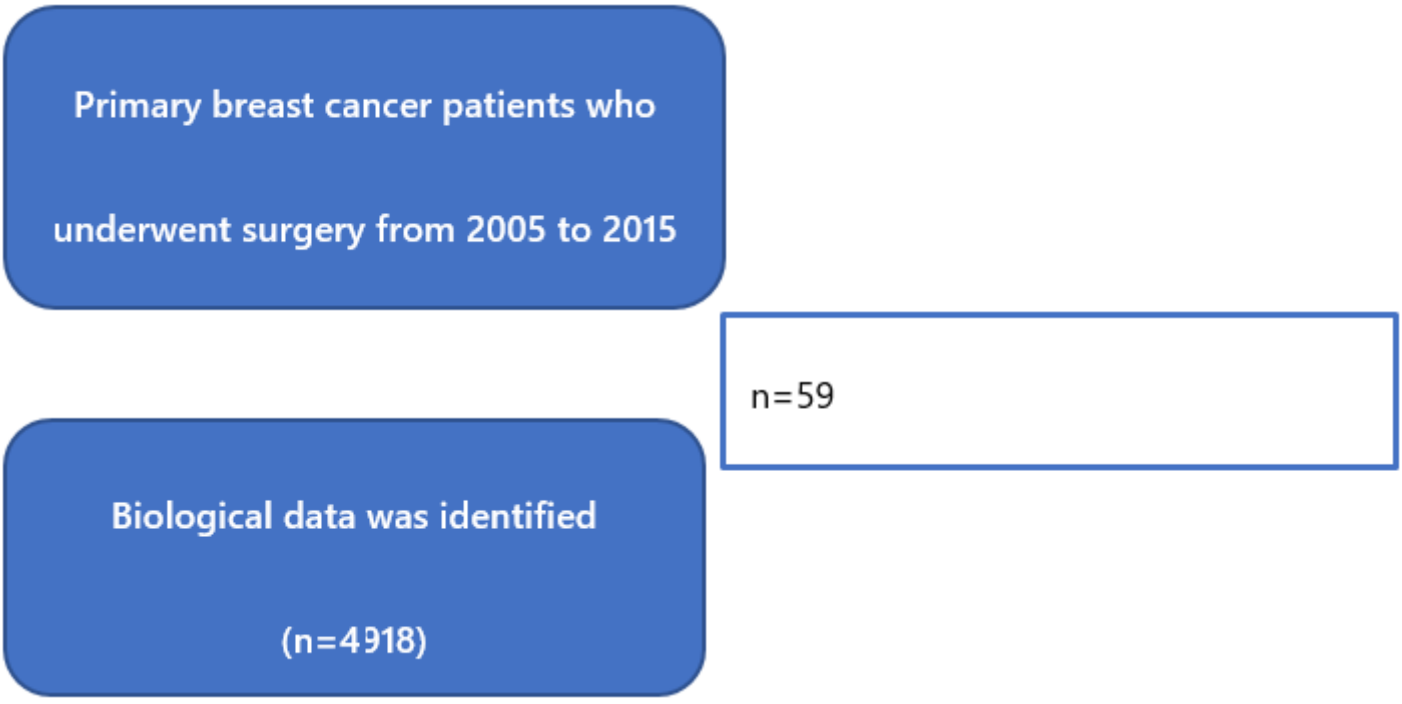

Figure 1

Study design

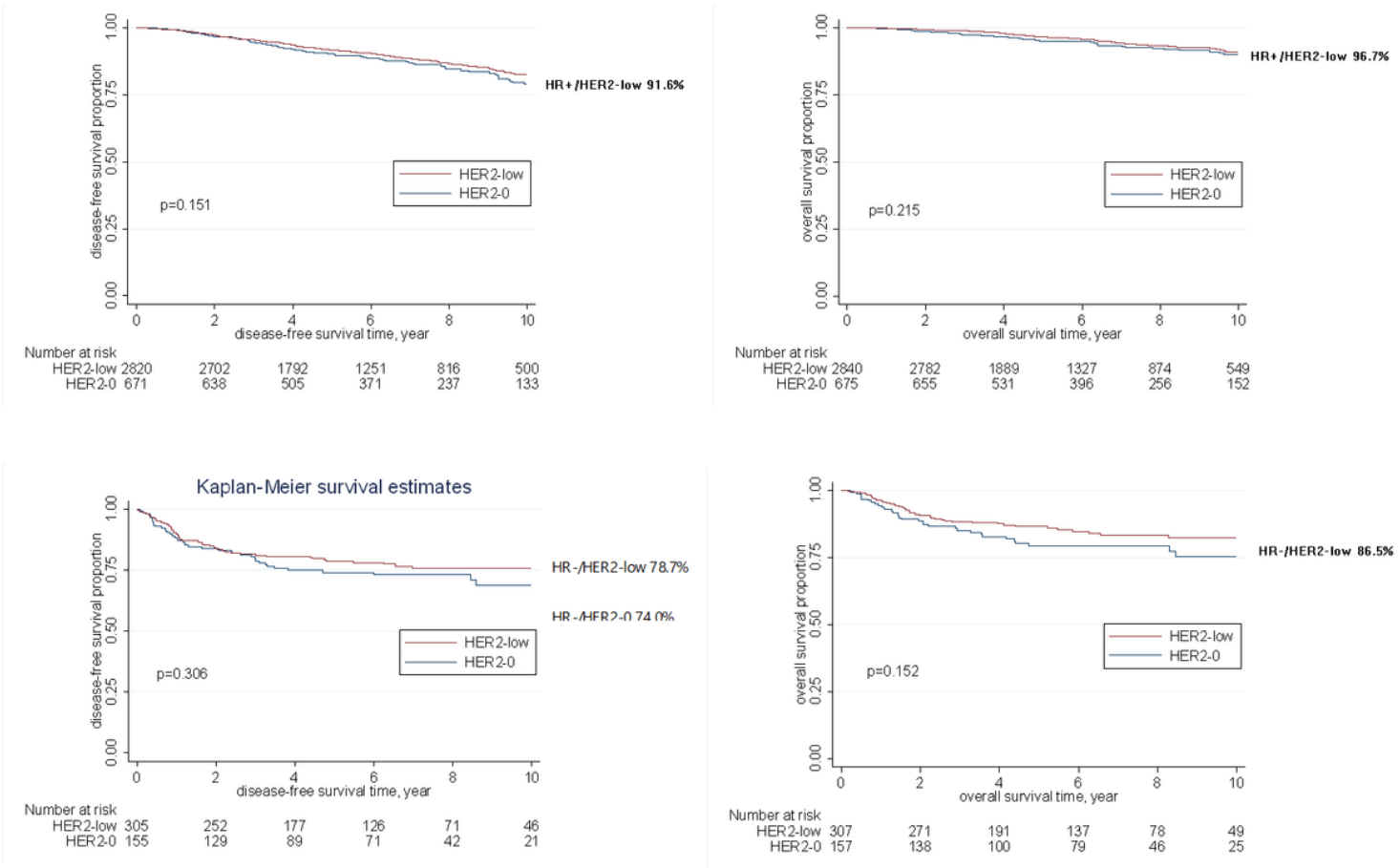

Figure 2

DFS and OS in HER2-0 and HER2-low patients according to HR status. Kaplan-Meier curves of DFS and OS are shown. DFS and OS of the HER2-low group vs the HER2-0 group in HR-positive patients are shown in A and B. DFS and OS of the HER2-low group vs the HER2-0 group in HR-negative patients are shown in C and D. The p-values for log-rank tests are reported in each Figure panel. A. DFS in HR-positive patients B. OS in HR-positive patients C. DFS in HR-negative patients D. OS in HR-negative patients